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Effects of Music Intervention on Inflammatory Markers in Critically Ill and Post-Operative Patients: A Systematic Review of the Literature

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Abstract

Background—Music listening has been shown to reduce anxiety, stress, and patient tolerance of procedures. Music may also have beneficial effects on inflammatory biomarkers in intensive care and post-operative patients, but the quality of evidence is not clear.

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Conflicts of Interest

None declared

Author Contributions

SK: data analysis, manuscript writing, study design; MK: data analysis, manuscript revision; DG: manuscript revision; SW: manuscript revision; LC: manuscript revision and technical insight; MB: manuscript revision and critical analysis; BK: study design, manuscript revision and critical analysis.

Objectives—We conducted a systematic review to evaluate the effects of music on inflammatory biomarkers in intensive care, and post-operative patients.

Methods—A comprehensive search of the literature was performed. After screening 1570 references, full text review of 26 studies was performed. Fourteen studies were selected for inclusion.

Results—Seven studies showed a significant decrease in cortisol levels, but the level of evidence was low. Three studies had low risk of methodological bias, while 11 studies had high risk of bias.

Conclusions—Music intervention may decrease cortisol levels, but other biomarkers remain unchanged. Given the low level of evidence, further research on music effects on inflammatory biomarkers is needed.

Keywords

Music; stress; delirium; cortisol; biomarkers; brain dysfunction

Introduction

As long ago as the Greek world, music was thought to play an important role in the healing art of medicine, with its rhythm producing psychological effects and augmenting a patient's energy. Over the centuries, with great advances in medical care, a re-evaluation of the role of music has become necessary as clinicians and researchers search for new tools to provide comfort and analgesia, while avoiding narcotics and anxiolytics due to their unpleasant side-effects. Systematic reviews of the literature have previously summarized music's benefits in reducing pain, anxiety, and physiologic parameters of stress for both hospitalized and non-hospitalized patients. (1) (2) Music listening increased relaxation, reduced heart rate and blood pressure (1). In mechanically ventilated patients, music also reduced anxiety and tolerance of invasive procedures. (3) (4) Music's effects are hypothesized to be secondary to entrainment of the autonomic nervous system, reducing the sympathetic drive. (5) (6) A study by Okada demonstrated reduced plasma adrenaline and noradrenaline levels in music therapy patients with vascular dementia, and reduced heart failure events, likely as a result of reduced plasma cytokine levels, and increase in parasympathetic nervous system activity.(7) Neuroimaging studies have also demonstrated increased regional cerebral blood flow while listening to pleasing music, while drumming was associated with increased immune cell function. Music may also activate the nucleus accumbens, and lead to increases in dopamine, with associated deactivation of areas of the brain related to stress and cortisol signaling.(8) A large systematic review by Fancourt found effects of music on various neurotransmitters, cytokines, and hormones, but some of the included studies included healthy volunteers.(9) This previously published work also offered a novel model for music's social, personal and physical effects on patient physiology, psychological well-being, and nervous system, with downstream effects on the central nervous system, autonomic nervous system, immune system, and endocrine system. The quality of evidence for music's effects on inflammatory biomarkers in post-operative and critically ill patients, where perhaps the largest changes in cytokine levels and a vigorous sympathetic nervous system response occur, are not entirely clear. Acting through the proposed model, on the

sympathetic nervous system, music listening may lead to lower levels of inflammatory cytokines, with downstream effects on various organ systems. If music can mediate anti-inflammatory effects, evidenced by decreased levels of inflammatory biomarkers, there may be biological plausibility for its use in the care of critically ill patients. Music is a non-pharmacological, low risk intervention with low implementation workload burden for the healthcare team, which makes it an attractive intervention for further study.

Objectives/Aims

We conducted a systematic review to evaluate the effects of music, and the quality of evidence for these effects on: 1) inflammatory biomarkers in intensive care patients, and 2) inflammatory biomarkers in post-operative patients.

Methods

A comprehensive search of the literature was performed by a medical librarian in Ovid MEDLINE, PubMed, Embase, the Cochrane Library, CINAHL, PsycINFO, Scopus, ClinicalTrials.gov, and Google Scholar. Bibliographies of relevant studies were also checked for additional references. All searches were performed in March 2017, and all databases were searched from inception.

The complete search strategies for each database are reported in Supplement 1. Results were limited to the adult population and to the English language. We conducted the initial search with the delirium term to identify music therapy's effects on delirium given its association with an inflammatory state, but only one study met inclusion criteria. We therefore focused our analysis on effects of music intervention on inflammatory biomarkers. Database-specific subject headings and keyword variants for major concepts of music therapy were identified and combined.

Study selection

Inclusion criteria: Randomized controlled trials (RCT) were included if they met the following criteria: (1) subjects aged 18 years or older; (2) a music intervention was compared with placebo, no treatment, or a different treatment; (3) primary or secondary outcomes included biomarkers of stress or inflammation.

