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Original Article

# Preterm infant physiological responses to music therapy: a systematic review

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## Abstract

***Background*** Prematurity is still the leading cause of mortality and morbidity in neonates. The premature change of the environment causes stress, which leads to hemodynamic instability. Music therapy may have a positive impact on hemodynamic parameters of preterm infants in the NICU.

***Objective*** To evaluate preterm infants' physiological responses to music therapy in NICU setting.

***Methods*** A systematic review was performed in 12 electronic databases from March 2000 - April 2018. Our review included all English language publications on parallel or crossover RCTs of music therapy versus standard care or placebo in preterm infants. The outcomes were physiological indicators [heart rate (HR), respiratory rate (RR), and oxygen saturation ($SaO_2$)]. Risk of bias was assessed using the revised Cochrane risk of bias tool for randomized trials (*RoB 2.0*).

***Results*** The search yielded 20 articles on 1,148 preterm infants of gestational age 28 and 37 weeks, who received recorded music, recorded maternal/male voice or lullaby, or live music interventions in the NICU with intensity of 30-76 dB. Recorded music improved all outcomes in 6, 6, and 4 of 16 studies for HR, RR, and $SaO_2$, respectively. Seven studies used classical music as melodic elements. However, eight studies showed no significant results on all outcomes.

***Conclusion*** Despite the finding that music interventions demonstrate promising results in some studies, the variation in quality of the studies, age groups, outcome measures, as well as type and timing of the interventions across the studies make it difficult to draw overall conclusions about the effects of music in preterm infants. **[Paediatr Indones. 2018;58:242-51; doi: http://dx.doi.org/10.14238/pi58.5.2018.242-51 ].**

***Keywords:*** *music therapy; physiological response; preterm infants*

The *World Health Organization* (WHO) defines preterm birth as all births before 37 complete weeks of gestation or fewer than 259 days since the first day of a woman's last menstrual period. The annual national preterm birth rates from 1990 to 2010 for 65 countries in Europe, America, and Australasia showed increasing absolute numbers, suggesting an increasing burden of preterm birth.[1] In 2010, the estimated preterm birth rate was 11.1% of 135 million live births worldwide.[2] Furthermore, Indonesia is included among 10 countries with the highest numbers of estimated preterm birth and rates of 15% or more.[1]

Preterm birth is a major cause of death and long-term loss of human potential amongst survivors around the world. Additionally, preterm birth is also a direct cause of 35% of all neonatal deaths and the second most common cause of under-5 deaths, after pneumonia.[1] Preterm birth also increases the risk of dying due to other causes, especially neonatal infections. Thus, preterm birth is considered to be a risk factor for at least 50% of all neonatal deaths.[3]

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While preterm birth is well known for causing a high mortality rate, it is also associated with injury to many organ systems. Therefore, special care of preterm infants is crucial in the NICU. Nonetheless, the NICU itself is a stressful environment, as some infants must undergo painful events several times a day. Such exposure to a great number of stressors in the NICU has been associated with brain development issues in preterm infants.[4]

Variations in heart rate, blood pressure, oxygen saturation, and breathing patterns are the most frequently used physiological indicators of pain. Pain causes an increase in heart rate and blood pressure, a decrease in oxygen saturation, and more rapid, shallow, or irregular breathing.[5] In response to pain, ATP degradation increases due to energy expenditure through behavioral and physiological reactions to pain, such as crying, facial grimacing, flailing, and tachycardia. Moreover, oxidative stress also increases due to painful stimuli, resulting in additional ATP utilization. Consequently, these processes could lead to energy deficits.[6] One of the most important effects of energy deficit in preterm infants is low weight gain, which can affect brain development, and lead to poor growth and development.[7] Therefore, controlling pain-induced physiological responses is key to preventing poor development in preterm infants. Moreover, supportive therapy such as oxygen supplementation, fluid maintenance, and mechanical ventilation may have detrimental side effects when not used properly. Preterm infants can possibly suffer from ventilator-induced lung injury,[8] bronchopulmonary dysplasia,[9] retinopathy of prematurity,[10] and other catastrophic problems.

As an alternative solution, music therapy is often introduced to stabilize effective hemodynamic parameters in preterm infants, as it is easy to implement, non–invasive, relatively low-cost, and has no known side effects. While some studies showed promising results, others led to contradictory conclusions. Therefore, this systematic review was done with the aim of evaluating preterm infants' physiological response to music therapy.

