Table 2 (*Continued*)

Study	Title	Aim/objective	Data source/search strategy	Study selection/ selection criteria
Gold et al[25]	Music therapy for autistic spectrum disorder	To review the effects of music therapy for individuals with autistic spectrum disorders.	The following databases were searched: CENTRAL, 2005 (issue 3); MEDLINE (1966 to July 2004); EMBASE (1980 to July 2004); LILACS (1982 to July 2004); PsycINFO (1872 to July 2004); CINAHL, (1872 to July 2004); ERIC (1966 to July 2004); ASSIA (1987 to July 2004); Sociofile (1963 to July 2004); Dissertation Abstracts International (late 1960s to July 2004). These searches were supplemented by searching specific sources for music therapy literature and manual searches of reference lists. Personal contacts to some investigators were made.	All RCTs or controlled clinical trials comparing music therapy added to standard care to "placebo" therapy, no treatment, or standard care.
Laopaiboon et al[26]	Music during caesarean section under regional anesthesia for improving maternal and infant outcomes	To evaluate the effectiveness of music during cesarean section under regional anesthesia for improving clinical and psychological outcomes for mothers and infants.	We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2008).	We included randomized controlled trials comparing music added to standard care during cesarean section under regional anesthesia to standard care alone.
Bradt and Dileo[27]	Music for stress and anxiety reduction in coronary heart disease patients	To examine the effects of music interventions with standard care versus standard care alone on psychological and physiological responses in persons with CHD.	We searched CENTRAL, MEDLINE, CINAHL, EMBASE, PsycINFO, LILACS, Science Citation Index, http://www.musictherapyworld.net, CAIRSS for Music, Pro Quest Digital Dissertations, ClinicalTrials.gov, Current Controlled Trials, and the National Research Register (all to May 2008). We handsearched music therapy journals and reference lists, and contacted relevant experts to identify unpublished manuscripts. There was no language restriction.	We included all RCTs that compared music interventions and standard care with standard care alone for persons with CHD.
Maratos et al[28]	Music therapy for depression	To examine the efficacy of music therapy with standard care compared with standard care alone among people with depression and to compare the effects of music therapy for people with depression against other psychological or pharmacological therapies.	CCDANCTR studies and CCDANCTR references were searched on November 7, 2007, and MEDLINE, PsycINFO, EMBASE, PsycLIT, PSYindex, and other relevant sites were searched in November 2006. Reference lists of retrieved articles were handsearched, as well as specialist music and arts therapies journals.	All RCTs comparing music therapy with standard care or other interventions for depression.