Exclusion criteria: Studies were excluded if they were performed primarily with or in the setting of dementia facilities, psychiatry units, or traumatic brain injury wards, as these limit broad applicability to critically ill patients. Studies in settings or with interventions not generalizable to hospital patients were also excluded.

Data abstraction and quality assessment

Titles and abstracts were screened by two reviewers (SK and MK). Full texts of potentially relevant studies were assessed. The reviewers independently assessed and abstracted pertinent data from trials using a standardized, pre-defined form. Abstracted data included study setting, methodology (randomization, blinding), duration and timing of music

intervention, outcomes measured, patient characteristics, and follow up. The methodological quality of each trial was assessed using the Jadad Quality Assessment Scale. (10) The scale yields scores of 0 to 5, with higher quality indicated by higher numerical scores. The Jadad scale emphasizes description and reporting of methodology of randomization, blinding, and accounting of withdrawal/dropouts. It is limited, however, in assessing certain aspects of methodological quality, such as allocation concealment.(11) To address these concerns, we strengthened our quality analysis by using Cochrane Handbook version 5.1.0 guidelines for risk of bias assessment. Per these guidelines, we assessed the following domains for each study: 1) selection bias, 2) performance bias, 3) detection bias, 4) attrition bias, 5) reporting bias, and 6) other bias (where applicable). This assessment was conducted using the Cochrane Collaboration tool for risk of bias.(12) (13) Summary of risk of bias for outcomes in the study across domains was performed as per recommendations. Studies were then rated as low risk, unclear risk, or high risk of bias. Using GRADE Working Group recommendations, a level of evidence was assigned to each study, rating level of evidence as high, low, or very low. (14) Each reviewer analyzed the studies independently, scoring the studies using the Jadad Score, Cochrane guidelines, and GRADE recommendations. Results were then compared between reviewers. The reviewers engaged in discussion in order to resolve disagreements related to inclusion or exclusion criteria, study quality, domains introducing risk of methodological bias, significance of likely sources of methodological bias, study design, and quality of scoring. If the two reviewers could not reach consensus, we followed the Cochrane Handbook guidelines, using arbitration by another investigator (BK), or if needed, seeking additional information from the authors of the studies being reviewed. Studies included in our analysis were heterogeneous in terms of the study design (control, intervention), population, and setting, which prevented from conducting a meta-analysis.

Results

A total of 2018 references were identified through database searching (Figure 1). After removing 448 duplicates, 1570 unique titles and abstracts were screened. References were excluded due to their primary study population involving dementia (n=519), schizophrenia (n=279), musical hallucinations after cochlear surgery (n=149), and studies not generalizable to the hospital setting (n=597). Full text review was performed for the remaining 26 papers, with 11 excluded due to their use of healthy volunteers. Fourteen studies were included in the analysis since 1 study focused on delirium in an orthopedic post-operative population but did not obtain biomarkers.

Study Characteristics

Table 1 shows the characteristics of 14 included studies, conducted in 8 countries and in a variety of patient settings. Study sizes ranged from 10 to 205 participants. Participant characteristics including baseline severity of illness, and mechanical ventilation are also presented in Table 1.

Music Genres and Delivery Mechanisms

Music intervention was delivered in the clinical trials through use of headphones (11 studies), and music via a pillow speaker system (three studies).

Playlists contained the following music types: classical, new age, patient-selected music (chosen from classical, country, pop, dance), instrumental, nature sounds (birds, ocean waves), synthesizer, and a mix of relaxing music genres. Four studies standardized their music selection by choosing a tempo rated at 60 to 80 beats a minute, 1 study used music rated at 107 beats per minute, and 1 study used a proprietary healthcare-focused music collection (Musicure®). Studies in which participants were able to select their music are indicated in Table 1 and 2.

Inflammatory Biomarkers

Inflammatory markers measured in the trials included serum cortisol, salivary cortisol, urinary free cortisol, salivary amylase, serum oxytocin, serum adrenocorticotropic hormone (ACTH), serum immunoglobulin A (IgA), serum c-reactive protein, blood epinephrine and norepinephrine levels, serum natural killer cell and lymphocyte levels, serum prolactin, serum leptin, serum enkephalin, and serum interleukin-6. Blood levels of growth hormone, prolactin monomere, dehydroepiandrosterone (DHEA) were also measured. Samples were collected before and after the interventions (Table 2).