## Methods

This systematic review was conducted according to the *Preferred Reporting Items for Systematic reviews and Meta-Analysis* (PRISMA) guidelines. Relevant studies were identified in twelve online databases from March 2000 - April 2018. **Figure 1** shows the overview of the study identification process using a PRISMA flowchart. We searched the *Cochrane Database for Systematic and Complete Reviews* to identify systematic reviews and/or meta-analyses, followed by manual search of reference lists to identify relevant articles that were not identified by the search engines. The authors selected potential articles by screening titles and abstracts independently from each other. After accounting for duplication, we reviewed the titles and corresponding abstracts of all studies to identify articles that met the inclusion criteria. Thus, the full texts of all potentially relevant studies were reviewed to determine final study selection.

Inclusion criteria were all studies that investigated the effects of music therapy on physiological responses [heart rate (HR), respiratory rate (RR), or oxygen saturation ($SaO_2$)] in preterm infants (<37 weeks' gestation) that were published in English. Study designs were parallel or crossover randomized clinical trials of music therapy versus standard care, or placebo. Music therapy was given in the form of recorded music, recorded maternal/male voice or lullaby, or live music intervention in the NICU. Music was defined as intentional sound with pleasing harmonies, dynamics, rhythm, tempo, and volume. Instrumental music played by recorder or audio player in/outside the incubator was defined as recorded music; maternal voice or lullaby was described separately.[11-13] Live music was defined as singing lullabies and/or accompanied by instrument music, which was played live. Studies that identified the effects of music therapy on intrauterine life were excluded. Furthermore, conference proceedings, abstracts, review articles (systematic and narrative), case series or case studies, editorials, theses, dissertations, commentaries, and opinion-based papers were also excluded.

From each study, we extracted the study design, subjects' characteristics, physiological outcomes (HR, RR, $SaO_2$), and compared the results between the intervention and control groups. The results are presented as the characteristics of music intervention (**Table 1**). The results of music therapy are shown in **Table 2**. The quality of included studies was assessed by the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) tool (**Table 3**).

Risk of bias was assessed using the revised Cochrane risk of bias tool for randomized trials (*RoB 2.0*), as shown in **Table 4**. There were five bias domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection bias. Overall bias of each articles were classified as low, some concerns, and high risk.

