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# Effect of music intervention on mental health in patients with diabetes mellitus: a protocol for a systematic review and meta-analysis of randomized controlled trials

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# Effect of music intervention on mental health in patients with diabetes mellitus: a protocol for a systematic review and meta-analysis of randomized controlled trials

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## ABSTACT

**Introduction** About 463 million adults aged 20 to 79 have diabetes globally and mental disorders often exist in diabetic patients as comorbidities. The comorbidities can lead to deterioration of diseases, increased difficulty in treatment, even as well as the terrible mortality. Music intervention has been applied in the treatment of the comorbidities for 12 years, but there are no any recommendations due to lacking of evidence. Thus, a meta-analysis is necessary to be conducted to evaluate the effect of music intervention.

**Methods and analysis** We will retrieve the following nine online electronic databases: PubMed, Web of Science, Embase, EBSCO, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journal Database (VIP) and Chinese Biomedical and Medical Database (CBM), from their inception until August 2019. Only randomized controlled trials (RCTs) of music intervention for depression or anxiety with diabetes will be involved. The primary outcomes include depression score and anxiety score measured by scales, and the secondary outcome is safety. Data extraction will be implemented by 2 researchers independently. Risk of bias will be evaluated through Cochrane Collaboration's Risk of Bias tool. Eventually, all the data will be analyzed via the software Review Manager V.5.3.

**Ethics and dissemination** This meta-analysis will provide information about music intervention applied to treat depression or anxiety in diabetic patients. There is no required ethical approval because this is a protocol for meta-analysis. The results of this study will be published to a peer reviewed journal.

**Trial registration number** CRD42019146439

**Strengths and limitations of this study**

· This meta-analysis will provide evidence of the effectiveness and safety of music intervention applied to treat depression or anxiety in diabetic patients for the first time.

· This systematic review will furnish evidence reference for guideline of relevant areas.

· This meta-analysis will be implemented on the basis of rigorous international gold-standard methodology and integrated search strategy.

· A language bias may exist in this meta-analysis because it will include studies only in English and Chinese on account of the language barrier.

## INTRODUCTION

### Description of the conditions

According to the newest "IDF Diabetes Atlas (9th edition)" published by International Diabetes Federation (IDF), about 463 million adults aged 20 to 79 have diabetes globally (1 in 11).[1] It is well known that diabetes has a significant influence on life quality because it can cause a lot of complications such as retinopathy, renal disease, cardiovascular disease, neurological disease and foot ulcers which may result in lower extremity amputation.[2]

In addition to physical complications, some mental disorders often exist in diabetic patients as comorbidities. A few studies suggested that depression was more prevalent in diabetic patients compared to those without.[3,4] At the same time, depression could also increase the risk of incident of diabetes,[5-7] which suggested that depression had a bidirectional association with diabetes. And the relation between anxiety and diabetes was confirmed to be the same. People with diabetes were more susceptible to concurrent anxiety[8,9] while reversely anxiety was a risk factor of diabetic incidents.[10] Individuals with chronic diseases and also comorbid depression or anxiety have obviously higher health-care utilization, functional disability, work absence and mortality risk than those without.[11,12]

### Description of the intervention

When it comes to the treatment of diabetes with depression or anxiety, conventional glucose-lowering treatment combined with drug therapy or psychological intervention are the routine treatments.[13,14] Music intervention is also a successful therapy using music for treatment by professionals, which can be divided into two major categories, namely music therapy and music medicine, although the distinction between them are often neglected.[15] A lot of studies suggested that music, no matter what type of it is, demonstrated a remarkable effect in alleviating depression and anxiety among patients with various diseases.[16-18] As for diabetes, recent studies showed that music intervention could improve fasting blood-glucose and systolic blood pressure in diabetic patients.[19,20] Good control of blood glucose, blood lipids and blood pressure can effectively

reduce the incidence of serious complications of diabetes.[21]

**How the intervention might work**

Music psychology researches have shown the special potential of music that music listening can give rise to complex emotional experiences[22, 23] and strengthen ability to deal with complex negative emotions in everyday life.[24] The proposed mechanisms of music intervention on depression and anxiety span several domains. Firstly, music intervention can exert neurophysiological and neurochemical effects, such as triggering endorphin release[25] and stimulating cognitive functioning.[26] Secondly, music intervention can promote positive self-emotions including enhancing the sense of happiness[27] and activating self-efficacy and self-confidence through experiences of success.[28] Lastly, music intervention can build up sociability, such as interaction skills[29] and interpersonal relationship.[30] Furthermore, there are published studies indicated that music intervention combined with diabetic routine treatments could improve depression score, anxiety score, fasting glucose and glycosylated hemoglobin (HbA1c).[31,32]

**Why it is important to this review**

From the above, many studies indicated the bidirectional relationship between diabetes and mental disorders. Music intervention, as a therapeutic method, was applied to alleviate depression and anxiety and improve related indicators of diabetes. By searching literatures, it can be found that some reviews evaluated the effect of music intervention on patients with mental disorders,[33-35] while no related systematic review and meta-analysis can be searched about the effect of music intervention on mental health of patients with diabetes. Therefore, if music intervention can be proved to be both valid and with few side effects through this study, it is worth being promoted and applicated in clinic all over the world to benefit more people since this method is easy to be operated.

**Objectives**

The purpose of this review is to systematically assess the effect of music intervention on depression

and anxiety of diabetic patients. We also look forward to furnish evidence reference for related guideline.

## METHODS

### Study registration

The protocol of the meta-analysis has been registered in International Prospective Register of Systematic Reviews (PROSPERO), and CRD42019146439 is the registration number. This systematic review protocol will be conducted and reported severely on the basis of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[36] statement guidelines, and the crucial protocol amendments will be documented in the full review.

### Eligibility criteria

We will severely screen studies that have compliance with following inclusion criteria.

Type of studies

We will only cover randomized controlled trials (RCTs) in English or Chinese, excepting Quasi-RCTs and cluster RCTs. Experiments on animals and nonrandomized clinical trials will be out of our consideration. Articles with significant overlap with other articles through print or e-publishing will fail to be included. Duplicate publications, that is results originated from a single experiment but measured by other standards and then published as disparate papers, will also be excluded. Publications with originality is our first choice. The publication status will not be restricted.

Type of Participants

Diabetic Patients with depression or anxiety symptoms, regardless of the type of diabetes and no restriction on gender, age, race, economic ability and education level. Patients of other disease or healthy persons will be excluded.

Type of interventions and controls

Interventions include music alone or music in combination with other interventions. No restriction on the type of music. Other interventions refer to: (1) routine treatment for diabetes which mainly includes pharmacologic approaches to glycemic treatment, lifestyle management, etc. according to the newest guideline of American Diabetes Association (ADA);[37,38] (2) Other therapies such as acupoint therapy,[39] metabolic surgery[40] etc. When intervention is music alone, controls can be no treatment, placebo or other active therapies. Notably, when intervention is music combined with active therapies, the control must be the same active therapies.

Type of outcome measures

This review aims at systematically assessing the effect of music intervention on depression or anxiety of diabetic patients, so we choose depression score and anxiety score as the primary outcomes which can give an index to the degree of depression and anxiety by scales such as SDS, HAMD, SAS or HAMA.

Primary outcomes: Depression score and anxiety score. Depression score is measured using self-rating depression scale (SDS) or Hamilton depression scale (HAMD). Anxiety score is measured using self-rating anxiety scale (SAS) or Hamilton anxiety scale (HAMA).

Secondary outcomes: Safety. Measurement via incidence of adverse effects.

**Search methods**

Search resources

We will retrieve the following nine online electronic databases: PubMed, Web of Science, Embase, EBSCO, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journal Database (VIP) and Chinese Biomedical and Medical Database (CBM), from their inception until August 2019. We also scrutinized the reference list of relevant publications for additional studies.

Search strategies

The search strategy will include the MeSH terms for diabetes mellitus, depression, anxiety and music therapy, combined with their respective free-text terms. The search details of the PubMed was simply shown in table 1.

**Table 1 Example of PubMed search strategy.**

| Number | Search terms |
|---|---|
| #1 | "Diabetes Mellitus"[Mesh] |
| #2 | "Depression"[Mesh]) OR Depressions[Title/Abstract]) OR Depressive Symptoms[Title/Abstract] OR Depressive Symptom[Title/Abstract] OR Symptom, Depressive[Title/Abstract] OR Symptoms, Depressive[Title/Abstract] OR Emotional Depression[Title/Abstract] OR Depression, Emotional[Title/Abstract] OR Depressions, Emotional[Title/Abstract] OR Emotional Depressions[Title/Abstract] |
| #3 | "Anxiety"[Mesh] OR Hypervigilance [Title/Abstract] OR Nervousness [Title/Abstract] |
| #4 | #2 OR #3 |
| #5 | "Music Therapy"[Mesh] OR Therapy, Music [Title/Abstract] |
| #6 | randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR placebo [Title/Abstract] |
| #7 | #1 AND #4 AND #5 AND #6 |

**Data collection and analysis**

Studies selection

Firstly, two researchers (L-yZ and YT) will respectively screen the keywords, titles and abstracts of all obtained studies using endnote x9 software and determine whether trials have compliance with inclusion criteria. Secondly, we will also get access to the full text of all studies of possible relevance for further assessment. Each of excluded study will be noted with reasons. Any

disagreements will be settled through consensus or referral to the third researcher (YZ). The specific selection steps were presented in the figure 1.

Data extraction

Two researchers (L-yZ and YT) will independently extract and tabulate the following data items via Microsoft Excel:

1. General information (including publication year and name of the first author).

2. Study design (including random method, allocation concealment and blinding).

3. Participants (including sample size, gender, age, depression score, anxiety score and course of disease).

4. Treatment (including interventions, controls, music type and the course of treatment).

5. Outcomes (SDS, HAMD, SAS or HAMA and safety).

If there is any different opinion, the final decision will go to the third researcher (X-xF) to be made. If the required data are unavailable from literatures, one researcher (YZ) will send an e-mail to the corresponding author and ask for further information

Assessment of risk of bias

The Cochrane Collaboration's Risk of Bias tool[41] will be applied to evaluate the risk of bias of all included RCT studies by two authors (L-zW and YZ). The following domains will be assessed: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other sources of bias. The assessments will be classified into "low", "unclear" or "high" of risk.

Data analysis

RevMan 5.3. software provided by the Cochrane collaboration will be used to analyze the data. Considering that all outcomes (depression score, anxiety score and safety) are continuous variables, the weighted mean difference (WMD) and 95% confidence interval (CI) will be calculated when

the quantitative data are from the same measurement method or small data scale. On the contrary, the standardized mean difference (SMD) and 95% CI will be calculated.

A meta-analysis will be implemented if the included studies are adequately homogenous. *P*-value and $I^2$ will be used to assess the heterogeneity of statistic. When *P*-value >0.05 and $I^2 \leq 50\%$, the fixed-effects model will be used for statistical combination. When *P*-value <0.05 or $I^2 > 50\%$, subgroup analyses or sensitivity analyses will be performed. If a meta-analysis is unavailable, descriptive summaries will be provided.

Assessment of reporting bias

Publication bias will be implemented, if there are more than 10 studies included, through a funnel plot.

Patient and public involvement

Patients and public involvement will fail to be included in this study.

Evidence assessed

GRADE guideline will be used to evaluate the quality of evidence.[42] To fulfil transparency and simplification, the quality of evidence can be assessed by 4 levels: “high”, “medium”, “low” and “very low”. GRADE profiler 3.2 will be applied for analysis.