Quality Assessment of Clinical Trials

Study results are presented below in order of overall risk of bias (Table 3). After discussion of each trial's results, a summary quality assessment and critical review of the studies is provided. Methodological strengths of several studies included blinded design, variety of music choices, scalable intervention designs using headphones and/or speakers, and use of clinically relevant biomarkers for analysis. Methodological weaknesses of the interventional studies included small sample sizes, per-protocol rather than intention-to-treat analyses, lack of accounting for attrition, consecutive or convenience sampling, and variable intervention times/adherence. Given the objective nature of biochemical outcomes, lack of blinding was not likely to cause significant bias by itself. In the majority of trials, participants received music intervention only once (other than studies by Chlan et al.), rather than multiple sessions over several days. This, along with methodological risks of bias, and limited sample sizes, reduced our overall confidence in the estimated effect of music interventions. Only two studies incorporated robust blinding measures. None of the included studies scored maximum points on the Jadad Score, most commonly due to lack of blinding. In line with Cochrane Handbook recommendations, description of individual bias risk is provided in the results below. Level of evidence in all studies was determined to be low.

Studies with Low Risk of Methodological Bias

Studies with Intensive Care Patients

Beaulieu-Boire investigated effects of music on stress markers in mechanically ventilated patients in a cross-over trial (15). Participants listened to classical music for 120 minutes, with blood samples collected immediately pre- and post-intervention. Group A listened to

music followed by one day of no intervention (washout) followed by a control stimulus (headphones without music), compared to group B receiving interventions in reverse order (control-washout-intervention). Cortisol decreased after music listening compared to placebo (pre- vs. post-music: 815 ± 126 vs. 727 ± 98 nmol/L, P = 0.02; pre- vs. post-placebo: 741 ± 71 vs. 746 ± 68 nmol/L, P = 0.83). The change was significant among survivors of the ICU (survivors: pre-music: 592 vs. post-music: 558 nmol/L, P = 0.0001; non-survivors: pre-music: 597 vs. post-music: 655 nmol/L, P = 0.56). Music was associated with significant differences in ACTH:cortisol ratios. Change in the ratio was +0.04 ± 0.016 in music arm vs. −0.028 ± 0.02 in placebo (P = 0.015). Average levels of MET-enkephalin, interleukin-6, and c-reactive protein did not show significant change. Prolactin decreased with music compared to placebo (pre-music: 29.3 ± 3.5 ug/L vs. post-music 27.4 ± 3.4 ug/L, P = 0.038), but the clinical significance of this is not certain.

In this trial, statistical analyses compared morning and evening listening periods separately, and given the one hour listening session, significant changes in cortisol level due to diurnal variation are less likely. While the risk of methodological bias on outcomes was low, the level of evidence was determined to be low due to the small sample size (n=55).

Studies in the Post-operative Setting

In a double-blind trial, Koelsch investigated effects of music on cortisol during (pre-operative and post-operative) spinal anesthesia in 40 participants, finding a statistically significant decrease in serum cortisol in the music group during the surgery (P < 0.05) (16). The duration of music listening was the longest among all trials included in our analysis due to the length of surgery (210 minutes). The effect, however, did not persist in the postoperative window since the music was stopped at the end of the procedure.

While methodological risk of bias on outcomes was low, confidence in the estimated effect is limited by the small sample size. The relatively short duration between cortisol measurements makes confounding from diurnal variation less likely, but the study did not clearly note the time of the intervention.

Migneault studied the effect of music on neuro-hormonal stress response in 30 gynecological surgery patients under general anesthesia finding no significant difference in blood norepinephrine, epinephrine, cortisol, or ACTH between groups (17). Participants received music via headphones vs. headphones without music while under general anesthesia, with a mean intervention time of 106 minutes. Samples were collected prior to surgery, during surgery, end of surgery, and in the recovery area.

The study benefited from blinded design but results of the study are significantly limited due to the intervention occurring only during general anesthesia/deep sedation, and the small sample size of the study (n=30). The time of day when the intervention was conducted was not clearly identified, and the duration of music listening was variable due to duration of surgery, which may have influenced the results. The risk of methodological bias in the study was low, and level of evidence was low.

Studies with High Risk of Methodological Bias

Studies with ICU Patients

Chlan's study randomized mechanically ventilated patients (n = 70) to patient-selected music vs. headphones without music vs. usual care, and 24-hour urinary free cortisol (UFC) was collected until the participant left the ICU (18). The 24-hour collection reduced interference from diurnal variation. In this design, participants listened to music as frequently as they desired for up to 30 days in the ICU. This was the only trial in our analysis which utilized multi-day music intervention, providing greater dose delivery compared to other trials. No statistically significant differences between groups were found in UFC levels. The study results were limited by various factors; participants were on mechanical ventilation for a median of 6 days prior to the study, adherence to the intervention varied (not fully described) as it was self-initiated by participants which excluded analysis of a dose-response relationship, and the study used a per protocol analysis. Exclusion of participants with poor renal function or on medications affecting the HPA axis limited external validity. Not all participants in the study provided UFC.