Data extraction/data collection and analysis	Main results	The authors' conclusions
Studies were independently selected, quality assessed, and data extracted by two authors. Continuous outcomes were synthesized using an SMD to enable a meta-analysis combining different scales, and to facilitate the interpretation of effect sizes. Heterogeneity was assessed using the I^2 statistic.	Three small studies were included (total n=24). These examined the short-term effect of brief music therapy interventions (daily sessions over 1 week) for autistic children. Music therapy was superior to "placebo" therapy with respect to verbal and gestural communicative skills (verbal, two RCTs, n=20, SMD 0.36, 95% CI 0.15–0.57; gestyrak, 2 RCTs, n=20, SMD 0.50, 95% CI 0.22–0.79). Effects on behavioral problems were not significant.	The included studies were of limited applicability to clinical practice. However, the findings indicate that music therapy may help children with autistic spectrum disorder to improve their communicative skills. More research is needed to examine whether the effects of music therapy are enduring, and to investigate the effects of music therapy in typical clinical practice.
Two review authors, Malinee Laopaiboon and Ruth Martis, independently assessed eligibility, risk of bias in included trials and extracted data. We analyzed continuous outcomes using an MD with a 95% CI.	One trial involving 76 women who planned to have their babies delivered by cesarean section met the inclusion criteria, but data were available for only 64 women. This trial was of low quality with unclear allocation concealment, and only a few main clinical outcomes reported for the women. The trial did not report any infant outcomes. It appears that music added to standard care during cesarean section under regional anesthesia had some impact on pulse rate at the end of maternal contact with the neonate in the intra-operative period (MD –7.50 fewer beats per minute, 95% CI 14.08 to –0.92) and after completion of skin suture for the cesarean section (MD –7.37 fewer beats per minute, 95% CI 13.37–1.37). There was also an improvement in the birth satisfaction score (maximum possible score of 35) (MD of 3.38, 95% CI 1.59–5.17). Effects on other outcomes were either not significant or not reported in the one included trial.	The findings indicate that music during planned cesarean section under regional anesthesia may improve pulse rate and birth satisfaction score. However, the magnitude of these benefits is small and the methodological quality of the one included trial is questionable. Therefore, the clinical significance of music is unclear. More research is needed to investigate the effects of music during cesarean section under regional anesthesia on both maternal and infant outcomes, in various ethnic pregnant women, and with adequate sample sizes.
Data were extracted and methodological quality was assessed, independently by the two reviewers. Additional information was sought from the trial researchers when necessary. Results are presented using weighted MDs for outcomes measured by the same scale and SMDs for outcomes measured by different scales. Post-test scores were used. In cases of significant baseline difference, we used change scores.	Twenty-three trials (1,461 participants) were included. Listening to music was the main intervention used, and 21 of the studies did not include a trained music therapist. Results indicated that listening to music has a moderate effect on anxiety in patients with CHD; however, results were inconsistent across studies. This review did not find strong evidence for reduction of psychological distress. Findings indicated that listening to music reduces heart rate, respiratory rate, and blood pressure. Studies that included two or more music sessions led to a small and consistent pain-reducing effect. No strong evidence was found for peripheral skin temperature. None of the studies considered hormone levels, and only one study considered QoL as an outcome variable.	Listening to music may have a beneficial effect on blood pressure, heart rate, respiratory rate, anxiety, and pain in persons with CHD. However, the quality of the evidence is not strong and the clinical significance unclear. Most studies examined the effects of listening to prerecorded music. More research is needed on the effect of music offered by a trained music therapist.
Data on participants, interventions, and outcomes were extracted and entered into a database independently by two review authors. The methodological quality of each study was also assessed independently by two review authors. The primary outcome was reduction in symptoms of depression, based on a continuous scale.	Five studies met the inclusion criteria of the review. Marked variations in the interventions offered and the populations studied meant that meta-analysis was not appropriate. Four of the five studies individually reported greater reduction in symptoms of depression among those randomized to music therapy than to those in standard care conditions. The fifth study, in which music therapy was used as an active control treatment, reported no significant change in mental state for music therapy compared with standard care. Dropout rates from music therapy conditions appeared to be low in all studies.	Findings from individual randomized trials suggest that music therapy is accepted by people with depression and is associated with improvements in mood. However, the small number and low methodological quality of studies mean that it is not possible to be confident about its effectiveness. High quality trials evaluating the effects of music therapy on depression are required.

(*Continued*)

Table 2 (*Continued*)