## DISCUSSION

Depression and anxiety often occur independently or simultaneously during the development of many chronic diseases. In recent years, the number of studies about comorbid depression or anxiety in diabetics are continually increasing, not only because the two-way relationship between depression/anxiety and diabetes can lead to deterioration of diseases, increased difficulty in treatment, even as well as the terrible mortality,[43-46] but also because therapeutic methods for treating the comorbidities is limited and unsatisfactory. On the one hand, some antidepressant drugs,

such as nortriptyline and sertraline, may complicate glycemic control.[47] On the other hand, psychotherapy requires a professional psychiatrist and it is expensive.

Music intervention has been proved by many literatures to have a beneficial effect on depression and anxiety, such as strengthening awareness and sensitiveness for positive emotions.[48] Noticeably, a few studies also show that music intervention can reduce blood glucose and HbA1c simultaneously.[20,49] Therefore, music intervention is an applicable method for treating depression and anxiety with diabetes. Additionally, music intervention, almost no side effects, is safer than pharmacotherapy, easier to be operated and costs less than psychotherapy, so it is conducive to clinical promotion and application.

Since 2007,[50] music intervention has been applied in the treatment of depression and anxiety with diabetes for 12 years. Nonetheless, no any systematic review or meta-analysis were conducted to evaluate the potential benefits and harms of this therapy method. Thus, this study intends to provide strong evidence for music intervention applied to treat mental disorders in diabetic patients and synchronously furnish evidence reference for related guideline.

However, a language bias may exist in this meta-analysis because it will include studies only in English and Chinese because of the language barrier. Therefore, some related studies from medical databases in other languages might be missed.

In conclusion, this meta-analysis will be conducive to assess underlying benefits and harms of music intervention on comorbid depression or anxiety with diabetes. Moreover, the results of this study might not merely furnish reference basis for related guideline, but also may attract more attention on music intervention, which can be a chance to facilitate its clinical application and ultimately benefit more patients.

## ETHICS AND DISSEMINATION

There is no required ethical approval because this is a protocol for meta-analysis. The results of this study will be published to a peer reviewed journal.

**Contributions** L-yZ and C-gX contributed to the conception of the study. The manuscript of the protocol was drafted by L-yZ, and was revised by XxF and C-gX. L-yZ and YT will also independently screen the potential studies and extract data from included studies. L-zW and YZ will assess the risk of bias and accomplish data synthesis. XxF will arbitrate any disagreements. C-gX will ensure that no errors occur during the review. All authors have approved the publication of the protocol.

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**Competing interests** None.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.



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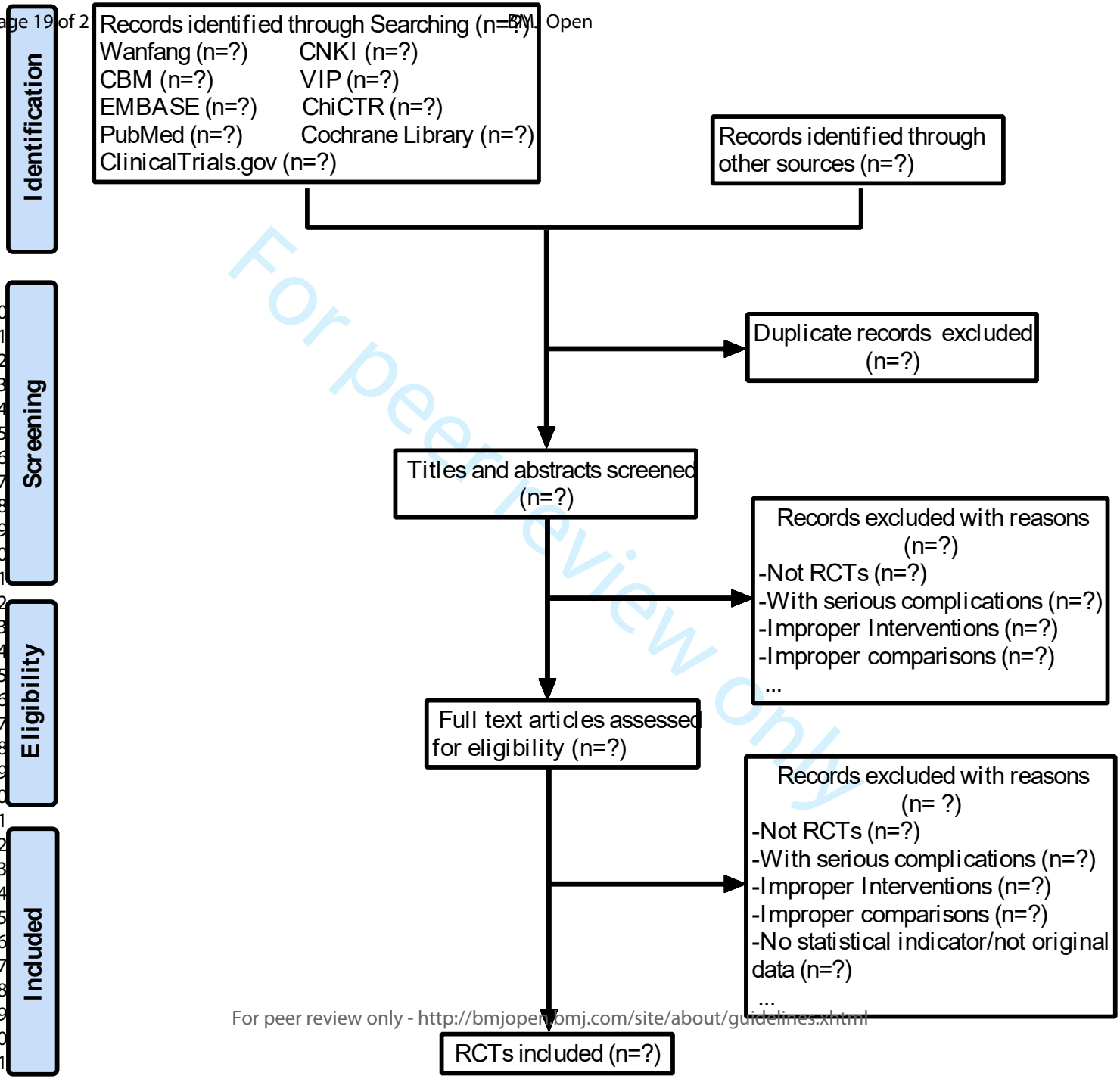

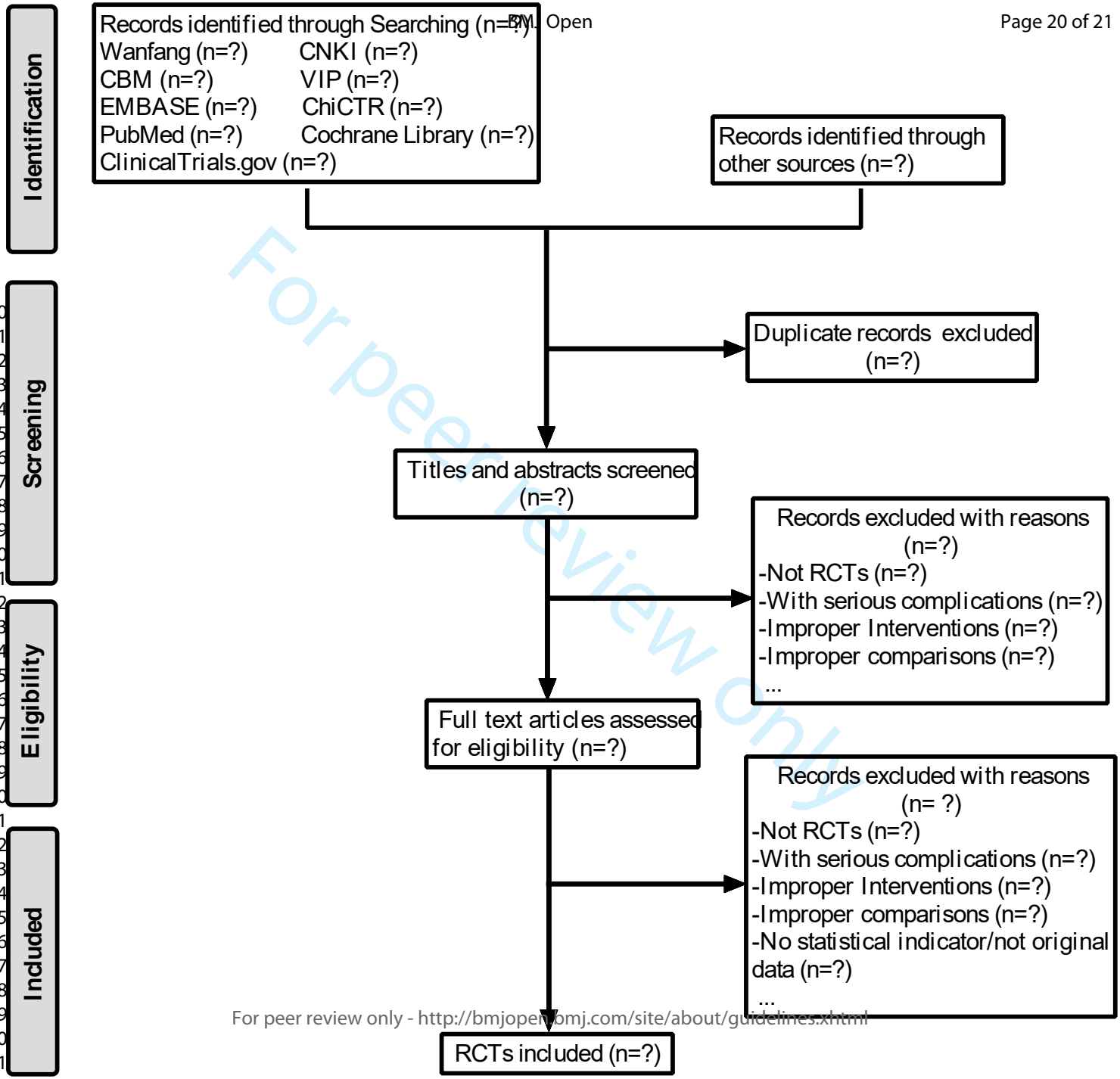

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item |
|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | |
| Title: | | |
| Identification $P_1$ | 1a | Identify the report as a protocol of a systematic review |
| Update None | 1b | If the protocol is for an update of a previous systematic review, identify as such |
| Registration $P_2$ | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number |
| Authors: | | |
| Contact $P_1$ | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author |
| Contributions $P_{11}$ | 3b | Describe contributions of protocol authors and identify the guarantor of the review |
| Amendments None | 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 |
| Support: | | |
| Sources $P_{12}$ | 5a | Indicate sources of financial or other support for the review |
| Sponsor None | 5b | Provide name for the review funder and/or sponsor |
| Role of sponsor or funder None | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol |
| **INTRODUCTION** | | |
| Rationale $P_{4-5}$ | 6 | Describe the rationale for the review in the context of what is already known |
| Objectives $P_{6-7}$ | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants $P_6$, interventions $P_7$, comparators $P_7$, and outcomes $P_7$ (PICO) |
| **METHODS** | | |
| Eligibility criteria $P_5$ | 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 |
| Information sources $P_6$, $P_7$, $P_9$ | 9 | Describe all intended information sources (such as electronic databases $P_7$, contact with study authors $P_9$, trial registers $P_6$ or other grey literature sources $P_7$) with planned dates of coverage $P_7$ |
| Search strategy $P_8$ | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated |
| Study records: | | |

| | | |
|---|---|---|
| Data management $P_9$ | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review |
| Selection process $P_{8-9}$ | 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) |
| Data collection process $P_9$ | 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 |
| Data items $P_9$ | 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 |
| Outcomes and prioritization $P_7$ | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale |
| Risk of bias in individual studies $P_9$ | 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 |
| Data synthesis $P_{9-10}$ | 15a | Describe criteria under which study data will be quantitatively synthesised $P_{9-10}$ |
| | 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 $I^2$, Kendall's $\tau$) $P_{9-10}$ |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) $P_{10}$ |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned $P_{10}$ |
| Meta-bias(es) $P_{10}$ | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) |
| Confidence in cumulative evidence $P_{10}$ | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) |

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# Effect of music intervention on mental health in patients with diabetes mellitus: a protocol for a systematic review and meta-analysis of randomized controlled trials

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# Effect of music intervention on mental health in patients with diabetes mellitus: a protocol for a systematic review and meta-analysis of randomized controlled trials

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## ABSTRACT

**Introduction** About 463 million adults aged 20 to 79 have diabetes globally and mental disorders often exist in diabetic patients as comorbidities. The comorbidities can lead to deterioration of diseases, increased difficulty in treatment, even as well as the great mortality. Music intervention has been applied in the treatment of the comorbidities for 12 years, but there are not recommendations due to lacking of evidence. Thus, a meta-analysis is necessary to be conducted to evaluate the effect of music intervention.