In Chlan's pilot study, not powered to show significant differences in biomarker levels (n = 10), there were no significant differences between groups in cortisol, epinephrine, norepinephrine, or adrenal corticotropin levels (19). Due to the pilot nature of the trial, its level of evidence was low.

In Chiu-Shiang Lee's study, music listening was associated with a significant decrease in serum cortisol after 30 minutes of slow tempo participant-selected music in post-operative intensive care participants on mechanical ventilation (serum cortisol 8.21 vs. 8.46 ug/L, P=0.02) (20). While the study had 85 enrolled participants, it suffered from lack of adequate blinding for outcome assessments, and allocation concealment was not ensured, increasing risk of bias. Adherence to the intervention also varied due to time in surgery but was not specified in the results. The intervention occurred in the post-operative ICU, without clear description of the time of day of the intervention. As a result, this study was determined to have high risk of bias with low level of evidence.

Studies in the Post-Operative Setting

Nilsson conducted three trials included in our systematic review. A study with cardiac surgery patients (n=58) found music listening was associated with lower cortisol levels after 30 minutes of intervention compared to controls who had bed rest only, (484.4 vs. 618.8 mmol/L, $P < 0.02$) (21). A second study in open hernia repair patients (n=75) also found decreased serum cortisol levels, but no difference in IgA or glucose levels (22). Patients in the study listened to new age music for approximately 40 minutes, and samples were collected before, at end of surgery, as well as 1, 2, 3, hours post-operatively. A third study in post-operative cardiac surgery patients (n=40) conducted on post-operative day 1, after 30 minutes of music, found oxytocin increased in the music treatment group compared to a decrease in non-music controls (3.95 pmol/l vs. − 5.45, $P = 0.024$) (23).

While these studies had a large number of participants, risk of bias was high due to consecutive sampling, insufficient blinding, and lack of allocation concealment. Cortisol

levels were obtained close together, but the exact timing of the blood draw was not described. In the oxytocin study, participants in the treatment arm had longer surgery times (mean 241 minutes vs. 190 minutes in the control group), and lower baseline oxytocin levels (62.2 pmol/l vs. 73.4 pmol/l, P = 0.013). For these reasons, the level of evidence was rated low.

Graversen's study found significantly decreased cortisol levels in the music group compared to controls (348 vs. 512 nmol/L, P < 0.001) using proprietary music playlists via a music pillow (24). Levels of CRP, also measured pre-operatively and 2 hours post-operatively, were not significantly different within or between groups (1.90 nmol/l in the music group vs. 1.45 nmol/l in the control group, P = 0.292). Consecutive sampling, lack of allocation concealment, analysis by protocol increased the risk of bias (high), despite an adequate sample size (n=75), and level of evidence was low. Those in the control arm had a longer waiting time for surgery, which may have also influenced these results. Duration of the intervention (approximately 255 minutes) was variable due to length of surgery. This four-hour window between cortisol measurements cortisol increased the possibility of change due to diurnal variation.

Good's study investigated salivary cortisol and found no significant change after 20 minutes of music listening post-operatively but was limited by risk of bias. Cortisol was collected in the morning and evening. While 205 participants enrolled, there was high drop-out, with 198 participants not providing saliva in the music arm. The correlation between salivary and serum cortisol in critically ill or post-operative patients is not well understood, limiting external validity. In addition, music was incorporated with jaw relaxation techniques, a potential confounder.

In a three-arm trial, the effect of music on lymphocytes was tested by Leardi (25). New-age music via headphones compared to patient-selected music via headphones vs. usual care in a post-operative (hernia repair, orthopedic surgery, varicose vein correction) population was investigated. Biomarkers were collected at pre-operative, intra-operative, and 3 hours post-operative time points. Levels of NK lymphocytes were lower in both music arms compared to controls (P < 0.05). With sample size of 20 participants per arm, this study had high risk of methodological bias due to lack of allocation concealment, variable interventions between groups, and the lack of blinding, decreasing confidence in the estimated effect and level of evidence is low. Time of day of intervention was not sufficiently described.

In 10 mechanically ventilated surgical ICU participants, Conrad investigated the effect of Mozart piano sonatas on inflammatory markers, on post-operative day 1, after sixty minutes of intervention. DHEA levels were higher in controls compared to the treatment arm (P < 0.05), growth hormone levels were higher in the music group (P < 0.05), IL-6 and epinephrine levels were lower in the treatment group (P < 0.05), while prolactin, ACTH, and cortisol levels were unchanged. Due to the small sample size, and methodological risk of bias, the level of evidence for these results is low.