**Table 1**. Characteristics of music intervention

| Author (year) | Music selection | Type of output | Intensity (dB) | Duration of study, length, and frequency of intervention | Timing of intervention |
|---|---|---|---|---|---|
| Butt (2000) | Brahms' Lullaby and recorded acapella version | Speakers | 76 | NR, 10 minutes, once daily | After heel lance procedure |
| Calabro (2003) | Lullabies (Brahms and Sandman) | Speaker, located 15–20 cm from PI | 60–70 | 4 days, 45 minutes, once daily | NR |
| Arnon (2006) | Live music and recorded music | Live music 1–2 m from bed. Recorded music: 2 speakers 1 m from bed | 55–70 | 3 consecutive days, 30 minutes, once daily | 1 hour after feeding |
| Lai (2006) | Lullabies (Western vocal, instrumental lullaby, aboriginal Taiwanese lullaby) | Speaker | NR | 3 days, 60 minutes, once daily | 1 hour after feeding |
| Johnston (2007) | Recorded mother's voice | Portable cassette tape player | 60–70 | 2 days, 10 minutes, 3 times daily | After feedings |
| Whipple (2008) | Pacifier–activated lullaby (PAL) | PAL, 6 inches from infant's head, bilaterally | 65 | 1 day, 10 minutes, only once | During heel stick procedure |
| Cassidy (2009) | Lullaby and classic music (Mozart) | Speaker (in incubator) | 65–75 | 5 days, 40 minutes, once daily | NR |
| Farhat (2010) | Lullaby music (Iranian females vocalists) | Headphones | 60–65 | 8 days, 20 minutes, once daily | ½-1 hour after feeding and diaper change |
| Schlez (2011) | Live harp music therapy a blend of Eastern and Western melody | Distance 1–2 m | 50–65 | Alternating 3–5 days apart, 30 minutes, once daily | 30 minutes after feeding, afternoon |
| Amini (2012) | Lullaby music (Iranian lullaby), classical music (Mozart sonata K448) | Two speakers in the corners of the incubator (30 cm from baby's ears) | 45–50 | 6 days (2 days for each intervention and control), 20 minutes | 1 hour after feeding |
| Alipour (2013) | Lullaby music | Headphones | 50–60 | 20 minutes | 30 minutes after the last feeding and nursing care |
| Auto (2013) | Recorded soft classical songs with low range, simple and direct rhythm (e.g., Mozart's) | NR | NR | Seven consecutive days of a week | Afternoon |
| Loewy (2013) | Live singing lullaby; live application of the Lullaby Ocean Disc; Gato Box (entrained live heartbeat sound) | Portholes of the incubators, isolettes or at bassinette side at the infants' midline | 55–65 | 3 interventions and control per week within 2 week period | Either morning or afternoon |
| Arnon (2014) | Live maternal singing | Live intervention | 60–70 | 2 days, 20 minutes, once daily | 30 minutes after feeding |
| Aydin (2014) | Classical Turkish music | Two speakers were put in the direction of infant's toes within distance 30 cm | 45 (max) | 3 days per week, 30 minutes, once daily | Afternoon |
| Dearn (2014) | Brahms' lullaby | Microspeaker, 30 cm from infant's head | 45–65 | 1 day, 12 minutes, only once | Morning and afternoon |
| Jabraelli (2016) | Brahm's lullaby and recorded mother's lullaby | NR | 65–70 | 3 consecutive days, 15 minutes, once daily | Between 10 am –7 pm |
| Taheri (2016) | Recorded male lullaby | Headphones | 50–60 | 3 days, 40 minutes, once daily | Same noon time |
| Wirth (2016) | Recorded lullabies and maternal voice group | Speaker, 20 cm from the infants' ears | 55–65 | 14 days, 30 minutes, once daily | Between 8–9 pm |
| Caparros-Gonzales (2017) | Relaxing tune by Melomics computer system | Speaker, located 20 cm from infant's left ear | 30–50 | 3 days, 20 minutes intervention, 3 times daily | In the morning (9-10 am), afternoon (2-3 pm), evening (9-10 pm) |

PI: preterm infants; NR: not recorded

## Results

The search strategy using MeSH terms (music, preterm infants, and physiologic responses) yielded 1,481 records. Further manuscript evaluation included screening for duplication, inclusion, and exclusion criteria (**Figure 1**).

Twenty articles were included, of which 12 were parallel and 8 were crossover randomized controlled trials. A total of 1,148 preterm infants between 28 and 37 weeks' gestational age admitted to the NICU either received recorded music, recorded maternal/male voice or lullaby, or live music interventions. All studies were published from 2000 to April 2018. Four studies investigated the effects of live music intervention, sixteen studies used recorded music, and three studies explored recorded maternal/male lullabies. Furthermore, three studies also compared two kinds of intervention groups (**Table 2**).

Four studies used live music intervention consisting of one live harp melody, one live wordless lullaby, one live maternal singing, and one crossover of live singing: *The Ocean Disc and the Gato Box*. Sound intensity ranged from 50-70 dB. The intervention