**Methods and analysis** We will search the following nine online electronic databases: PubMed, Web of Science, Embase, EBSCO, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journal Database (VIP) and Chinese Biomedical and Medical Database (CBM), from their inception until the present. We also plan to search other relevant resources, including grey literatures and the reference lists of relevant publications. Only randomized controlled trials (RCTs) of music intervention for depression or anxiety with diabetes will be involved. The primary outcomes include depression score and anxiety score measured by scales, and the secondary outcome is safety. Data extraction will be implemented by two researchers independently. Risk of bias will be evaluated through Cochrane Collaboration's Risk of Bias tool. Eventually, all the data will be analyzed via the software Review Manager V.5.3.

**Ethics and dissemination** This meta-analysis will provide information about music intervention applied to treat depression or anxiety in diabetic patients. There is no required ethical approval because this is a protocol for meta-analysis. The results of this study will be published to a peer reviewed journal.

**Trial registration number** CRD42019146439

**Strengths and limitations of this study**

· This meta-analysis will provide evidence of the effectiveness and safety of music intervention applied to treat depression or anxiety in diabetic patients for the first time.

· This systematic review will furnish evidence reference for guideline of relevant areas.

· This meta-analysis will be implemented on the basis of rigorous international gold-standard methodology and integrated search strategy.

· A language bias may exist in this meta-analysis because it will include studies only in English and Chinese on account of the language barrier.

## INTRODUCTION

### Description of the condition

According to the newest "IDF Diabetes Atlas (9th edition)" published by International Diabetes Federation (IDF), about 463 million adults aged 20 to 79 have diabetes globally (1 in 11).[1] It is well known that diabetes has a significant influence on life quality because it can cause a lot of complications such as retinopathy, renal disease, cardiovascular disease, neurological disease and foot ulcers which may result in lower extremity amputation.[2]

In addition to physical complications, some mental disorders often exist in diabetic patients as comorbidities. Some studies have indicated that depression is more prevalent in diabetic patients compared to those without this disease.[3,4] At the same time, depression could also increase the risk of incidence of diabetes,[5-7] which suggests that depression has a bidirectional association with diabetes. And the relation between anxiety and diabetes has been confirmed to be the same. People with diabetes are more susceptible to concurrent anxiety[8,9] while reversely anxiety is a risk factor of diabetic incidents.[10] Individuals with chronic diseases and also comorbid depression or anxiety have obviously higher health-care utilization, functional disability, work absence and mortality risk than those without them.[11,12]

### Description of the intervention

When it comes to the treatment of diabetes with depression or anxiety, conventional glucose-lowering treatment combined with drug therapy or psychological intervention are the routine treatments.[13,14] Music intervention is also a successful therapy using music for treatment by professionals, which can be divided into two major categories, namely music therapy and music medicine.[15] The official definition of music therapy is the "…clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program".[16] A trained music therapist leads the treatment process, choosing the type of music, the form of music presentation (pre-recorded or live), and the treatment setting (singing, playing instruments,

composing, etc.) based on the patient's condition, ultimately resulting in a therapeutic scheme that is best for the patient. By comparison, music medicine is defined as the passive listening to pre-recorded music, which can be implemented independently by medical or healthcare professionals instead of music therapists.[17] In brief, music therapy focuses on active music therapy and personalized treatments while music medicine belongs to passive music listening and non-personalized therapy. It is significant to emphasize the distinction between music therapy and music medicine because some literatures suggest that the effect of the former is better than the latter in a great many outcomes.[18-19]

A lot of studies have suggested that music, no matter what type of it is, demonstrates a remarkable effect in alleviating depression and anxiety among patients with various diseases.[20-22] As for diabetes, recent studies have showed that music intervention could improve fasting blood-glucose and systolic blood pressure in diabetic patients.[23,24] Good control of blood glucose, blood lipids and blood pressure can effectively reduce the incidence of serious complications of diabetes.[25]

**How the intervention might work**

Researches about music psychology have shown the special potential of music. Music, as a stimulus, can not only trigger a variety of emotional experiences,[26, 27] but also strengthen ability to deal with negative emotions in everyday life.[28] The proposed mechanisms of music intervention on depression and anxiety span several domains. Firstly, music intervention can exert neurophysiological and neurochemical effects, such as triggering endorphin release[29] and stimulating cognitive functioning.[30] Secondly, music intervention can promote positive self-emotions including enhancing the sense of happiness[31] and activating self-efficacy and self-confidence through experiences of success.[32] Lastly, music intervention can build up sociability, such as interaction skills[33] and interpersonal relationship.[34] Furthermore, there are published studies indicating that music intervention combined with diabetic routine treatments could improve depression score, anxiety score, fasting glucose and glycosylated hemoglobin (HbA1c).[35,36]

### Why it is important to do this review

From the above, many studies have indicated the bidirectional relationship between diabetes and mental disorders. Music intervention, as a therapeutic method, has been applied to alleviate depression and anxiety and improve related indicators of diabetes. By searching literatures, it can be found that some reviews evaluated the effect of music intervention on patients with mental disorders,[37-39] while no related systematic review and meta-analysis can be searched about the effect of music intervention on mental health of patients with diabetes. Therefore, if music intervention can be proved to be both valid and with few side effects through this study, it is worth being promoted and applicated in clinic all over the world to benefit more people since this method is easy to be operated.

### Objectives

The purpose of this review is to systematically assess the effect of music intervention and compare the effects between music therapy and music medicine on depression and anxiety of diabetic patients. Additionally, it is also our expectation to furnish evidence reference for related guideline.

## METHODS

### Study registration

The protocol of the meta-analysis has been registered in International Prospective Register of Systematic Reviews (PROSPERO), and CRD42019146439 is the registration ID. This protocol has been planned severely on the basis of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)[40] statement guidelines. The results will be reported in conformity to the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Healthcare Interventions.[41]

### Eligibility criteria

We will severely screen studies that have compliance with following inclusion criteria.

Type of studies

We will only cover randomized controlled trials (RCTs) in English or Chinese, excepting Quasi-RCTs and cluster RCTs. Experiments on animals and nonrandomized clinical trials will be out of our consideration. Articles with significant overlap with other articles through print or e-publishing will fail to be included. Duplicate publications, that is results originated from a single experiment but measured by other standards and then published as disparate papers, will also be excluded. Publications with originality is our first choice. The publication status will not be restricted.

Type of Participants

Diabetic Patients with depression or anxiety symptoms, regardless of the type of diabetes and no restriction on gender, age, race, economic ability and education level. Patients of other disease or healthy persons will be excluded.

Type of interventions and controls

Interventions include music intervention (music therapy or music medicine) alone or music intervention in combination with other interventions. No restriction on the type of music. Other interventions refer to: (1) routine treatments for diabetes which mainly include pharmacologic approaches to glycemic treatment, diabetes self-management education and support (DSMES),, etc. according to the newest guideline of American Diabetes Association (ADA);[42,43] (2) other therapies such as acupoint therapy,[44] metabolic surgery,[45] etc. When intervention is music intervention alone, controls can be no treatment, placebo or other active therapies. Notably, when intervention is music intervention combined with active therapies, the control must be the same active therapies.

Type of outcome measures

This review aims at systematically assessing the effect of music intervention on depression or

anxiety of diabetic patients, so we choose depression score and anxiety score as the primary outcomes, which can give an index to the degree of depression and anxiety by scales.

Primary outcomes: Depression score and anxiety score. Depression score is measured using self-rating depression scale (SDS), Hamilton depression scale (HAMD) or other validated scales for depression. Anxiety score is measured using self-rating anxiety scale (SAS), Hamilton anxiety scale (HAMA) or other validated scales for anxiety.

Secondary outcomes: Safety. Measurement via incidence of adverse effects.

**Search methods**

Search resources

We will search the following nine online electronic databases: PubMed, Web of Science, Embase, EBSCO, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journal Database (VIP) and Chinese Biomedical and Medical Database (CBM), from their inception to the present. We also plan to search other relevant resources as far as possible, including: (1) grey literatures (like conference literatures and dissertations) from the following four sources: OpenGrey (www.opengrey.eu/), CNKI (www.cnki.net), Open Access Theses and Dissertations (oatd.org) and British Library EThOS (ethos.bl.uk/); (2) the reference lists of relevant publications for additional studies.

Search strategies

The search strategy will include the MeSH terms for diabetes mellitus, depression, anxiety, music therapy, music and singing, combined with their respective free-text terms. The search details of the PubMed are simply shown in table 1.

**Table 1 Example of PubMed search strategy.**

| Number | Search terms |
|---|---|
| #1 | "Diabetes Mellitus"[Mesh] |
| #2 | "Depression"[Mesh] OR Depressions[Title/Abstract] OR Depressive Symptoms[Title/Abstract] OR Depressive Symptom[Title/Abstract] OR Symptom, Depressive[Title/Abstract] OR Symptoms, Depressive[Title/Abstract] OR Emotional Depression[Title/Abstract] OR Depression, Emotional[Title/Abstract] OR Depressions, Emotional[Title/Abstract] OR Emotional Depressions[Title/Abstract] |
| #3 | "Anxiety"[Mesh] OR Hypervigilance [Title/Abstract] OR Nervousness [Title/Abstract] |
| #4 | #2 OR #3 |
| #5 | "Music Therapy"[Mesh] OR Therapy, Music [Title/Abstract] |
| #6 | "Music"[Mesh] OR music intervention[Title/Abstract] OR music medicine[Title/Abstract] OR music listening[Title/Abstract] OR audio recording[Title/Abstract] OR mp3 hearing[Title/Abstract] |
| #7 | "Singing"[Mesh] OR sing[Title/Abstract] OR sings[Title/Abstract] OR song[Title/Abstract] OR compose[Title/Abstract] OR composing[Title/Abstract] |
| #8 | #5 OR #6 OR #7 |
| #9 | randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR placebo [Title/Abstract] |
| #10 | #1 AND #4 AND #8AND #9 |

**Data collection and analysis**

Studies selection

Firstly, two researchers (L-yZ and YT) will respectively screen the keywords, titles and abstracts of all obtained studies using endnote x9 software and determine whether trials have compliance with inclusion criteria. Secondly, we will also get access to the full text of all studies of possible relevance for further assessment. Each of excluded study will be noted with reasons. Any disagreements will be settled through consensus or referral to the third researcher (YZ). The

specific selection steps are presented in the figure 1.