Study	Title	Aim/objective	Data source/search strategy	Study selection/ selection criteria
de Dreu et al[29]	Rehabilitation, exercise therapy and music in patients with Parkinson's disease: a meta-analysis of the effects of music-based movement therapy on walking ability, balance and quality of life	To study that people with PD benefit from MbM therapy when compared with conventional therapy or no therapy in terms of standing balance, transfers, gait performance, severity of freezing, and QoL.	We searched PubMed, EMBASE, Cochrane, CINAHL, and SPORTDiscus for articles published until 1st August, 2011.	The following selection criteria were applied: 1) people with PD were targeted, 2) the study was an RCT of high quality (PEDro score of >4), 3) the intervention contained MbM, and 4) the rhythmic cues were embedded in music.
Cogo-Moreira et al[30]	Music education for improving reading skills in children and adolescents with dyslexia	To study the effectiveness of music education on reading skills (ie, oral reading skills, reading comprehension, reading fluency, phonological awareness, and spelling) in children and adolescents with dyslexia.	We searched the following electronic databases in June 2012: CENTRAL (2012, Issue 5), MEDLINE (1948 to May week 4 2012), EMBASE (1980 to 2012 week 22), CINAHL (searched June 7, 2012), LILACS (searched June 7, 2012), PsycINFO (1887 to May week 5 2012), ERIC (searched June 7, 2012), Arts and Humanities Citation Index (1970 to 6 June 2012), Conference Proceedings Citation Index – Social Sciences and Humanities (1990 to June 2012), and WorldCat (searched June 7, 2012). We also searched the WHO ICTRP and reference lists of studies. We did not apply any date or language limits.	We planned to include RCTs. We looked for studies that included at least one of our primary outcomes. The primary outcomes were related to the main domain of reading: oral reading skills, reading comprehension, reading fluency, phonological awareness, and spelling measured through validated instruments. The secondary outcomes were self-esteem and academic achievement.
Drahota et al[31]	Sensory environment on health-related outcomes of hospital patients	To assess the effect of hospital environments on adult patient health-related outcomes.	We searched: CENTRAL (last searched January 2006); MEDLINE (1902 to December 2006); EMBASE (January 1980 to February 2006); 14 other databases covering health, psychology, and the built environment; reference lists; and organization websites. This review is currently ongoing (MEDLINE last search October 2010), see Studies awaiting classification.	RCTs and non-randomized controlled trials, before-and-after studies, and interrupted times series of environmental interventions in adult hospital patients reporting health-related outcomes.

Data extraction/data collection and analysis	Main results	The authors' conclusions
Two reviewers extracted relevant data from the included studies. A meta-analysis of RCTs on the efficacy of MbM therapy, including individual rhythmic music training and partnered dance classes, was performed. Identified studies (N=6) were evaluated on methodological quality, and SESs were calculated.	Studies were generally small (total N=168). Significant homogeneous SESs were found for the Berg Balance Scale, Timed Up and Go test, and stride length (SESs, 4.1, 2.2, and 0.11; *P*-values <0.01; I^2, 0%, 0%, and 7%, respectively). A sensitivity analysis on type of MbM therapy (dance- or gait-related interventions) revealed a significant improvement in walking velocity for gait-related MbM therapy but not for dance-related MbM therapy. No significant effects were found for UPDRS-motor score, freezing of gait, and QoL.	MbM therapy appears promising for the improvement of gait and gait-related activities in PD. Future studies should incorporate larger groups and focus on long-term compliance and follow-up.
Two authors (HCM and RBA) independently screened all titles and abstracts identified through the search strategy to determine their eligibility. For our analysis we had planned to use MD for continuous data, with 95% CIs, and to use the random-effects statistical model when the effect estimates of two or more studies could be combined in a meta-analysis.	We retrieved 851 references via the search strategy. No RCTs testing music education for the improvement of reading skills in children with dyslexia could be included in this review.	There is no evidence available from RCTs on which to base a judgment about the effectiveness of music education for the improvement of reading skills in children and adolescents with dyslexia. This uncertainty warrants further research via RCTs, involving an interdisciplinary team: musicians, hearing and speech therapists, psychologists, and physicians.
Two review authors independently undertook data extraction and "risk of bias" assessment. We contacted authors to obtain missing information. For continuous variables, we calculated an MD or SMD, and 95% CIs for each study. For dichotomous variables, we calculated RR with 95% CI. When appropriate, we used a random-effects model of meta-analysis. Heterogeneity was explored qualitatively and quantitatively based on risk of bias, case mix, hospital visit characteristics, and country of study.	Overall, 102 studies were included in this review. Interventions explored were: "positive distracters", to include aromas (two studies), audiovisual distractions (five studies), decoration (one study), and music (85 studies); interventions to reduce environmental stressors through physical changes, to include air quality (three studies), bedroom type (one study), flooring (two studies), furniture and furnishings (one study), lighting (one study), and temperature (one study); and multifaceted interventions (two studies). We did not find any studies meeting the inclusion criteria to evaluate: art, access to nature for example through hospital gardens, atriums, flowers, and plants, ceilings, interventions to reduce hospital noise, patient controls, technologies, way-finding aids, or the provision of windows. Overall, it appears that music may improve patient-reported outcomes such as anxiety; however, the benefit for physiological outcomes, and medication consumption has less support. There are few studies to support or refute the implementation of physical changes, and except for air quality, the included studies demonstrated that physical changes in the hospital environment at least did no harm.	Music may improve patient-reported outcomes in certain circumstances, so support for this relatively inexpensive intervention may be justified. For some environmental interventions, well designed research studies have yet to take place.