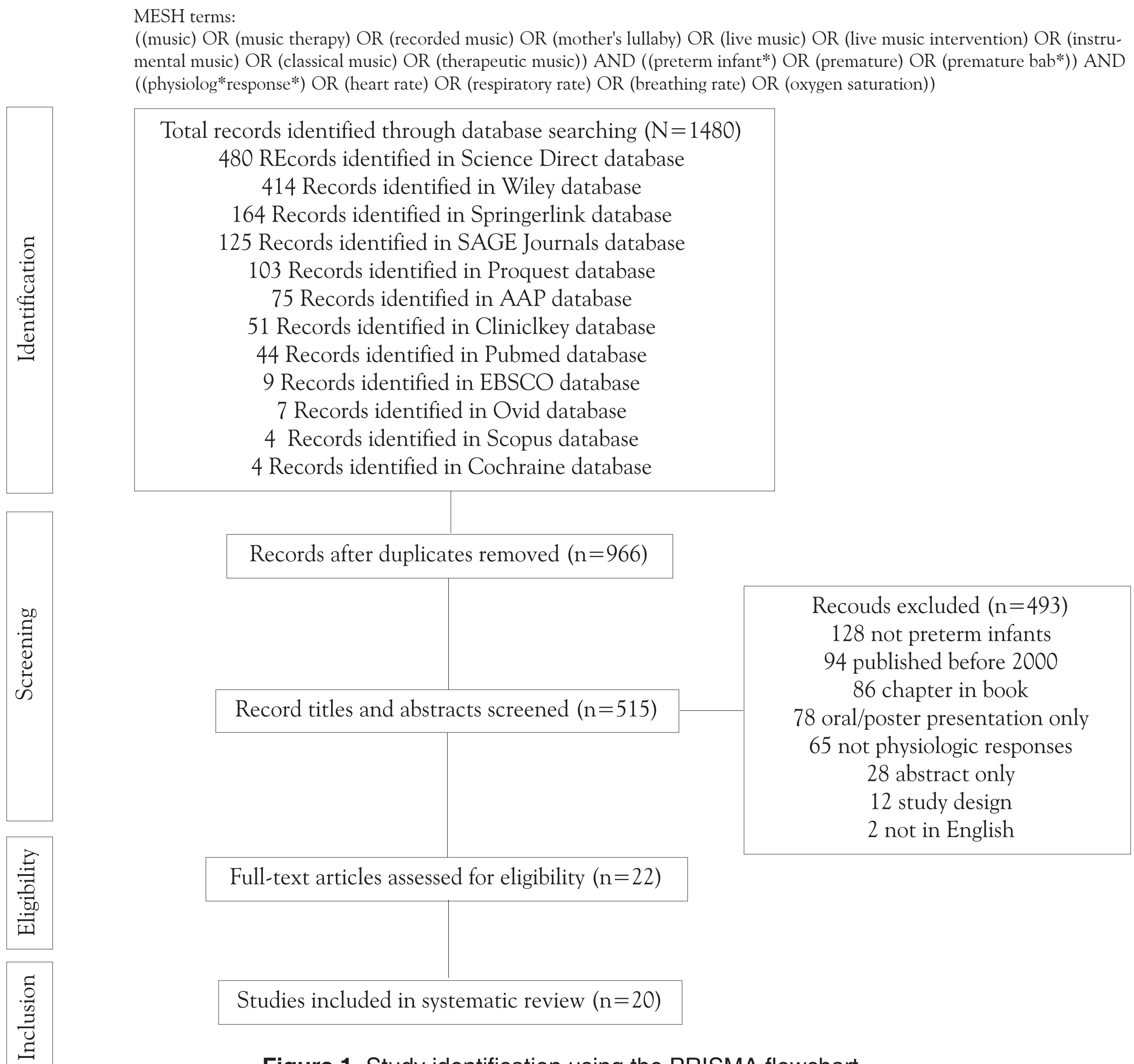


**Figure 1**. Study identification using the PRISMA flowchart

**Table 2**. Results of music therapy for preterm infants

| Authors(years) | Subjects | Intervention(s) and comparator | Measures | Results |
|---|---|---|---|---|
| Butt (2000) | 14 PI, GA 29–36 weeks | IG: Lullabies music<br>CG: No intervention | HR, $SaO_2$, behavioral state of arousal (Brazelton), pain response (NFCS) | Significant for all parameters |
| Calabro (2003) | 22 PI, GA 34 weeks, with chronic lung disorder | IG: Lullabies music<br>CG: No intervention | HR, RR, $SaO_2$, PBAF | NS for all parameters |
| Arnon (2006) | PI, GA ≥ 32 weeks, BW ≥ 1500 g | IG: (1)Live music and (2)recorded music<br>CG: No music therapy | HR, $SaO_2$, RR, behavior | HR decreased significantly |
| Lai (2006) | 30 PI (GA ≤ 37 weeks) with BW 1500 g | IG: Lullaby music during KC<br>CG: No intervention | HR, RR, $SaO_2$, behavioral state, maternal anxiety | NS for all parameters except maternal anxiety state |
| Johnston (2007) | 20 PI, GA 32–36 weeks | IG: Recorded maternal voice<br>CG: No acoustic stimulation | HR, $SaO_2$ | NS |
| Whipple (2008) | 60 PI (GA 32–37 weeks) with BW < 2500 g | IG: Pacifier–activated lullaby (PAL)<br>CG: Pacifier only, no contact | HR, RR, $SaO_2$ | Significant only in RR; HR and $SaO_2$ NS |
| Cassidy (2009) | 63 PI,<br>GA 28–33 weeks | IG: Recorded lullaby music followed by classic music and same music in reverse order<br>CG: Standard NICU care | HR, RR, $SaO_2$, head circumference | NS |
| Farhat (2010) | 44 VLBW PI, GA ≤ 34 weeks | IG: Lullaby music<br>CG: No music | HR, RR, $SaO_2$, weight gain | RR and $SaO_2$ significantly reduced; HR: NS |
| Schlez (2011) | 52 stable PI,<br>GA 32–37 weeks | IG: KC + live harp music therapy<br>CG: KC only | HR, RR, $SaO_2$ | NS |
| Amini (2012) | 25 stable PI (GA: 28–36 weeks, BW: 1000–2500 g) | IG: Lullaby music and classical music<br>CG: No music | HR, RR, $SaO_2$ | Significant in HR and RR reduction for all intervention; NS for $SaO_2$ |
| Alipour (2013) | 90 PI, GA 28–37 weeks, Apgar min. 7, appropriate weight for GA | IG: Lullaby music headphones with music played and silence headphones<br>CG: No intervention | HR, $SaO_2$, RR, behavioral state | NS for all parameters |