Data extraction

Two researchers (L-yZ and YT) will independently extract and tabulate the following data items via Microsoft Excel:

1. General information (including publication year and name of the first author).

2. Study design (including random method, allocation concealment and blinding).

3. Participants (including sample size, gender, age, area, depression score, anxiety score and course of disease).

4. Treatment (including interventions, controls, music type and the course of treatment).

5. Outcomes (including depression score, anxiety score and safety).

If there is any different opinion, the final decision will go to the third researcher (X-xF) to be made.

Assessment of risk of bias

The Cochrane Collaboration's Risk of Bias tool[46] will be applied to evaluate the risk of bias of all included RCT studies by two authors (L-zW and YZ). The following domains will be assessed: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other sources of bias. The assessments will be classified into "low", "unclear" or "high" of risk.

Measures of treatment effect

Considering that all outcomes (depression score, anxiety score and safety) are continuous variables, the mean difference (MD) and 95% confidence interval (CI) will be calculated when the quantitative data are from the same measurement method or small data scale. On the contrary, the standardized mean difference (SMD) and 95% CI will be calculated.

Unit of analysis issues

For the standard research which has one experimental group with one control group, the unit of analysis is based on the individual. For the multi-arm study which has more than two intervention groups, the recommended method is to create a single pair-wise comparison through combining groups.

Dealing with missing data

If the required data are unavailable from literatures, one researcher (YZ) will send an e-mail to the corresponding author and ask for further information.

Assessment of heterogeneity

A meta-analysis will be implemented if the included studies are adequately homogenous. *P*-value and $I^2$ will be used to assess the heterogeneity of statistic. When *P*-value >0.05 and $I^2 \leq 50\%$, the heterogeneity is regarded as acceptable. When *P*-value <0.05 or $I^2 > 50\%$, the heterogeneity is considered as significant.

Assessment of reporting bias

Publication bias will be implemented, if there are more than 10 studies included, through a funnel plot.

Data synthesis

RevMan 5.3. software provided by the Cochrane collaboration will be used to analyze the data. If the included studies are adequately homogenous, fixed-effects model will be used for statistical combination. Since all outcomes are continuous variables, the mean difference (MD) and 95% confidence interval (CI) will be calculated when the outcomes are from the same measurement method or small data scale. On the contrary, the standardized mean difference (SMD) and 95% CI will be calculated. If there is significant heterogeneity among the included studies, subgroup

analyses or sensitivity analyses will be performed. If a meta-analysis is unavailable, descriptive summaries will be provided.

Subgroup analysis

The subgroup analyses are planned as follows:

1. Type of music intervention (music therapy or music medicine).

2. Type of scales (SDS, HAMD, SAS, HAMA or other validated scales for depression or anxiety).

3. Different age groups.

Sensitivity analysis

Sensitivity analyses will be performed through including or excluding a specific study, such as a study without a clear allocation concealment or randomization method, to observe whether the results changed.

Patient and public involvement

Patients and public involvement will fail to be included in this study.

Evidence assessed

GRADE guideline will be used to evaluate the quality of evidence.[47] To fulfil transparency and simplification, the quality of evidence can be assessed by 4 levels: “high”, “medium”, “low” and “very low”. GRADE profiler 3.2 will be applied for analysis.

## DISCUSSION

Depression and anxiety often occur independently or simultaneously during the development of many chronic diseases. In recent years, the number of studies about comorbid depression or anxiety in diabetics are continually increasing, not only because the two-way relationship between depression/anxiety and diabetes can lead to deterioration of diseases, increased difficulty in

treatment, even as well as the great mortality,[48-51] but also because therapeutic methods for treating the comorbidities are limited and unsatisfactory. On the one hand, some antidepressant drugs, such as nortriptyline and sertraline, may complicate glycemic control.[52] On the other hand, psychotherapy based on verbal communication requires a professional psychiatrist and it is expensive.

Music intervention has been proved by many literatures to have a beneficial effect on depression and anxiety, such as strengthening awareness and sensitiveness for positive emotions.[53] Noticeably, a few studies also show that music intervention can reduce blood glucose and HbA1c simultaneously.[24,54] Therefore, music intervention is an applicable method for treating depression and anxiety with diabetes. Additionally, music intervention, almost no side effects, is safer than pharmacotherapy, easier to be operated and costs less than psychotherapy based on verbal communication, so it is conducive to clinical promotion and application.

Since 2007,[55] music intervention has been applied in the treatment of depression and anxiety with diabetes for 12 years. Nonetheless, there are not systematic review or meta-analysis conducted to evaluate the potential benefits and harms of this therapy method. Thus, this study intends to provide strong evidence for music intervention applied to treat mental disorders in diabetic patients and synchronously furnish evidence reference for related guideline.

However, a language bias may exist in this meta-analysis because it will include studies only in English and Chinese because of the language barrier. Therefore, some related studies from medical databases in other languages might be missed.

In conclusion, this meta-analysis will be conducive to assess underlying benefits and harms of music intervention on comorbid depression or anxiety with diabetes. Moreover, the results of this study might not merely furnish reference basis for related guideline, but also may attract more attention on music intervention, which can be a chance to facilitate its clinical application and ultimately benefit more patients.

## ETHICS AND DISSEMINATION

There is no required ethical approval because this is a protocol for meta-analysis. The results of this study will be published to a peer reviewed journal.

**Figure legend**

**Figure 1** Flowchart to present the search process.

**Contributions** L-yZ and C-gX contributed to the conception of the study. The manuscript of the protocol was drafted by L-yZ, and was revised by XxF and C-gX. L-yZ and YT will also independently screen the potential studies and extract data from included studies. L-zW and YZ will assess the risk of bias and accomplish data synthesis. XxF will arbitrate any disagreements. C-gX will ensure that no errors occur during the review. All authors have approved the publication of the protocol.

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**Competing interests** None.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.



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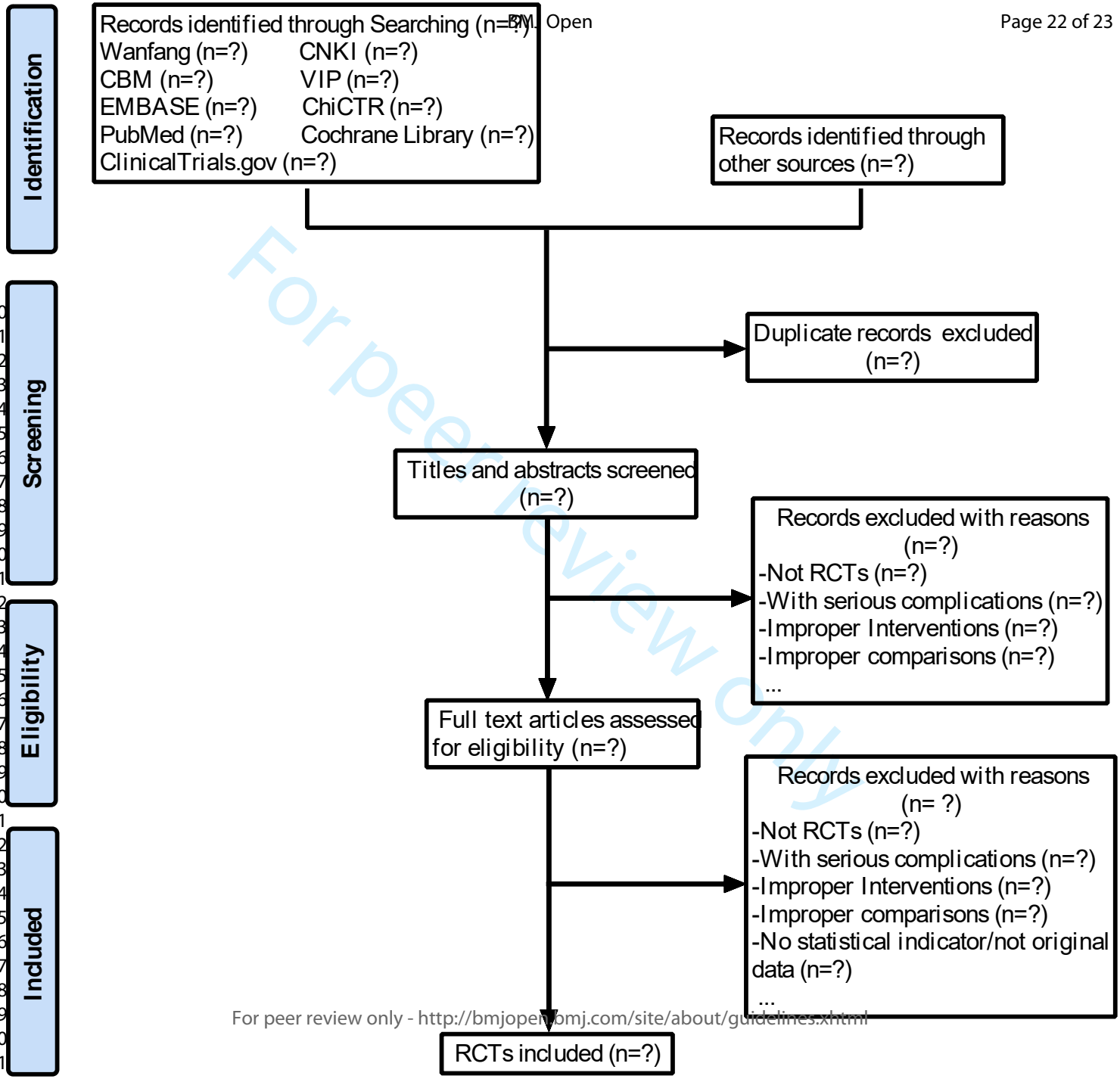

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item |
|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | |
| Title: | | |
| Identification $P_1$ | 1a | Identify the report as a protocol of a systematic review |
| Update None | 1b | If the protocol is for an update of a previous systematic review, identify as such |
| Registration $P_2$ | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number |
| Authors: | | |
| Contact $P_1$ | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author |
| Contributions $P_{14}$ | 3b | Describe contributions of protocol authors and identify the guarantor of the review |
| Amendments None | 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 |
| Support: | | |
| Sources $P_{14}$ | 5a | Indicate sources of financial or other support for the review |
| Sponsor None | 5b | Provide name for the review funder and/or sponsor |
| Role of sponsor or funder None | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol |
| **INTRODUCTION** | | |
| Rationale $P_{4-6}$ | 6 | Describe the rationale for the review in the context of what is already known |
| Objectives $P_{7-8}$ | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants $P_7$, interventions $P_7$, comparators $P_7$, and outcomes $P_{7-8}$ (PICO) |
| **METHODS** | | |
| Eligibility criteria $P_{6-7}$ | 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 |
| Information sources $P_6$, $P_8$, $P_{11}$ | 9 | Describe all intended information sources (such as electronic databases $P_8$, contact with study authors $P_{11}$, trial registers $P_6$ or other grey literature sources $P_8$) with planned dates of coverage $P_8$ |
| Search strategy $P_9$ | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated |
| Study records: | | |

| | | |
|---|---|---|
| Data management $P_{10}$ | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review |
| Selection process $P_{9-10}$ | 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) |
| Data collection process $P_{10}$ | 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 |
| Data items $P_{10}$ | 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 |
| Outcomes and prioritization $P_{7-8}$ | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale |
| Risk of bias in individual studies $P_{10}$ | 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 |
| Data synthesis $P_{10-12}$ | 15a | Describe criteria under which study data will be quantitatively synthesised $P_{11}$ |
| | 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 $I^2$, Kendall's $\tau$) $P_{10-11}$ |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) $P_{12}$ |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned $P_{12}$ |
| Meta-bias(es) $P_{11}$ | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) |
| Confidence in cumulative evidence $P_{12}$ | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

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# Effect of music intervention on mental health in patients with diabetes mellitus: a protocol for a systematic review and meta-analysis of randomized controlled trials

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# Effect of music intervention on mental health in patients with diabetes mellitus: a protocol for a systematic review and meta-analysis of randomized controlled trials

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## ABSTRACT

**Introduction** About 463 million adults aged 20 to 79 have diabetes globally and mental disorders often exist in diabetic patients as comorbidities. The comorbidities can lead to deterioration of diseases, increased difficulty in treatment, even as well as the great mortality. Music intervention has been applied in the treatment of the comorbidities for 12 years, but there are not recommendations due to lacking of evidence. Thus, a meta-analysis is necessary to be conducted to evaluate the effect of music intervention.