(*Continued*)

Table 2 (*Continued*)

Study	Title	Aim/objective	Data source/search strategy	Study selection/ selection criteria
Chan et al[32]	The effectiveness of music listening in reducing depressive symptoms in adults: a systematic review	To review trials of the effectiveness of listening to music in reducing depressive symptoms in adults, and identify areas requiring further study.	A comprehensive search strategy was employed to identify all published papers in English language between January 1989 and March 2010. We searched nine databases with initial search terms including "music", "depression", or "depressive symptoms".	We searched the published literature for RCTs and quasi-experimental trials that included an intervention with music listening designed to reduce the depression level, compared with a control group. The intervention was music listening, it is defined as listening to music via any form of music device or live music, without the active involvement of a music therapist.
Naylor et al[33]	The effectiveness of music in pediatric healthcare: a systematic review of randomized controlled trials	To systematically review the effectiveness of music on pediatric health-related outcomes.	The following international electronic databases were searched on March 4, 2009: Ovid Medline (Medical Literature Analysis and Retrieval System Online), 1950 to February, week 3, 2009; EMBASE, 1980–2009 week 9; PsycINFO, 1967 to February, week 4, 2009; AMED (Allied and Complementary Medicine), 1985–February 2009; and CINAHL, 1983–2008.	Studies were included if they met the following six criteria: 1) examined the effectiveness of a music intervention; 2) involved a clinical population in a health care, research, or education setting; 3) involved children and adolescents between 1 and 18 years of age (or reported a mean age within this range); 4) used an RCT design (parallel or crossover); 5) reported at least one quantifiable outcome measure; and 6) was published between 1984 and 2009.
Irons et al[34]	Singing for children and adults with cystic fibrosis	To evaluate the effects of a singing intervention in addition to usual therapy on the QoL, morbidity, respiratory muscle strength, and pulmonary function of children and adults with cystic fibrosis.	We searched the Group's Cystic Fibrosis Trials Register, the CENTRAL, major allied complementary databases, and clinical trial registers. Handsearching for relevant conference proceedings and journals was also carried out. Date of search of trials register: September 2, 2009. Date of additional searches: September 17, 2009.	RCTs in which singing (as an adjunctive intervention) is compared with either a sham intervention or no singing in people with cystic fibrosis.
Irons et al[35]	Singing for children and adults with bronchiectasis	To evaluate the effects of a singing intervention as a therapy on the QoL, morbidity, respiratory muscle strength, and pulmonary function of children and adults with bronchiectasis.	We searched the CAG trial register, CENTRAL, major allied complementary databases, and clinical trials registers. Professional organizations and individuals were also contacted. CAG performed searches in February 2011, and additional searches were carried out in February 2011.	RCTs in which singing (as an intervention) is compared with either a sham intervention or no singing in patients with bronchiectasis.
de Niet et al[36]	Music-assisted relaxation to improve sleep quality: meta-analysis	To evaluate the efficacy of music-assisted relaxation for sleep quality in adults and elders with sleep complaints with or without a comorbid medical condition.	We conducted searches in EMBASE (1997–July 2008), Medline (1950–July 2008), Cochrane (2000–July 2008), PsycINFO (1987–July 2008) and CINAHL (1982–July 2008) for studies published in English, German, French, or Dutch.	We included published RCTs performed in an adult (18–60 years) or elderly (60 years or older) population with primary sleep complaints or sleep complaints comorbid with a medical condition. Studies involving active use of music, such as playing instruments, were excluded.