Summary of Music Effects

Based on our analysis, music listening may be associated with decreases in serum cortisol levels in both intensive care and post-operative hospital patients. Studies in our analysis with measured serum cortisol outcomes had music duration of at least 30 minutes, but a dose-response analysis, or a comparison of benefits of personalized vs. non-personalized music was not possible given the one-dose design of the trials. Studies showing no effect of music on serum cortisol were not adequately powered to show efficacy, or provided the intervention during general anesthesia, likely blunting any response to the music. In studies where the music intervention was over 60 minutes in length, reduced serum cortisol levels were found, but the timing of the cortisol evaluation was not clearly identified, with influence of diurnal variation difficult to rule out. Clinical trials with small sample sizes provided conflicting results on the effects of music on norepinephrine and epinephrine. All of the trials were limited by methodological weaknesses including lack of blinding (due to the nature of the intervention), per-protocol analyses and dropouts, and there was heterogeneity due to differences in baseline patient characteristics and duration of music listening sessions. The trials had small sample sizes and their sample size estimates were based on studies conducted on healthy patients rather than those in the intensive care unit or undergoing surgery. As a result of methodological weaknesses and small sample sizes, level of evidence in the included studies was low.

Discussion

In the trials with low risk of methodological bias, music appeared to decrease cortisol levels (patients were not receiving supplemental corticosteroids), suggesting a possible decrease in the level of systemic stress and inflammation. This suggests a potential role for music listening in alleviating inflammatory states. However, confidence in the level of evidence is low due to weaknesses in trial design, lack of large multi-center randomized trials, and the inherent variation in cortisol levels based on diurnal rhythms. The trials with low risk of bias performed cortisol assessments immediately after intervention and compared morning and evening groups separately, which helped address the chance of cortisol variation due to biological rhythms.

Music intervention in the trials included in our analysis appeared simple enough to implement in a variety of clinical settings (ICU, operating room, post-operative recovery). Based on the current evidence, clinical meaningfulness of results of the trials relating to patient outcomes (mortality, days in the intensive care unit, hospital length of stay) is not yet clear and requires further study.

We identified several gaps in the literature. Our initial search strategy included delirium, but we found only one study (not included in the final analysis due to lack of biomarkers). The studies were limited by risk of methodological bias, and small sample sizes. All except one study provided only a single day of intervention. Taken together, these factors led to determination of a low level of evidence supporting the study findings, since larger trials, with more robust methodology, and greater music doses may alter the estimated effect of music on biomarkers. A dose-response relationship was difficult to determine, and in all but Chlan’s trials, participants received music intervention only once. Only two studies

investigated music effects on catecholamines, and one examined efficacy of music for reduction of interleukin-6. The trials did not conclusively provide evidence for whether personalized music listening is more efficacious compared to generic slow tempo music. The persistence of a beneficial effect of music was also unclear based on study results. In one study, the effect on cortisol disappeared 2 hours post-operatively.

Strengths of our review include a sensitive search strategy, and rigorous evaluation of clinical trial quality, including use of a quality assessment scale. Our review also has limitations. The heterogeneity and methodological weaknesses of the included trials resulting in a lack of high quality evidence prevented us from drawing strong conclusions. However, music-based interventions are a low risk non-pharmacological tool that may relieve discomfort and anxiety for hospital patients in a variety of settings. While we searched for broad terms, exclusion of non-English language publications may contribute publication bias.