**Methods and analysis** We will search the following nine online electronic databases: PubMed, Web of Science, Embase, EBSCO, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journal Database (VIP) and Chinese Biomedical and Medical Database (CBM), from their inception until March 2020. We also plan to search other relevant resources, including grey literatures and the reference lists of relevant publications. Only randomized controlled trials (RCTs) of music intervention for depression or anxiety with diabetes will be involved. The primary outcomes include depression score and anxiety score measured by scales, and the secondary outcome is safety. Data extraction will be implemented by two researchers independently. Risk of bias will be evaluated through Cochrane Collaboration's Risk of Bias tool. Eventually, all the data will be analyzed via the software Review Manager V.5.3.

**Ethics and dissemination** This meta-analysis will provide information about music intervention applied to treat depression or anxiety in diabetic patients. There is no required ethical approval because this meta-analysis is on the basis of published data. The results of this systematic review will be published to a peer reviewed journal.

**Trial registration number** CRD42019146439

**Strengths and limitations of this study**

· This meta-analysis will furnish evidence of the effectiveness and safety of music intervention applied to treat depression or anxiety in diabetic patients without precedent.

· On the basis of our comprehensive search strategy, the relevant original studies will fail to be omitted.

· Two authors will implement data extraction and estimation of the risk of bias separately.

· We will only cover randomized controlled trials (RCTs) in this study.

· A language bias may exist in this meta-analysis because it will include studies only in English and Chinese on account of the language barrier.

## INTRODUCTION

### Description of the condition

According to the newest "IDF Diabetes Atlas (9th edition)" published by International Diabetes Federation (IDF), about 463 million adults aged 20 to 79 have diabetes globally (1 in 11).[1] It is well known that diabetes has a significant influence on life quality because it can cause a lot of complications such as retinopathy, renal disease, cardiovascular disease, neurological disease and foot ulcers which may result in lower extremity amputation.[2]

In addition to physical complications, some mental disorders often exist in diabetic patients as comorbidities. Some studies have indicated that depression is more prevalent in diabetic patients compared to those without this disease.[3,4] At the same time, depression could also increase the risk of incidence of diabetes,[5-7] which suggests that depression has a bidirectional association with diabetes. And the relation between anxiety and diabetes has been confirmed to be the same. People with diabetes are more susceptible to concurrent anxiety[8,9] while reversely anxiety is a risk factor of diabetic incidents.[10] Individuals with chronic diseases and also comorbid depression or anxiety have obviously higher health-care utilization, functional disability, work absence and mortality risk than those without them.[11,12]

### Description of the intervention

When it comes to the treatment of diabetes with depression or anxiety, conventional glucose-lowering treatment combined with drug therapy or psychological intervention are the routine treatments.[13,14] Music intervention is also a successful therapy using music for treatment by professionals, which can be divided into two major categories, namely music therapy and music medicine.[15] The official definition of music therapy is the "…clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program".[16] A trained music therapist leads the treatment process, choosing the type of music, the form of music presentation (pre-recorded or live), and the treatment setting (singing, playing instruments,

composing, etc.) based on the patient's condition, ultimately resulting in a therapeutic scheme that is best for the patient. By comparison, music medicine is defined as the passive listening to pre-recorded music, which can be implemented independently by medical or healthcare professionals instead of music therapists.[17] In brief, music therapy focuses on active music therapy and personalized treatments while music medicine belongs to passive music listening and non-personalized therapy. It is significant to emphasize the distinction between music therapy and music medicine because some literatures suggest that the effect of the former is better than the latter in a great many outcomes.[18-19]

A lot of studies have suggested that music, no matter what type of it is, demonstrates a remarkable effect in alleviating depression and anxiety among patients with various diseases.[20-22] As for diabetes, recent studies have showed that music intervention could improve fasting blood-glucose and systolic blood pressure in diabetic patients.[23,24] Good control of blood glucose, blood lipids and blood pressure can effectively reduce the incidence of serious complications of diabetes.[25]

**How the intervention might work**

Researches about music psychology have shown the special potential of music. Music, as a stimulus, can not only trigger a variety of emotional experiences,[26, 27] but also strengthen ability to deal with negative emotions in everyday life.[28] The proposed mechanisms of music intervention on depression and anxiety span several domains. Firstly, music intervention can exert neurophysiological and neurochemical effects, such as triggering endorphin release[29] and stimulating cognitive functioning.[30] Secondly, music intervention can promote positive self-emotions including enhancing the sense of happiness[31] and activating self-efficacy and self-confidence through experiences of success.[32] Lastly, music intervention can build up sociability, such as interaction skills[33] and interpersonal relationship.[34] Furthermore, there are published studies indicating that music intervention combined with diabetic routine treatments could improve depression score, anxiety score, fasting glucose and glycosylated hemoglobin (HbA1c).[35,36]

**Why it is important to do this review**

From the above, many studies have indicated the bidirectional relationship between diabetes and mental disorders. Music intervention, as a therapeutic method, has been applied to alleviate depression and anxiety and improve related indicators of diabetes. By searching literatures, it can be found that some reviews evaluated the effect of music intervention on patients with mental disorders,[37-39] while no related systematic review and meta-analysis can be searched about the effect of music intervention on mental health of patients with diabetes. Therefore, if music intervention can be proved to be both valid and with few side effects through this study, it is worth being promoted and applicated in clinic all over the world to benefit more people since this method is easy to be operated.

**Objectives**

The purpose of this review is to systematically assess the effect of music intervention and compare the effects between music therapy and music medicine on depression and anxiety of diabetic patients. Additionally, it is also our expectation to furnish evidence reference for related guideline.

## METHODS

**Study registration**

Our protocol for the meta-analysis has been registered on the International Prospective Register of Systematic Reviews (PROSPERO), and CRD42019146439 is the registration ID. This protocol has been planned severely on the basis of Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)[40] statement guidelines. The results will be reported in conformity to the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Healthcare Interventions.[41]

**Eligibility criteria**

Studies that have compliance with the following inclusion criteria will be rigorously screened.

Type of studies

We will merely cover randomized controlled trials (RCTs) in English or Chinese, excepting Quasi-RCTs and cluster RCTs. Experiments on animals and nonrandomized clinical trials will be out of our consideration. Articles with significant overlap with other articles through print or e-publishing will fail to be included. Duplicate publications, that is results originated from a single experiment but measured by other standards and then published as disparate papers, will also be excluded. Publications with originality is our first choice. The publication status will not be restricted.

Type of Participants

Diabetic Patients with depression or anxiety symptoms, regardless of the type of diabetes and no restriction on gender, age, race, economic ability and education level. Patients of other disease or healthy persons will be excluded.

Type of interventions and controls

Interventions include music intervention (music therapy or music medicine) alone or music intervention in combination with other interventions. No restriction on the type of music. Other interventions refer to: (1) routine treatments for diabetes which mainly include pharmacologic approaches to glycemic treatment, diabetes self-management education and support (DSMES), etc. according to the newest guideline of American Diabetes Association (ADA);[42,43] (2) other therapies such as acupoint therapy,[44] metabolic surgery,[45] etc. When intervention is music intervention alone, controls can be no treatment, placebo or other active therapies. Notably, when intervention is music intervention combined with active therapies, the control must be the same active therapies.

Type of outcome measures

This review aims at systematically assessing the effect of music intervention on depression or

anxiety of diabetic patients, so we choose depression score and anxiety score as the primary outcomes, which can give an index to the degree of depression and anxiety by scales.

Primary outcomes: Depression score and anxiety score. Depression score is measured using self-rating depression scale (SDS), Hamilton depression scale (HAMD) or other validated scales for depression. Anxiety score is measured using self-rating anxiety scale (SAS), Hamilton anxiety scale (HAMA) or other validated scales for anxiety.

Secondary outcomes: Safety. Measurement via incidence of adverse effects.

**Search methods**

Search resources

We will search the following nine online electronic databases: PubMed, Web of Science, Embase, EBSCO, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journal Database (VIP) and Chinese Biomedical and Medical Database (CBM), from their inception to March 2020. We also plan to search other relevant resources as far as possible, including: (1) grey literatures (like conference literatures and dissertations) from the following four sources: OpenGrey (www.opengrey.eu/), CNKI (www.cnki.net), Open Access Theses and Dissertations (oatd.org) and British Library EThOS (ethos.bl.uk/); (2) the reference lists of relevant publications for additional studies.

Search strategies

The search strategy will include the MeSH terms for diabetes mellitus, depression, anxiety, music therapy, music and singing, combined with their respective free-text terms. The search details of the PubMed are simply shown in table 1.

**Table 1 Example of PubMed search strategy.**

| Number | Search terms |
|---|---|
| #1 | "Diabetes Mellitus"[Mesh] |
| #2 | "Depression"[Mesh] OR Depressions[Title/Abstract] OR Depressive Symptoms[Title/Abstract] OR Depressive Symptom[Title/Abstract] OR Symptom, Depressive[Title/Abstract] OR Symptoms, Depressive[Title/Abstract] OR Emotional Depression[Title/Abstract] OR Depression, Emotional[Title/Abstract] OR Depressions, Emotional[Title/Abstract] OR Emotional Depressions[Title/Abstract] |
| #3 | "Anxiety"[Mesh] OR Hypervigilance [Title/Abstract] OR Nervousness [Title/Abstract] |
| #4 | #2 OR #3 |
| #5 | "Music Therapy"[Mesh] OR Therapy, Music [Title/Abstract] |
| #6 | "Music"[Mesh] OR music intervention[Title/Abstract] OR music medicine[Title/Abstract] OR music listening[Title/Abstract] OR audio recording[Title/Abstract] OR mp3 hearing[Title/Abstract] |
| #7 | "Singing"[Mesh] OR sing[Title/Abstract] OR sings[Title/Abstract] OR song[Title/Abstract] OR compose[Title/Abstract] OR composing[Title/Abstract] |
| #8 | #5 OR #6 OR #7 |
| #9 | randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR placebo [Title/Abstract] |
| #10 | #1 AND #4 AND #8AND #9 |

**Data collection and analysis**

Studies selection

Firstly, two researchers (L-yZ and YT) will respectively screen the keywords, titles and abstracts of all obtained studies using endnote x9 software and determine whether trials have compliance with inclusion criteria. Secondly, we will also get access to the full text of all studies of possible relevance for further assessment. Each of excluded study will be noted with reasons. Any disagreements will be settled through consensus or referral to the third researcher (XxF). The

specific selection steps are presented in the figure 1.