Data extraction/data collection and analysis	Main results	The authors' conclusions
The data extracted included specific details about the interventions, populations, study methods, and outcomes of significance to the review question and specific objectives. Two studies were pooled together for meta-analysis due to similarity in outcome measures and intervention time points.	Listening to music over a period of time helps to reduce depressive symptoms in the adult population. Daily intervention does not seem to be superior over weekly intervention, and it is recommended that music listening sessions be conducted repeatedly over a time span of more than 3 weeks to allow an accumulative effect to occur.	All types of music can be used as listening material, depending on the preferences of the listener. It is recommended that the listeners are given choices over the kind of music they listen to. There is a need to conduct more studies, which replicate the designs used in the existing studies that met the inclusion criteria, on the level of efficacy of music listening and on the reduction of depressive symptoms for a more accurate meta-analysis of the findings and which would reflect with greater accuracy the significant effects that music has on the level of depressive symptoms.
Data extraction includes information about each study (authorship, year of publication, country, recruitment setting, and experimental design), participants (sample size, sex, population, and age), intervention (treatment, delivery, participant involvement, and dosage), and quality rating. Because of heterogeneity in the study populations, interventions used, and outcome measures applied, it was neither feasible nor appropriate to conduct a meta-analysis.	Qualitative synthesis revealed significant improvements in one or more health outcomes within four of seven trials involving children with learning and developmental disorders; two of three trials involving children experiencing stressful life events; and four of five trials involving children with acute and/or chronic physical illness. No significant effects were found for two trials involving children with mood disorders and related psychopathology.	These findings offer limited qualitative evidence to support the effectiveness of music on health-related outcomes for children and adolescents with clinical diagnoses. Recommendations for establishing a consensus on research priorities and addressing methodological limitations are put forth to support the continued advancement of this popular intervention.
No trials were found that met the selection criteria.	No meta-analysis could be performed.	As no studies that met the criteria were found, this review is unable to support or refute the benefits of singing as a therapy for people with cystic fibrosis. Future RCTs are required to evaluate singing therapy for people with cystic fibrosis.
Two authors independently reviewed the titles, abstracts, and citations to assess potential relevance for full review. No eligible trials were identified and thus no data were available for analysis.	No meta-analysis could be performed.	In the absence of data, we cannot draw any conclusion to support or refute the adoption of singing as an intervention for people with bronchiectasis. Given the simplicity of the potentially beneficial intervention, future RCTs are required to evaluate singing therapy for people with bronchiectasis.
Pre and post-test means and standard deviations, demographic data, and condition properties were extracted from each included study. Review Manager 5.0.12 (The Cochrane Collaboration, Oxford, UK) was used to calculate the effect sizes of the individual studies and for calculation of the pooled MD.	Five RCTs with six treatment conditions and a total of 170 participants in intervention groups and 138 controls met our inclusion criteria. Music-assisted relaxation had a moderate effect on the sleep quality of patients with sleep complaints (SMD −0.74; 95% CI −0.96 to −0.46). Subgroup analysis revealed no statistically significant contribution of accompanying measures.	Music-assisted relaxation can be used without intensive investment in training and materials and is therefore cheap, easily available, and can be used by nurses to promote music-assisted relaxation to improve sleep quality.