| Auto (2013) | 61 hospitalized PI (31 IG, 30 CG), GA ≥ 32 weeks, at least 10 days of life | IG: Music therapy with multimodal stimulation with background music<br>CG: Only multimodal stimulation | Body weight gain, HR, RR | Significant reduction in HR and RR |
| Loewy (2013) | 272 PI (GA 32–37 weeks) with RDS, clinical sepsis, SGA | IG: Live music (Lullaby, ocean disc, Gato Box)<br>CG: No intervention | HR, RR, $SaO_2$, activity level | Significant reduction in HR after all intervention |
| Arnon (2014) | 86 PI, GA 32–36 weeks | IG: KC + live maternal singing<br>CG: KC | HR, RR, $SaO_2$, behavioral state, STAI Score | NS for all parameters except maternal anxiety |
| Aydin (2014) | 60 PI GA < 37 weeks<br>(30 IG, 30 CG) | IG: classical Turkish music + standard care<br>CG: standard care | Peaked HR, $SaO_2$, RR, LOS | NS for all parameters |
| Dearn (2014) | 22 PI, GA > 28 weeks | IG: Brahms' lullaby<br>CG: standard NICU care | HR | NS |
| Jabraelli (2016) | 66 PI, GA 29–34 weeks | Brahms' and maternal lullaby<br>CG: Standard NICU care | $SaO_2$ | Significantly increased $SaO_2$ |
| Taheri (2016) | 52 PI, < 37 weeks | IG: recorded male lullaby<br>CG: no music | HR, $SaO_2$ | Significant reduction HR and $SaO_2$ |
| Wirth (2016) | 61 PI (IG Lullabies: 20; IG Maternal Voice 20; CG 21). GA 30–36 weeks | IG: (1) Lullabies and (2) maternal voice<br>CG: Standard care | HR, RR, activity | Significant decreased HR and RR |
| Caparros-Gonzalez (2018) | 17 PI (IG: 9; CG: 8), GA 32–36 weeks | IG: Relaxing tune Melomics computer system<br>CG: Silence | HR, RR, $SaO_2$, systolic BP, diastolic BP | HR and RR significant |

BW=birth weight; CG=control group(s); HR=heart rate; IG=intervention group(s); GA=gestational age; KC=kangaroo care; LOS=length of stay; NIPS=neonatal infant pain scale; NS=not significant; $SaO_2$=oxygen saturation; PI=preterm infants; PBAF=*Physiological and Behavioral Assessment Form*; REE=resting energy expenditure; RR=respiratory rate; $TcPaO_2$=transcutaneous arterial $O_2$ pressure; VLBW=very low birth weight was applied 3 days/week up to once daily for 20–30 minutes, and given for 1-3 days. Music therapy was given 30-60 minutes after feeding,[14-16] either in the morning or afternoon.[17]