Data extraction

Two researchers (L-yZ and YT) will independently extract and tabulate the following data items via Microsoft Excel:

1. General information (including publication year and name of the first author).

2. Study design (including random method, allocation concealment and blinding).

3. Participants (including sample size, gender, age, area, depression score, anxiety score and course of disease).

4. Treatment (including interventions, controls, music type and the course of treatment).

5. Outcomes (including depression score, anxiety score and safety).

If there is any different opinion, the final decision will go to the third researcher (XxF) to be made.

Assessment of risk of bias

The Cochrane Collaboration's Risk of Bias tool[46] will be applied to evaluate the risk of bias of all included RCT studies by two authors (L-zW and YZ). The following domains will be assessed: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting and other sources of bias. The assessments will be classified into "low", "unclear" or "high" of risk.

Measures of treatment effect

Considering that all outcomes (depression score, anxiety score and safety) are continuous variables, the mean difference (MD) and 95% confidence interval (CI) will be calculated when the quantitative data are from the same measurement method or small data scale. On the contrary, the standardized mean difference (SMD) and 95% CI will be calculated.

Unit of analysis issues

For the standard research which has one experimental group with one control group, the unit of analysis is based on the individual. For the multi-arm study which has more than two intervention groups, the recommended method is to create a single pair-wise comparison through combining groups.

Dealing with missing data

If the required data are unavailable from literatures, one researcher (YZ) will send an e-mail to the corresponding author and ask for further information.

Assessment of heterogeneity

A meta-analysis will be implemented if the included studies are adequately homogenous. *P*-value and $I^2$ will be used to assess the heterogeneity of statistic. When *P*-value >0.05 and $I^2 \leq 50\%$, the heterogeneity is regarded as acceptable. When *P*-value <0.05 or $I^2 > 50\%$, the heterogeneity is considered as significant.

Assessment of reporting bias

Publication bias will be implemented, if there are more than 10 studies included, through a funnel plot.

Data synthesis

RevMan 5.3. software provided by the Cochrane collaboration will be used to analyze the data. If the included studies are adequately homogenous, fixed-effects model will be used for statistical combination. Since all outcomes are continuous variables, the mean difference (MD) and 95% confidence interval (CI) will be calculated when the outcomes are from the same measurement method or small data scale. On the contrary, the standardized mean difference (SMD) and 95% CI will be calculated. If there is significant heterogeneity among the included studies, subgroup

analyses or sensitivity analyses will be performed. If a meta-analysis is unavailable, descriptive summaries will be provided.

Subgroup analysis

The subgroup analyses are planned as follows:

1. Type of music intervention (music therapy or music medicine).

2. Type of scales (SDS, HAMD, SAS, HAMA or other validated scales for depression or anxiety).

3. Different age groups.

Sensitivity analysis

Sensitivity analyses will be performed through including or excluding a specific study, such as a study without a clear allocation concealment or randomization method, to observe whether the results changed.

Evidence assessed

GRADE guideline will be used to evaluate the quality of evidence.[47] In the light of the GRADE method, the quality of evidence can be assessed by 4 levels: “high”, “medium”, “low” and “very low”. GRADE profiler 3.2 will be applied for analysis.

Patient and public involvement

Since this study is a systematic review, patients or the public will fail to participate.

## DISCUSSION

Depression and anxiety often occur independently or simultaneously during the development of many chronic diseases. In recent years, the number of studies about comorbid depression or anxiety in diabetics are continually increasing, not only because the two-way relationship between depression/anxiety and diabetes can lead to deterioration of diseases, increased difficulty in

treatment, even as well as the great mortality,[48-51] but also because therapeutic methods for treating the comorbidities are limited and unsatisfactory. On the one hand, some antidepressant drugs, such as nortriptyline and sertraline, may complicate glycemic control.[52] On the other hand, psychotherapy based on verbal communication requires a professional psychiatrist and it is expensive.

Music intervention has been proved by many literatures to have a beneficial effect on depression and anxiety, such as strengthening awareness and sensitiveness for positive emotions.[53] Noticeably, a few studies also show that music intervention can reduce blood glucose and HbA1c simultaneously.[24,54] Therefore, music intervention is an applicable method for treating depression and anxiety with diabetes. Additionally, music intervention, almost no side effects, is safer than pharmacotherapy, easier to be operated and costs less than psychotherapy based on verbal communication, so it is conducive to clinical promotion and application.

Since 2007,[55] music intervention has been applied in the treatment of depression and anxiety with diabetes for 12 years. Nonetheless, there are not systematic review or meta-analysis conducted to evaluate the potential pros and cons of this therapy method. Thus, this study intends to provide strong evidence for music intervention applied to treat mental disorders in diabetic patients and synchronously furnish evidence reference for related guideline.

However, a language bias may exist in this meta-analysis because it will include studies only in English and Chinese because of the language barrier. Therefore, some related studies from medical databases in other languages might be missed.

In conclusion, this meta-analysis will be conducive to assess underlying benefits and harms of music intervention on comorbid depression or anxiety with diabetes. Moreover, the results of this study might not merely furnish evidence reference for guideline of relevant areas, but also may attract more attention on music intervention, which can be a chance to facilitate its clinical application and ultimately benefit more patients.

## ETHICS AND DISSEMINATION

There is no required ethical approval because this meta-analysis is on the basis of published data. The results of this systematic review will be published to a peer reviewed journal.

**Figure legend**

**Figure 1** Flowchart to present the search process.

**Contributions** L-yZ and C-gX contributed to the conception of the study. The manuscript of the protocol was drafted by L-yZ, and was revised by XxF and C-gX. L-yZ and YT will also independently screen the potential studies and extract data from included studies. L-zW and YZ will assess the risk of bias and accomplish data synthesis. XxF will arbitrate any disagreements. C-gX will ensure that no errors occur during the review. All authors have approved the publication of the protocol.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.



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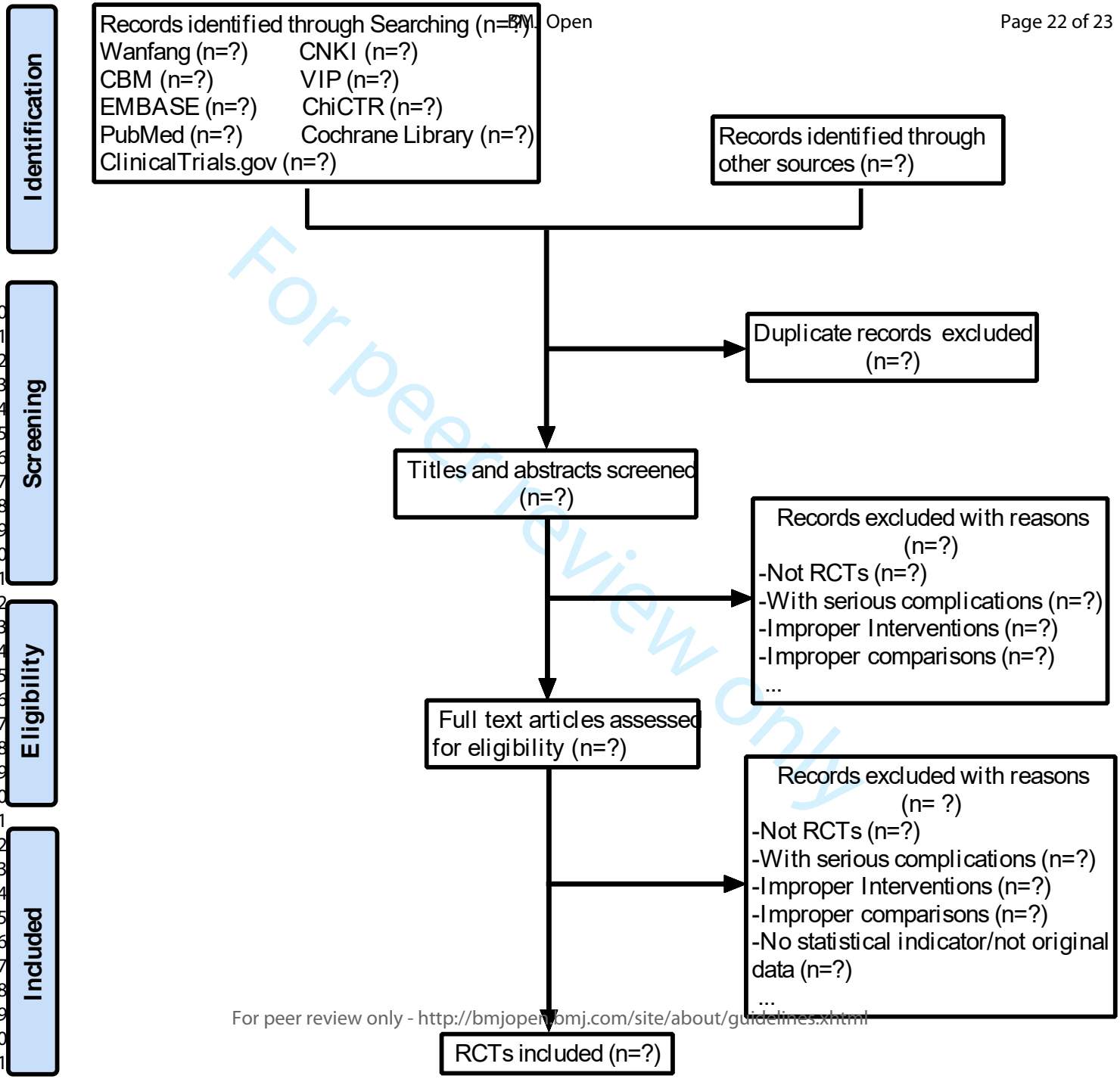

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item |
|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | |
| Title: | | |
| Identification $P_1$ | 1a | Identify the report as a protocol of a systematic review |
| Update None | 1b | If the protocol is for an update of a previous systematic review, identify as such |
| Registration $P_2$ | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number |
| Authors: | | |
| Contact $P_1$ | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author |
| Contributions $P_{14}$ | 3b | Describe contributions of protocol authors and identify the guarantor of the review |
| Amendments None | 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 |
| Support: | | |
| Sources $P_{14}$ | 5a | Indicate sources of financial or other support for the review |
| Sponsor None | 5b | Provide name for the review funder and/or sponsor |
| Role of sponsor or funder None | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol |
| **INTRODUCTION** | | |
| Rationale $P_{4-6}$ | 6 | Describe the rationale for the review in the context of what is already known |
| Objectives $P_{7-8}$ | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants $P_7$, interventions $P_7$, comparators $P_7$, and outcomes $P_{7-8}$ (PICO) |
| **METHODS** | | |
| Eligibility criteria $P_{6-7}$ | 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 |
| Information sources $P_6$, $P_8$, $P_{11}$ | 9 | Describe all intended information sources (such as electronic databases $P_8$, contact with study authors $P_{11}$, trial registers $P_6$ or other grey literature sources $P_8$) with planned dates of coverage $P_8$ |
| Search strategy $P_9$ | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated |
| Study records: | | |

| | | |
|---|---|---|
| Data management $P_{10}$ | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review |
| Selection process $P_{9-10}$ | 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) |
| Data collection process $P_{10}$ | 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 |
| Data items $P_{10}$ | 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 |
| Outcomes and prioritization $P_{7-8}$ | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale |
| Risk of bias in individual studies $P_{10}$ | 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 |
| Data synthesis $P_{10-12}$ | 15a | Describe criteria under which study data will be quantitatively synthesised $P_{11}$ |
| | 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 $I^2$, Kendall's $\tau$) $P_{10-11}$ |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) $P_{12}$ |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned $P_{12}$ |
| Meta-bias(es) $P_{11}$ | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) |
| Confidence in cumulative evidence $P_{12}$ | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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BMJ Open

# Effect of music intervention on mental health in patients with diabetes mellitus: protocol for a systematic review and meta-analysis of randomized controlled trials

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# Effect of music intervention on mental health in patients with diabetes mellitus: protocol for a systematic review and meta-analysis of randomized controlled trials

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## ABSTRACT

**Introduction** About 463 million adults aged 20 to 79 have diabetes globally. Mental disorders often exist in diabetic patients as comorbidities, which can lead to aggravation of the diseases, increased difficulties in treatment, as well as elevated mortality rates. Music intervention has been applied in the treatment of comorbidities for 12 years now, but there are still no recommendations due to the lack of evidence. Thus, a meta-analysis is necessary to evaluate the effect of music intervention in treating mental disorders of diabetic patients.