(*Continued*)

Table 2 (*Continued*)

Study	Title	Aim/objective	Data source/search strategy	Study selection/ selection criteria
Gold et al[37]	Dose–response relationship in music therapy for people with serious mental disorders: systematic review and meta-analysis	To examine the benefits of music therapy for people with serious mental disorders.	A comprehensive search strategy was applied to identify all relevant studies. The trial database PsiTri, which contains structured information on published and unpublished clinical trials in mental health, based on multiple database searches as well as handsearches by several Cochrane groups, was searched for entries containing the word "music" in any field. PubMed was searched using its "Clinical Queries" search strategy designed to identify scientifically strong studies of therapy outcome, which was expanded with the MeSH term "Evaluation Studies", and crossed with the MeSH terms "Music Therapy" and "Mentally Ill Persons" or "Mental Disorders".	Study participants eligible for this review were adults with serious mental disorders diagnosed by an international classification system. This included psychotic disorders as well as some non-psychotic disorders such as borderline personality disorder, depression, bipolar disorder, and suicidality connected to a mental disorder. Studies were included only if participants were offered music therapy, according to the definition above. Most importantly, this excluded interventions of the "music medicine" type, where music alone is provided as a treatment, rather than using music as a medium within a psychotherapeutic process and relationship. Secondly, it had to be possible to disentangle music therapy from other therapies.

Abbreviations: ASSIA, Applied Social Sciences Index and Abstracts; BPRS, Brief Psychiatric Rating Scale; CAG, Cochrane Airways Group; CAIRSS, Computer-Assisted Information Retrieval System; CCDANCTR, Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register; CDCIG, Cochrane Dementia and Cognitive Improvement Group; CENTRAL, Cochrane Central Register of Controlled Trials; CHD, coronary heart disease; CI, confidence interval; CINAHL, Cumulative Index of Nursing and Allied Health Literature; ERIC, Education Resource Information Centre; Ham-D, Hamilton Depression Scale; ICTRP, International Clinical Trials Registry Platform; LILACS, Latin American and Caribbean Health Sciences Literature; MbM, music-based movement; MD, mean difference; MeSH, Medical Subject Headings; NIH, National Institutes of Health; NNT, number needed to treat; PANSS, Positive and Negative Symptoms Scale; PD, Parkinson's disease; PEDro, Physiotherapy Evidence Database; QoL, quality of life; RAS, rhythmic auditory stimulation; RCT, randomized controlled trial; RR, risk ratio; SANS, Scale for the Assessment of Negative Symptoms; SDS, Self-rating Depression Scale; SDSI, Social Disability Schedule for Inpatients; SES, summary effect size; SMD, standardized mean difference; STAI-S, State-Trait Anxiety Inventory – State; UPDRS, Unified Parkinson's Disease Rating Scale; WHO, World Health Organization.

Research protocol registration

We submitted and registered our research protocol to the PROSPERO (no 42012002950). PROSPERO is an international database of prospectively registered SRs in health and social care.[15] Key features from the review protocol are recorded and maintained as a permanent record in PROSPERO. This provides a comprehensive listing of SRs registered at inception, and enables comparison of reported review findings with what was planned in the protocol. PROSPERO is managed by UK Centre for Reviews and Dissemination (CRD) and funded by the UK National Institute for Health Research. Registration was recommended because it encourage full publication of the review's findings and transparency in changes to methods that could bias findings.[16]

Results

Study selection

The literature searches included potentially relevant articles (Figure 1). Abstracts from those articles were assessed, and 63 papers were retrieved for further evaluation (checks for relevant literature). Forty-two publications were excluded because they did not meet the eligibility criteria (Table S1). A total of 21 studies[17–37] met all inclusion criteria (Table 1). The language of all eligible publications was English.

Study characteristics

The contents of all articles were summarized as structured abstracts (Table 2). Sinha et al[17] reported that there was no evidence that auditory integration therapy or other sound therapies are effective as treatments for autism spectrum disorders. Mossler et al[18] concluded that MT as an addition to standard care helps people with schizophrenia to improve their global state, mental state (including negative symptoms), and social functioning if a sufficient number of MT sessions are provided by qualified music therapists. Bradt et al[19] indicated that music interventions may have beneficial effects on anxiety, pain, mood, and quality of life (QoL) in people with cancer. Bradt and Dileo[20] reported that there may be a benefit of MT on QoL