Our systematic review found that music listening in the hospital may reduce serum cortisol, albeit with low level of evidence. Single music listening sessions were associated with a decrease in select inflammatory biomarkers. High quality, adequately powered, randomized controlled trials are needed to evaluate meaningful clinical outcomes associated with music listening in the intensive care and post-operative setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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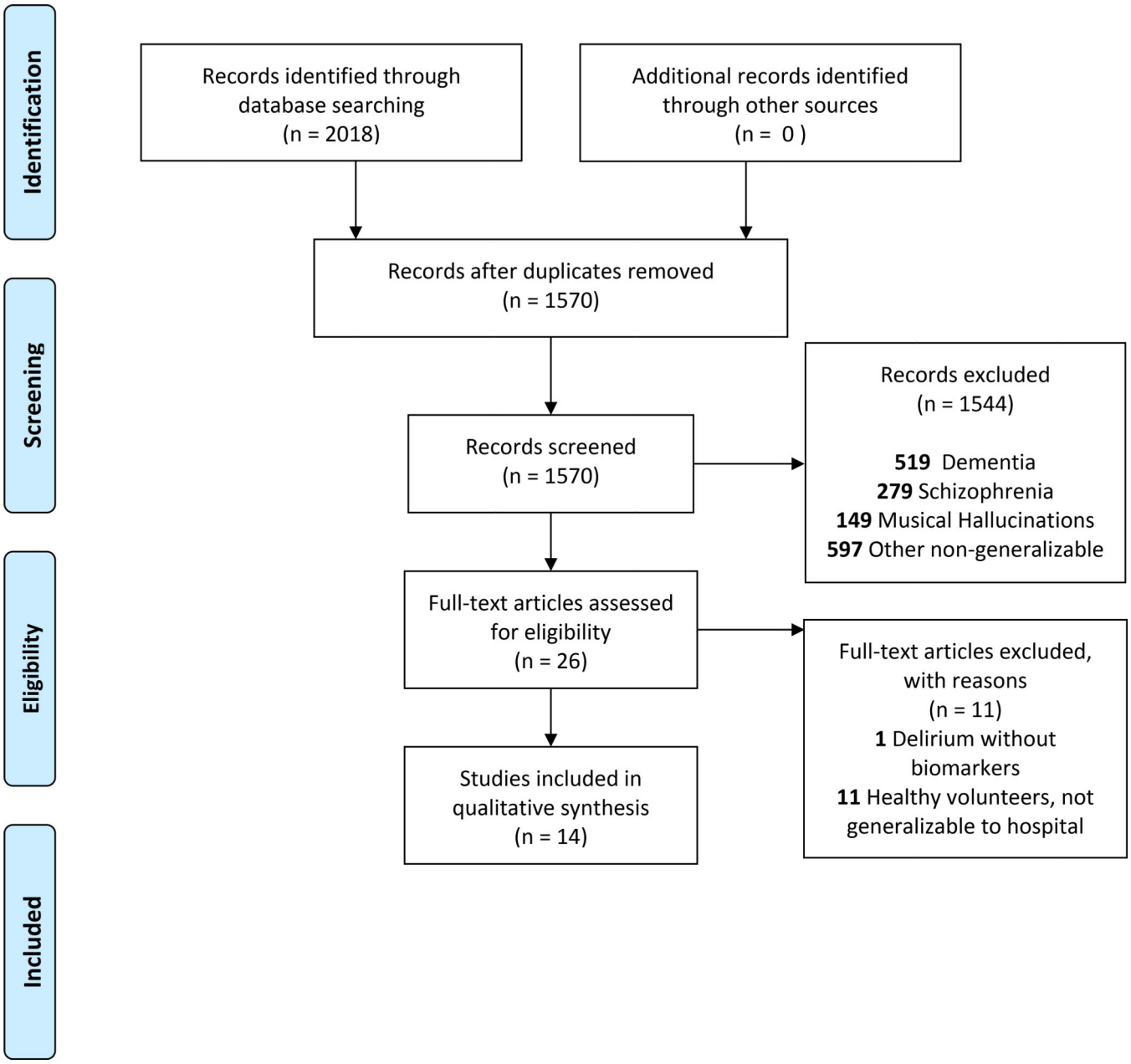

Figure 1.
Search Results for Systematic Review

Table 1

Characteristics of Included Studies

Study	Study Author/Year/Country	# of sites	n	Mean Age, y	% Male	APACHE or ASA	Patient Type	Mechanical Ventilation
Music and biological stress dampening in mechanically-ventilated patients at the intensive care unit ward - a prospective interventional randomized crossover trial	G. Beaulieu-Boire; 2013; Canada	1	55	62	65.3	APACHE II 26	Medical Surgical ICU	Yes
Effects of music listening on cortisol levels and propofol consumption during spinal anesthesia	Stefan Koelsch; 2011; Germany	1	40	66	37.5	ASA II and III	Elective orthopedic surgery (hip)	No
The effect of music on the neurohormonal stress response to surgery under general anesthesia	Brigitte Migneault; 2004; Canada	1	30	49.3	0	ASA I (40%), ASA II (53%)	Gynecologic surgery	Yes
Effects on postoperative salivary cortisol of relaxation/music and patient teaching about pain management	Marion Good; 2012; USA	1	205	47	33	N/A	Post abdominal surgery	No
Soothing music can increase oxytoxin levels during bed rest after open-heart surgery	Ulrica Nilsson; 2009; Sweden	1	40	65.5	80	ASA III	Post Cardiovascular surgery (CABG, aortic valve replacement)	Yes
The effect of music intervention in stress response to cardiac surgery in randomized clinical trial	Ulrica Nilsson; 2009; Sweden	1	58	Not provided	50%	Not indicated	CABG or aortic valve surgery	Yes
Intra-operative natural sound decreases salivary amylase activity of patients undergoing inguinal hernia repair under epidural anesthesia	Y.C.P. Arai; 2008; Japan	1	32	63	84.4	ASA I and II	Inguinal hernia repair	No
Influence of music on the stress response in patients receiving mechanical ventilatory support: a pilot study	Linda L. Chlan; 2007; USA	1	10	64.9	40	N/A	Medical ICU	Yes
Does music influence stress in mechanically ventilated patients?	Linda L. Chlan; 2013; USA	12	70	56.8	61	APACHE III 57.2	Medical Surgical ICU	Yes
Effects of Music Intervention on State Anxiety and Physiological Indices in Patients Undergoing Mechanical Ventilation in ICU	Chiu-Shiang Lee; 2016; Taiwan	1	85	59	43	N/A	Medical Surgical ICU	Yes
Perioperative music may reduce pain and fatigue in patients undergoing laparoscopic cholecystectomy	M. Graversen; 2013; Denmark	1	75	47	26.7	ASA I and II	Laparoscopic cholecystectomy	Not indicated
RCT examining the effect of music therapy in stress response to day surgery	S. Leardi; 2007; Italy	1	60	65	50	N/A	Orthopedic surgery, hernia repair surgery, varicose vein correction surgery	No