**Methods and analysis** We will search the following nine online electronic databases from their inception until March 2020: PubMed, Web of Science, Embase, EBSCO, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journal Database (VIP) and Chinese Biomedical and Medical Database (CBM). We also plan to search other relevant resources, including grey literature and the reference lists of relevant publications. Only randomized controlled trials (RCTs) of music intervention to treat depression or anxiety in diabetic patients will be involved. The primary outcomes include the depression score and anxiety score measured on certain scales, and the secondary outcome is safety. Data extraction will be independently implemented by two researchers. The risk of bias will be evaluated through the Cochrane Collaboration's Risk of Bias tool. Eventually, all the data will be analyzed via the Review Manager 5.3 software.

**Ethics and dissemination** This meta-analysis will provide information about applying music intervention to treat depression or anxiety in diabetic patients. No ethical approval is required because this meta-analysis is based on published data. The results of this systematic review will be published in a peer-reviewed journal.

**PROSPERO registration number** CRD42019146439

**Strengths and limitations of this study**

· This meta-analysis will be the first to provide evidence on the effectiveness and safety of applying music intervention to treat depression or anxiety in diabetic patients.

· Based on our comprehensive search strategy, the relevant original studies will be included.

· Two authors will separately implement data extraction and estimation of the risk of bias.

· We will only cover randomized controlled trials (RCTs) in this study.

· A language bias may exist in this meta-analysis because it will include only the studies in English and Chinese due to the language barrier.

## INTRODUCTION

According to the newest "IDF Diabetes Atlas (9th edition)" published by the International Diabetes Federation (IDF), about 463 million adults aged 20 to 79 have diabetes mellitus globally (1 in 11).[1] Diabetes has a well-known significant influence on the patient's quality of life (QoL) due to its complications, such as retinopathy, cardiovascular, neurological or renal diseases, as well as foot ulcers, which may result in the amputation of lower extremity.[2]

In addition to the physical complications, diabetic patients may also develop mental disorders as comorbidities. Some studies have indicated that depression is more prevalent in diabetic patients compared with non-diabetics.[3,4] Meanwhile, depression could also increase the risk of diabetes,[5-7] which suggests a bidirectional diabetes-depression relation; a similar relation has been confirmed between anxiety and diabetes: people with diabetes are more susceptible to concurrent anxiety[8,9] while anxiety is a risk factor of diabetes.[10] Individuals with chronic diseases who have comorbid depression or anxiety have obviously higher healthcare utilization, functional disability, work absence, and mortality risk than healthy ones.[11,12]

When it comes to the treatment of diabetes with comorbid depression or anxiety, conventional glucose-lowering treatments combined with antidepressants, anti-anxiety medications, or psychological intervention are the routine treatments.[13,14] Music intervention is also a successful therapy, which can be divided into two major categories: music therapy and music medicine.[15] The official definition of music therapy is the "clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program".[16] Based on the patient's condition, a trained music therapist conducts the treatment by choosing the type of music, the form of music presentation (pre-recorded or live), and the treatment setting (singing, playing instruments, composing, etc.), ultimately resulting in a therapeutic scheme that is best suited for the patient. On the other hand, music medicine is defined as passive listening to pre-recorded music, which can be independently implemented by medical or healthcare professionals instead of music therapists.[17] In brief, music therapy focuses on active music therapy and

personalized treatments, while music medicine belongs to passive music listening and non-personalized therapy. It is important to emphasize the distinction between music therapy and music medicine because some studies suggest that the effect of the former is better than the latter with regard to many outcomes.[18-19]

A lot of studies suggested that music, with all its types, demonstrates a remarkable effect in alleviating depression and anxiety among patients with various diseases.[20-22] As for diabetes, recent studies have shown that music intervention could improve fasting blood glucose and systolic blood pressure in diabetic patients.[23,24] Good control of blood glucose and blood pressure can effectively reduce the incidence of serious complications of diabetes.[25]

Previous research on music psychology showed the special potential of music. As a stimulus, music can not only trigger a variety of emotional experiences,[26, 27] but it can also strengthen the ability to deal with negative emotions in everyday life.[28] The proposed mechanisms behind the effects of music intervention on depression and anxiety span across several domains. Firstly, music intervention can exert neurophysiological and neurochemical effects, such as triggering the release of endorphin[29] and stimulating cognitive functioning.[30] Secondly, music intervention can promote positive self-conscious emotions including enhancing the sense of happiness[31] and activating self-efficacy and self-confidence through experiencing success.[32] Lastly, music intervention can enhance the sociable aspects, such as interaction skills[33] and interpersonal relationships.[34] Furthermore, many published studies indicated that music intervention combined with the diabetic routine treatments could improve the depression score, anxiety score, and the values of fasting glucose and glycosylated hemoglobin (HbA1c).[35,36]

By searching the literature, it can be found that some reviews evaluated the effect of music intervention on the patients with mental disorders,[37-39] while no related systematic reviews or meta-analyses can be found about the effect of music intervention on the mental health of diabetic patients. Therefore, a review that can show music intervention to be both valid and with few side effects would be useful to indicate that this intervention is worth being promoted and clinically applied to benefit more people with this easy-operated method.

## OBJECTIVE

In this review, we present a meta-analysis to systematically assess the effect of music intervention and compare the effects of music therapy and those of music medicine on depression and anxiety of diabetic patients. Additionally, it serves to establish an evidence reference for related guidelines.

## METHODS AND ANALYSIS

### Study registration

Our protocol for the meta-analysis has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration ID of CRD42019146439. This protocol has been strictly planned based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P)[40] statement guidelines. The results will be reported in accordance with the PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Healthcare Interventions.[41]

### Eligibility criteria

Type of studies

This analysis will merely cover the randomized controlled trials (RCTs) in English or Chinese, except for Quasi-RCTs and cluster RCTs. The experiments on animals and nonrandomized clinical trials will not be considered. The articles with a significant overlap with other articles through printing or e-publishing will not be included. Duplicate publications, in which the results originated from a single experiment but were measured by other standards and then published as disparate papers, will also be excluded. The main choice is original publications, regardless of the publication status.

Type of participants

Diabetic patients with depression or anxiety symptoms, regardless of the type of diabetes, gender, age, race, economic ability, and education level. Patients with other diseases or healthy persons will be excluded.

Type of interventions and controls

The interventions include music intervention (music therapy or music medicine, no restriction on the type of music) alone or combined with other interventions that refer to the following therapies: (1) routine treatments for diabetes, which mainly include pharmacologic approaches to glycemic treatment, diabetes self-management education and support (DSMES), and others, according to the newest guideline of the American Diabetes Association (ADA);[42,43] (2) other therapies such as acupoint therapy,[44] metabolic surgery,[45] etc. When the used intervention is the music intervention alone, the controls can be people with no treatment, placebo, or other active therapies, while the same therapies should be used with the controls when the music intervention is used combined with active therapies.

Type of outcome measures

Since this review aims at the systematic assessment of the effect of music intervention on depression or anxiety in diabetic patients, we will choose the depression and anxiety scores as the primary outcomes, which can indicate the degree of depression and anxiety on certain scales.

The depression score is measured using the self-rating depression scale (SDS), Hamilton depression scale (HAMD), or other validated scales for depression. The anxiety score is measured using the self-rating anxiety scale (SAS), Hamilton anxiety scale (HAMA), or other validated scales for anxiety.

The secondary outcome is the safety, measured via the incidence of adverse effects.

**Search methods**

Search resources

The following nine online electronic databases will be searched from their inception to March 2020: PubMed, Web of Science, Embase, EBSCO, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, Chinese Scientific Journal Database (VIP) and Chinese Biomedical and Medical Database (CBM). We also plan to search other relevant resources as far as possible, including: (1) grey literature (like conference literature and dissertations) from the following four sources: OpenGrey (www.opengrey.eu/), CNKI (www.cnki.net), Open Access Theses and Dissertations (oatd.org), and the British Library EThOS (ethos.bl.uk/); (2) the reference lists of relevant publications for additional studies.

Search strategies

The search strategy will include the MeSH terms of diabetes mellitus, depression, anxiety, music therapy, music and singing, combined with their respective free-text terms. The search details of PubMed are simplified in table 1.

**Table 1** Example of PubMed search strategy

| Number | Search terms |
|---|---|
| #1 | "Diabetes Mellitus"[Mesh] |
| #2 | "Depression"[Mesh] OR Depressions[Title/Abstract] OR Depressive Symptoms[Title/Abstract] OR Depressive Symptom[Title/Abstract] OR Symptom, Depressive[Title/Abstract] OR Symptoms, Depressive[Title/Abstract] OR Emotional Depression[Title/Abstract] OR Depression, Emotional[Title/Abstract] OR Depressions, Emotional[Title/Abstract] OR Emotional Depressions[Title/Abstract] |
| #3 | "Anxiety"[Mesh] OR Hypervigilance [Title/Abstract] OR Nervousness [Title/Abstract] |
| #4 | #2 OR #3 |
| #5 | "Music Therapy"[Mesh] OR Therapy, Music [Title/Abstract] |
| #6 | "Music"[Mesh] OR music intervention[Title/Abstract] OR music medicine[Title/Abstract] OR music listening[Title/Abstract] OR audio recording[Title/Abstract] OR mp3 hearing[Title/Abstract] |
| #7 | "Singing"[Mesh] OR sing[Title/Abstract] OR sings[Title/Abstract] OR song[Title/Abstract] OR compose[Title/Abstract] OR composing[Title/Abstract] |
| #8 | #5 OR #6 OR #7 |
| #9 | randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR placebo [Title/Abstract] |
| #10 | #1 AND #4 AND #8AND #9 |

**Data collection and analysis**

Studies selection

First, two researchers (L-yZ and YT) will respectively screen the keywords, titles, and abstracts of all the obtained studies using the EndNote X9 software and determine whether the trials comply with the inclusion criteria. Then, we will also get access to the full text of all the studies with possible relevance for further assessment. Each of the excluded studies will be noted with the exclusion reasons. Any disagreements will be settled through consensus or referral to a third researcher (XxF). The specific selection steps are presented in figure 1.