Sixteen studies used recorded lullabies with or without vocals, or classical music such as those of Brahms, Sandman, and Mozart. In two studies, the music was delivered using headphones,[11,12] eleven studies used speakers or MP3 players inside or close to the incubator; one study used PAL,[13] two studies did not clearly state the delivery mode used.[18, 19] The decibel levels were set between 45-76 dB. The intervention was offered 1-3 times daily for 10-60 minutes, and given for 1 to 8 days. Music therapy began 30-60 minutes after feeding, nursing, as well as during or after heel stick procedures, at 9-10 AM, 10 AM - 7 PM, 2-3 PM, 8-9 PM, 9-10 PM, or either morning or afternoon.[11-14, 18-27]

Three studies used recorded maternal voice reading a book or singing a song. The recordings were delivered using a tape player or speaker placed inside the incubator, except for one study that did not explain the music delivery method.[19] Sound intensity was set within the range of 55-70 dB. The intervention was given for 10-15 minutes, 1-3 times daily, for 2, 3, or 14 consecutive days. Timing of intervention was after feedings,[28] between 10 AM - 7 PM,[19] and 8-9 PM.[26]

The level of evidence demonstrated by all included studies was level 1b (individual randomized controlled trial). Variations in trial durations showing beneficial effects led to one level of evidence downgrading, although all outcomes were important (**Table 3**). The effects observed in one day[13,25] or two days[16,28] may have influenced potential effects a few days later. Furthermore, the difference of length and timing of intervention also contributed indirectly to quality assessment of the included studies.

Risk of bias analysis of the included studies showed 4 high risk, 14 with some concerns, and 4 low risk (**Table 4**). Participants in 18 studies were explicitly using randomization for grouping. However, only 8 studies reported their randomization methods. Assessors were blinded to group allocation in thirteen studies, not blinded in one study, and the methods for the rest of the studies were not described. Two studies clearly stated a double-blind trial, however, most of the other studies gave no information regarding blinding participants.

## Discussion

Music therapy was shown to significantly decrease the heart rate[12,14,17,18,20,23,26,27] and respiratory rate,[13,18,22,23,26,27] and increase oxygen saturation.[12,19,20,22] Participants in all studies started from 28 weeks' gestational age. According to fetal auditory development, myelination occurs at the 27$^{th}$ week of gestation, from the cochlea to the auditory thalamus,[29] and external auditory input begins to reorganize the auditory cortex.[30] Music is a complex sound that stimulates multiple sites in the brain, especially the superior temporal lobe. The right hemisphere is primarily responsible for processing some musical components, but a few of these, including perceptual analysis and emotional response,[31] are processed in the other hemisphere.

Neonates are sensitive to temporal stimulus parameters (sound duration) and to higher-order temporal structure (repetition of sound patterns).[32]

**Table 3**. GRADE quality assessment

| Certainty assessment | | | | | | | No. of patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | imprecision | Other considerations | Music therapy | Control | Relative (95%CI) | Absolute (95%CI) | Certainty | Importance |
| Heart rate 19 | randomized trials | not serious | not serious | serious | not serious | none | 811/1064 (76.2%) | 223/1064 (21.0%) | not pooled | not pooled | MODERATE | IMPORTANT |
| Respiratory rate 15 | randomized trials | not serious | not serious | serious | not serious | none | 739/956 (77.3%) | 187/956 (19.6%) | not pooled | not pooled | MODERATE | IMPORTANT |
| Oxygen saturation 16 | randomized trials | not serious | not serious | serious | not serious | none | 749/961 (77.9%) | 182/961 (18.9%) | not pooled | not pooled | MODERATE | IMPORTANT |