Study	Study Author/Year/Country	# of sites	n	Mean Age, y	% Male	APACHE or ASA	Patient Type	Mechanical Ventilation
Stress reduction and analgesia in patients exposed to calming music postoperatively: A RCT	Ulrica Nilsson; 2004; Sweden	1	75	56	96	ASA I (96%)	Open hernia repair	Yes
Overture for growth hormone: Requiem for interleukin-6?	C. Conrad; 2007; USA	1	10	59.9	90	APACHE II > 16	Surgical ICU (Post-operative)	Yes

Abbreviations:
APACHE: Acute Physiology And Chronic Health Evaluation Score
ASA: American Society of Anesthesiologists Physical Status Classification
CABG: Coronary Artery Bypass Graft Surgery
ICU: Intensive Care Unit
POD: Post-operative Day

Table 2

Study Designs and Efficacy for Music Interventions

Study Author/Year/Country	Compared Intervention	Music Type	Outcomes Measured	Intervention Setting	Music Duration	Time of Assessment	Results (Treatment vs. control)
G. Beaulieu-Boire; 2013; Canada	Music via headphones vs. headphones without music	Classical music	Serum cortisol, ACTH, prolactin, MET-enkephalin, leptin, IL-6, CRP	ICU; Intervention-washout-control vs. Control-washout-intervention	120 minutes	Immediately pre- and post morning and evening sessions	Cortisol, prolactin decreased, P = 0.038. ACTH/ cortisol ratio increased, P = 0.015. Cortisol responders had increased MET-enkephalin, P = 0.01
Stefan Koelsch; 2011; Germany	Relaxing music via headphones vs. white noise via headphones	Joyful instrumental mix, 107 beats per minute (mean) vs. ocean wave breaking sounds	Serum cortisol, ACTH, IgA	Pre- and intra-operative	Variable, approx. 210 minutes	2 hours pre-op, intra-op, hours post, 24 hours post	Serum cortisol decreased, P < 0.05
Brigitte Migneault; 2004; Canada	Music via headphones vs. headphones without music	Classical, jazz, new age, piano music	Serum epinephrine, norepinephrine, cortisol and ACTH	Intraoperative	Variable, 106 minutes (mean)	Incision, at skin closure, 30 minutes after arrival at recovery area	No significant change in cortisol, ACTH, norepinephrine, epinephrine
Marion Good; 2012; USA	Relaxing music with jaw relaxation techniques vs. pain management coaching vs. music + pain management coaching vs. usual care	Slow tempo, 60 to 80 bpm	Salivary cortisol	POD 1 and 2	20 minutes	Before and after intervention	No significant change in salivary cortisol
Ulrica Nilsson; 2009; Sweden	Music pillow vs. music pillow without music	Slow tempo, 60 to 80 bpm	Serum oxytocin	POD 1	30 minutes	Pre, 30, 60 mins	Serum oxytocin increased within treatment group, +3.95 vs. − 5.45; P = 0.024
Ulrica Nilsson; 2009; Sweden	Music pillow vs. music pillow with no music	Slow tempo, 60 to 80 bpm	Serum cortisol	POD 1	30 minutes	Pre-intervention, 30 minutes after initiating intervention, and 60 minutes after initiating intervention	Serum cortisol decreased, P < 0.02
Y.C.P. Arai; 2008; Japan	Relaxing music via headphones vs.	Spring forest breeze, bird sounds	Alpha-amylase	Intraoperative	42 minutes (mean)	Intraoperative	Salivary amylase at wound closure