Data extraction

Two researchers (L-yZ and YT) will independently extract and tabulate the following data items using the Microsoft Excel software:

1. General information (including the publication year and name of the first author).

2. Study design (including the random method, allocation concealment, and blinding).

3. Participants (including the sample size, gender, age, area, depression score, anxiety score, and course of disease).

4. Treatment (including the interventions, controls, music type, and the course of treatment).

5. Outcomes (including the depression score, anxiety score, and safety).

In the case of different opinions, the final decision will be made by the third researcher (XxF).

Assessment of risk of bias

In order to evaluate the risk of bias of all the included RCT studies, the Cochrane Collaboration's Risk of Bias tool[46] will be applied by two authors (L-zW and YZ). The assessed domains will be the following: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. The assessments will be classified into "low", "unclear" or "high" risk.

Measures of treatment effect

Considering that all the outcomes (depression score, anxiety score, and safety) are continuous variables, when the quantitative data are from the same measurement method or a small data scale, the mean difference (MD) and 95% confidence interval (CI) will be calculated. Otherwise, the standardized mean difference (SMD) and 95% CI will be calculated.

Unit of analysis issues

For the standard research that has one experimental group with one control group, the unit of

analysis is the individual. For the multi-arm study with more than two intervention groups, the recommended method is to create a single pair-wise comparison by combining the groups.

Dealing with missing data

If the required data are unavailable from the literature, one researcher (YZ) will contact the corresponding author via email and ask for further information.

Assessment of heterogeneity

A meta-analysis will be implemented if the included studies are adequately homogenous. The p value and $I^2$ are used to assess the heterogeneity of the statistics. The heterogeneity is considered to be acceptable when p value > 0.05 and $I^2 \leq 50\%$ and significant when p value < 0.05 or $I^2 > 50\%$.

Assessment of reporting bias

The publication bias will be implemented if more than 10 studies are included through a funnel plot.

Data synthesis

The Review Manager 5.3 software, provided by the Cochrane collaboration, will be used to analyze the data. If the included studies are adequately homogenous, then a fixed-effects model will be used for the statistical combination. Since all the outcomes are continuous variables in this meta-analysis, we will calculate the mean difference (MD) and 95% confidence interval (CI) when the outcomes are from the same measurement method or a small data scale. Otherwise, we will calculate the standardized mean difference (SMD) and 95% CI. If there is significant heterogeneity among the included studies, subgroup or sensitivity analyses will be performed. If a meta-analysis is unavailable, descriptive summaries will be provided.

Subgroup analysis

The subgroup analyses are planned as follows:

1. The type of music intervention (music therapy or music medicine).

2. The type of scales (SDS, HAMD, SAS, HAMA, or other validated depression or anxiety scales).

3. The different age groups.

Sensitivity analysis

The sensitivity analyses will be performed by including or excluding a specific study, such as a study without clear allocation concealment or a randomization method, to observe whether the results change.

Evaluating the evidence

The GRADE guideline will be used to evaluate the quality of evidence.[47] Based on the GRADE method, the quality of evidence can be assessed by 4 levels: “high”, “medium”, “low” and “very low”. The GRADE profiler 3.2 software will be applied for the analysis.

Patient and public involvement

No patients or volunteers from the public will be involved in this study.

## DISCUSSION

Depression and anxiety often occur independently or simultaneously during the development of many chronic diseases. In recent years, an increasing number of studies have been investigating the comorbid depression or anxiety in diabetics. This increased interest is not only because the bidirectional relationship between depression/anxiety and diabetes can lead to deterioration of the diseases, increased difficulties in treatment, as well as elevated mortality rates,[48-51] but also because the therapeutic methods for treating the comorbidities are limited and unsatisfactory. On

the one hand, some antidepressant drugs, such as nortriptyline and sertraline, may complicate the glycemic control.[52] On the other hand, psychotherapy that is based on verbal communication requires a professional psychiatrist and is expensive.

Music intervention has been proved by many studies to have a beneficial effect on depression and anxiety, as it strengthens the awareness and sensitiveness for positive emotions.[53] Noticeably, a few studies also showed that music intervention can simultaneously reduce blood glucose and HbA1c levels.[24,54] Therefore, music intervention is an applicable method to treat depression and anxiety in diabetic patients. Additionally, this almost side-effect-free intervention is safer than pharmacotherapy, easier to be operated and costs less than psychotherapy based on verbal communication; thus, it is conducive to clinical promotion and application.

Although music intervention has been applied in the treatment of depression and anxiety with diabetes for 12 years now,[55] there is still no systematic review or meta-analysis to evaluate the potential pros and cons of this therapeutic method. Thus, this study intends to provide strong evidence on the benefits of applying music intervention to treat mental disorders in diabetic patients and synchronously provide evidence to which related guidelines can refer.

However, a language bias may exist in this meta-analysis because it includes only the studies in English and Chinese due to the language barrier. Therefore, some related studies from the medical databases in other languages might be missed.

In conclusion, this meta-analysis will help to assess the underlying benefits and harms of music intervention on comorbid depression or anxiety in diabetic patients. Moreover, the results of this study will represent a reference for the guidelines of relevant areas, attracting more attention to the music intervention, and facilitating its clinical application to benefit more patients.

## ETHICS AND DISSEMINATION

Since this meta-analysis used published data, no ethical approval was required. The results of this systematic review will be published in a peer-reviewed journal.

**Figure legend**

**Figure 1** Flowchart to present the search process.

**Contributions** L-yZ and C-gX contributed to the conception of the study. The manuscript of the protocol was drafted by L-yZ and revised by XxF and C-gX. L-yZ and YT will independently screen the potential studies and extract the data from the included studies. L-zW and YZ will assess the risk of bias and accomplish data synthesis. XxF will arbitrate any disagreements. C-gX will ensure that no errors occur during the review. All the authors approved the publication of the protocol.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.



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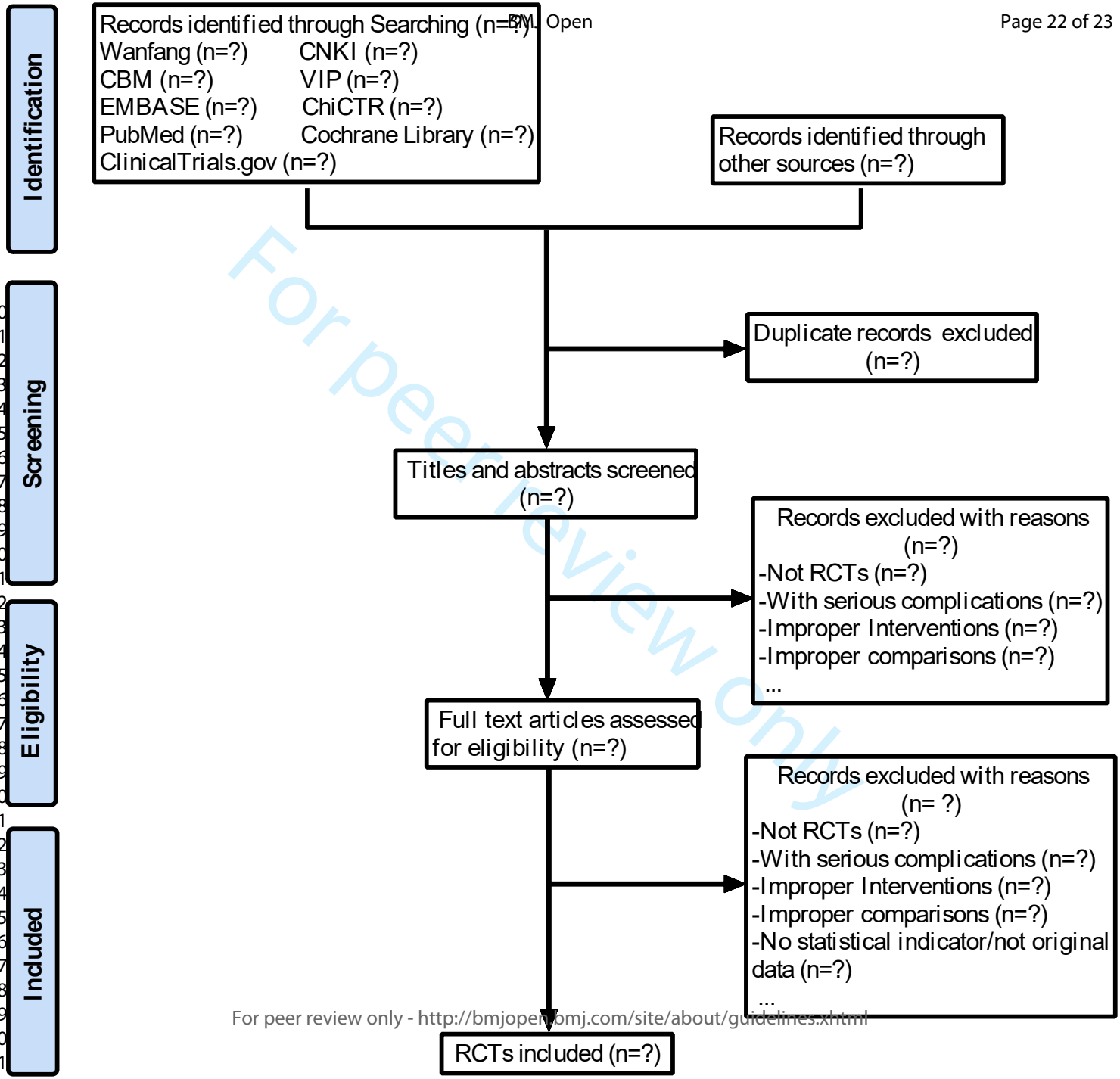

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item |
|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | |
| Title: | | |
| Identification $P_1$ | 1a | Identify the report as a protocol of a systematic review |
| Update None | 1b | If the protocol is for an update of a previous systematic review, identify as such |
| Registration $P_2$ | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number |
| Authors: | | |
| Contact $P_1$ | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author |
| Contributions $P_{14}$ | 3b | Describe contributions of protocol authors and identify the guarantor of the review |
| Amendments None | 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 |
| Support: | | |
| Sources $P_{14}$ | 5a | Indicate sources of financial or other support for the review |
| Sponsor None | 5b | Provide name for the review funder and/or sponsor |
| Role of sponsor or funder None | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol |
| **INTRODUCTION** | | |
| Rationale $P_{4-5}$ | 6 | Describe the rationale for the review in the context of what is already known |
| Objectives $P_{6-7}$ | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants $P_{6-7}$, interventions $P_7$, comparators $P_7$, and outcomes $P_7$ (PICO) |
| **METHODS** | | |
| Eligibility criteria $P_{6-7}$ | 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 |
| Information sources $P_{6-8}$, $P_{11}$ | 9 | Describe all intended information sources (such as electronic databases $P_{7-8}$, contact with study authors $P_{11}$, trial registers $P_6$ or other grey literature sources $P_8$) with planned dates of coverage $P_8$ |
| Search strategy $P_9$ | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated |

| | | |
|---|---|---|
| Study records: | | |
| Data management $P_{10}$ | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review |
| Selection process $P_{9}$ | 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) |
| Data collection process $P_{10}$ | 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 |
| Data items $P_{10}$ | 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 |
| Outcomes and prioritization $P_{7}$ | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale |
| Risk of bias in individual studies $P_{10}$ | 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 |
| Data synthesis $P_{10-12}$ | 15a | Describe criteria under which study data will be quantitatively synthesised $P_{10-11}$ |
| | 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 $I^2$, Kendall's $\tau$) $P_{11}$ |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) $P_{12}$ |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned $P_{11}$ |
| Meta-bias(es) $P_{11}$ | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) |
| Confidence in cumulative evidence $P_{12}$ | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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