**Table 4.** Revised Cochrane risk of bias tool for randomized trials (RoB 2.0)

| | | Randomization process | | | | | Deviations from intended interventions | | | | | Missing outcome data | | | Outcome measurenemt | | Seleciton bias | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author (year) | Design | Random sequence generation | Allocation concealment | Baseline imbalances | Equal proportion | Analysis of period effects | Blinding participants | Blinding carers and trial personnel | Deviation from intended interventions | Carry over effects dissapeared | Analyzed in different group | Complete outcome data | Similar proportions and reasons of missing outcome | Evidence of robustness of the missing outcome data | Not blinding assessors | Invluenced by knowledge of intervention | Selective measurement analysis | Overall bias |
| Butt (2000) | C | NI (some concerns) | | No | Yes | NPS | NI (some concerns) | NI | No | NI | NA | Yes (low) | NA | NA | NI (some concerns) | NI | PN (low) | High |
| Calabro (2003) | P | Yes (low) | Yes | No | NA | NA | NI | No | No | NA | No | Yes (low) | NA | NA | No (low) | NA | No | Low |
| Arnon (2006) | C | Yes (some concerns) | NI | No | NI | NPS | NI (some concerns) | NI | No | NI | NA | Yes (low) | NA | NA | No (low) | NA | No | Some concerns |
| Lai (2006) | P | Yes (low) | Yes | No | NA | NA | NI (low) | NI | No | NA | No | Yes (low) | NA | NA | No (low) | NA | No (low) | Low |
| Johnston (2007) | C | Yes (low) | Yes | No | Yes | NPS | NI (low) | NI | No | Yes | NA | Yes (low) | NA | NA | NI (some concerns) | NI | No (low) | Some concerns |
| Whipple (2008) | P | Yes (some concerns) | NI | No | NA | NA | NI (low) | No | No | NA | No | Yes (low) | NA | NA | No (some concerns) | NI | No (low) | Some concerns |
| Cassidy (2009) | P | NI (some concerns) | NI | No | NA | NA | NI (low) | No | No | NA | No | Yes (low) | NA | NA | No (some concerns) | NI | PN (low) | Some concerns |
| Farhat (2010) | C | Yes (some concerns) | NI | No | NA | NA | NI (low) | NI | No | NA | No | Yes (low) | NA | NA | NI (some concerns) | Ni | No (low) | Some concerns |
| Schlez (2011) | C | Yes (some concerns) | NI | No | NI | NPS | NI (low) | NI | No | Yes | NA | Yes (low) | NA | NA | NI (some concerns) | NI | No (low) | Some concerns |
| Amini (2012) | C | Yes (some concerns) | NI | No | Yes | NPS | NI (some concerns) | NI | No | NI | NA | Yes (low) | NA | NA | No (some concerns) | NI | No (low) | High |
| Alipour (2013) | P | Yes (some concerns) | NI | No | NA | NA | Yes (low) | NI | No | NA | No | Yes (low) | NA | NA | No (low) | NA | No (low) | Some concerns |
| Auto (2013) | P | Yes (low) | Yes | No | NA | NA | NI (low) | NI | No | NA | No | Yes (low) | NA | NA | NI (some concerns) | NI | No (low) | Some concerns |
| Loewy (2013) | C | Yes (low) | Yes | No | Yes | NPS | Yes (some concerns) | NI | No | NI | NA | Yes (low) | NA | NA | NI (some concerns) | NI | No (low) | Some concerns |
| Arnon (2014) | C | Yes (some concerns) | Yes | No | NI | NPS | NI (some concerns) | NI | No | NI | NA | Yes (low) | NA | NA | No (low) | NA | No (low) | Some concerns |
| Aydin (2014) | P | Yes (some concerns) | NI | No | NA | NA | NI (low) | No | No | NA | No | Yes (low) | NA | NA | NI (some concerns) | NI | No (low) | Some concerns |
| Dearn (2014) | P | Yes (some concerns) | NI | No | NA | NA | NI (low) | No | No | NA | No | Yes (low) | NA | NA | No (some concerns) | NI | No (low) | Some concerns |
| Jabraeili (2016) | P | Yes (low) | Yes | No | NA | NA | NI (low) | Yes | No | NA | No | Yes (low) | NA | NA | No | NA | No (low) | Low |
| Taheri (2016) | P | Yes (low) | Yes | No | NA | NA | Yes (low) | Yes | No | NA | No | Yes (low) | NA | NA | No (low) | NA | No (low) | Low |
| Wirth (2016) | P | Yes (some concerns) | NI | No | NA | NA | No (low) | No | No | NA | No | Yes (low) | NA | NA | Yes (some concerns) | NI | No (low) | Some concerns |
| Caparros Gonzales (2017) | P | Yes (some concerns) | NI | No | NA | NA | Yes (low) | Yes | No | NA | No | Yes (low) | NA | NA | No (low) | NA | No (low) | Some concerns |

Note: C=crossover randomized trial; NA=pot applicable; NI=No information; NPS=not present significantly; P=parallel randomized trial; PN=probably no; PY=probably yes. *Only applicable in crossover randomized trials. +Only applicable in parallel randomized trials. Overall bias obtained from risk of bias judgement for each bias domains. High risk bias resulted either at least one domain or three or more some concerns. At least one some concerns in each domain makes some concerns in overall bias. Meanwhile, low risk for all domains resulted in low risk of overall bias.