Study Author/Year/Country	Compared Intervention	Music Type	Outcomes Measured	Intervention Setting	Music Duration	Time of Assessment	Results (Treatment vs. control)
	headphones without music						decreased, p = 0.021
Linda L. Chlan; 2007; USA	Participant-selected music program via headphones vs. quiet rest	Classical, new age, easy listening, country music	Serum cortisol, corticotropin, epinephrine, norepinephrine	ICU	60 minutes	Baseline, 15 mins post-baseline, 30 mins post-baseline, 60 minutes post-baseline	No significant difference in cortisol, epinephrine, norepinephrine, or corticotropin
Linda L. Chlan; 2013; USA	Participant-selected music via headphones vs. headphones without music vs. usual care	Patient preferred music	Urinary free cortisol (24 hour)	ICU	Variable, while on MV, up to 30 days	Daily 24 hour urine collection (0700 to 0700)	No significant differences between groups
C. Conrad; 2007; USA	Music via headphones vs. headphones without music	Mozart piano sonatas	DHEA, growth hormone, epinephrine, norepinephrine, ACTH, cortisol, IL-6, prolactin, prolactin monomere	POD 1	60 minutes	Immediately pre- and post morning session	DHEA significantly decreased, growth hormone significantly increased, IL-6 significantly decreased, epineprhine significantly decreased (P < 0.05)
M. Graversen; 2013; Denmark	Music pillow vs. music pillow with no music	Soft music by Musicure®	Serum cortisol and C-reactive protein (CRP)	Pre-, intra-, postoperative, until discharge from surgical unit	Variable, approx. 255 minutes	Pre-operative, 2 hours after surgery	Post-operative serum cortisol significantly lower in treatment arm compared to controls, P < 0.001
S. Leardi; 2007; Italy	Music via headphones vs. patient-selected music via headphones vs. usual care	New age music, or patient-selected (classical, country, pop, dance)	Serum cortisol, NK cell, lymphocyte levels	Pre-, intra-operative	Variable, approx. 60 mins	Pre-operative, peri-operative, 3 hours post-operative	Post-operative cortisol higher in new age compared to patient selected music, P < 0.050. NK lymphocytes decreased in both music arms, lower in new age compared to usual care, P < 0.050

Study Author/Year/Country	Compared Intervention	Music Type	Outcomes Measured	Intervention Setting	Music Duration	Time of Assessment	Results (Treatment vs. control)
Chiu-Shiang Lee; 2016; Taiwan	Music choice via headphones vs. headphones without music	Slow tempo, 60 to 80 bpm, Western and Chinese classical music, natural sounds	Serum cortisol	Postoperative ICU	30 minutes	Pre, post	Serum cortisol, 8.21 vs. 8.46 ug/l; P = 0.02
Ulrica Nilsson; 2004; Sweden	Music via headphones (intraoperatively) + headphones without music (postoperatively) vs. headphones without music (intraoperatively) + music via headphones (postoperatively) vs. headphones without music (intraoperatively and postoperatively)	New age synthesizer	Serum cortisol, IgA, glucose	Intraoperative and postoperative	Variable, approx. 40 mins	Pre-operative, end of surgery, then at 1, 2, 3 hrs in recovery unit	Significant decrease in cortisol in post-operative arm. No difference in IgA and glucose levels.

Abbreviations:
ICU: Intensive Care Unit
POD: Post-operative Day

Table 3

Methodological Bias and Level of Evidence

Study Author/Year/Country	Blinding	Jadad Score	Domain Analysis	Risk of Bias	Level of Evidence
G. Beaulieu-Boire; 2013; Canada	Bedside clinical nurses only	3	Per protocol statistical analysis; outcome assessments not blinded	Low	Low
Stefan Koelsch; 2011; Germany	Double blind	4	Per protocol analysis	Low	Low
Brigitte Migneault; 2004; Canada	Double blind	2	None	Low	Low
Marion Good; 2012; USA	None	3	Per protocol analysis; attrition bias; lack of blinding	High	Low
Ulrica Nilsson; 2009; Sweden	None	3	Consecutive sampling, baseline characteristics differed; outcome assessments not blinded	High	Low
Ulrica Nilsson; 2009; Sweden	None	3	Consecutive sampling, allocation not concealed; not intention-to-treat analysis; outcome assessments not blinded	High	Low
Y.C.P. Arai; 2008; Japan	None	1	Lack of blinding	High	Low
Linda L. Chlan; 2007; USA	None	0	Small sample size, baseline characteristics not equal between groups; convenience sample	High	Low
Linda L. Chlan; 2013; USA	None	2	Exploratory analysis; per protocol analysis; variable intervention duration	High	Low
C. Conrad; 2007; USA	Bedside clinical nurses only	1	Allocation concealment not described; baseline characteristics not fully described; only bedside nurses blinded	High	Low
M. Graversen; 2013; Denmark	None	2	Consecutive sampling; allocation not concealed; per-protocol analysis; one group with longer listening time	High	Low
S. Leardi; 2007; Italy	None	1	Lack of blinding; allocation not concealed; variable intervention duration	High	Low
Chiu-Shiang Lee; 2016; Taiwan	None	2	Per protocol analysis; attrition bias; did not reach intended sample size	High	Low
Ulrica Nilsson; 2004; Sweden	None	2	Baseline characteristics unequal between groups	High	Low