Winkler *et al.*[33] showed that neonates can detect musical beat, as measured by the brain's event-related potentials (ERP). Moreover, Norazadan reported that selective enhancement of neural responses in the brain for beat and meter frequency is induced by music. Different musical rhythms influence brain waves, as measured by electroencephalogram (EEG).[34] Relaxed music induces high power alpha waves and low power beta waves. Alpha waves can influence sympathetic activity.[35] For sounds higher than 100 dB, increased beta power indicates a disturbed state.36 However, the *American Academy of Pediatrics* (AAP) recommends a maximum sound intensity of 65 dB for neonates.[37]

Yamamoto *et al.* found that slow music also decreased norepinephrine levels.[38] In addition, pleasant music increased serotonin and endorphin levels,[39] possibly by reducing cortisol level. Schwilling *et al.* showed a significant decrease in salivary cortisol in very low birth weight infants after music therapy.[40]

Most studies used lullabies or classical music as the intervention. Lullabies have a simple musical structure that infants can clearly differentiate, comprising lower pitch and slower tempo that are used and recognized across cultures.[41] On the other hand, classical music is not soothing, constant, or stable, and is relatively diverse, which may produce alert responses in infants and preterm infants who are still unable to discriminate complicated frames of tunes.[42] However, Amini et al. conducted a study to observe the effects of lullabies and classical music on physiological instability. Both musical types significantly reduced infant heart rate.[23] Among classical music studies, Verrusio *et al.* showed the Mozart effect, in which music increased the alpha band and activity more than Beethoven's music did.[43] Keidar *et al.* found that Mozart's music significantly lowered the resting energy expenditure (REE) for preterm infants to a greater degree than Bach's music.[44]

Most studies that showed significant results in HR, RR, and/or $SaO_2$ used music intervention between 55-70 dB, lasting for 30 minutes, and given for at least 3 days. We also noted that significant results were obtained in studies that included more mature neonates > 32 weeks. This finding was in line with a trial by Wirth *et al.* they found that preterm neonates with higher gestational age experienced significantly stronger effects on heart rate.[26] Doheny *et al.* also reported that effects of maternal voice on the cardiorespiratory system were observed only in infants ≥33 weeks gestation.[45] Maturation of neurological function occurs during the third trimester of gestation. This might explain the insignificant effects of auditory stimuli on physiological signs in younger infants, since they were not yet able to coordinate the stimuli to an autonomic response.[26] Furthermore, inconsistent results between the Taheri *et al.*[12] and Arnon *et al.*[14] studies might have been related to the differences in duration of intervention, 3 days *vs.* 1 day, respectively. Moreover, subjects' mean gestational ages were 33–34 weeks *vs.* 29 weeks, in the respective studies.[11,16] Arnon *et al.* also stated that preterm neonates at 32 weeks or more who were given live music for 30 minutes showed an improvement in physiological responses.[14] Schlez *et al.* and Lai *et al.* used *Kangaroo Care* (KC) for both treatment and control groups, with no significant effect on HR, RR, or $SaO_2$, possibly due to stable autonomic activity during KC.[15,21] Skin-to-skin contact leads to multimodal stimulation, including of the tactile-sensory system that develops earlier than the auditory system. Thus, the effect of music might have been masked by the KC intervention.[15]

Although the short-term potential effect of music therapy in preterm infants is still debatable, Schmidt *et al*. showed that, in the long run, musical stimuli increased frontal lobe activity and heart rate (reflecting re-organization and the emergence of emotion) in 9-12 month old infants.[46] As a complementary therapeutic approach, music therapy also offers patient–centered solutions for patient care, comfort, and pleasure, and serves as a low-cost, non-invasive, and easily-implemented method.

Heterogeneity in gestational age of preterm infants, as well as in type, duration, length, frequency, timing of intervention, and outcome measures prevented the authors from performing a meta-analysis. Overall bias in 2 studies was high, and some concerns were raised in 14 studies. Furthermore, larger RCTs are needed to optimize the effects of music therapy.

In conclusion, despite the finding that musical interventions demonstrate promising results in some studies, the variation in quality of the studies, age groups, outcome measures, as well as type and timing of the interventions across the studies, make it difficult to make a definitive conclusion on the effects of music in preterm NICU infants.

## Conflict of Interest

None declared.

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