Data extraction/data collection and analysis	Main results	The authors' conclusions
Results for the same type of outcome were combined across studies in a meta-analysis. Results of different outcomes were not combined. If the same outcome was measured with different scales in the same study, both using equally valid methods (in terms of rater blinding and standardization and validity of instrument), the average effect size of these measures was used.	Results showed that music therapy, when added to standard care, has strong and significant effects on global state, general symptoms, negative symptoms, depression, anxiety, functioning, and musical engagement. Significant dose–effect relationships were identified for general, negative, and depressive symptoms, as well as functioning, with explained variance ranging from 73% to 78%. Small effect sizes for these outcomes are achieved after 3–10, large effects after 16–51 sessions.	The findings suggest that music therapy is an effective treatment which helps people with psychotic and non-psychotic severe mental disorders to improve global state, symptoms, and functioning. Slight improvements can be seen with a few therapy sessions, but longer courses or more frequent sessions are needed to achieve more substantial benefits.

of people in end-of-life care. Vink et al[21] reported that the methodological quality and the reporting of the included studies on dementia were too poor to draw any useful conclusions. Bradt et al[22] indicated that listening to music may have a beneficial effect on heart rate, respiratory rate, and anxiety in mechanically ventilated patients. Cepeda et al[23] reported that listening to music reduces pain intensity levels and opioid requirements on patients with chronic, acute, neuropathic, and cancer pain or experimental pain, but the magnitude of these benefits is small and therefore its clinical importance unclear. Bradt et al[24] reported that rhythmic auditory stimulation might be beneficial for gait improvement in people with stroke. Gold et al[25] indicated that MT may help children with autistic spectrum disorder to improve their communicative skills. Laopaiboon et al[26] indicated that music during planned cesarean section under regional anesthesia may improve pulse rate and birth satisfaction score. Bradt and Dileo[27] reported that listening to music may have a beneficial effect on blood pressure, heart rate, respiratory rate, anxiety, and pain in persons with coronary heart disease. Maratos et al[28] suggested that MT is accepted by people with depression and is associated with improvements in mood, but the small number and low methodological quality of studies meant that it is not possible to be confident about its effectiveness. de Dreu et al[29] reported that music-based movement therapy appeared promising for the improvement of gait and gait-related activities in Parkinson's disease. Cogo-Moreira et al[30] concluded that there is no evidence available on which to base a judgment about the effectiveness of music education for the improvement of reading skills in children and adolescents with dyslexia. Drahota et al[31] reported that music may improve patient-reported outcomes in certain circumstances such as anxiety for hospital patients. Chan et al[32] concluded that listening to music over a period of time helps to reduce depressive symptoms in the adult population. Naylor et al[33] reported that there is limited qualitative evidence to support the effectiveness of music on health-related outcomes for children and adolescents with clinical diagnoses. Irons et al[34] concluded that because no studies that met the criteria were found, their

review was unable to support or refute the benefits of singing as a therapy for people with cystic fibrosis. Irons et al[35] reported that they could not draw any conclusion to support or refute the adoption of singing as an intervention for people with bronchiectasis because of the absence of data. de Niet et al[36] concluded that music-assisted relaxation could be without intensive investment in training and materials and is therefore cheap, easily available and can be used by nurses to promote music-assisted relaxation to improve sleep quality. Gold et al[37] reported that MT is an effective treatment which helps people with psychotic and nonpsychotic severe mental disorders to improve global state, symptoms, and functioning.

Based on ICD-10, we identified a disease targeted in each article (Table 3). Among 21 studies, eight studies were about "Mental and behavioural disorders (F00-99)". There were two studies in "Diseases of the nervous system (G00-99)" and "Diseases of the respiratory system (J00-99)", and one study in "Endocrine, nutritional and metabolic diseases (E00-90)", "Diseases of the circulatory system (I00-99)", and "Pregnancy, childbirth and the puerperium (O60)". Because there were a variety of target diseases, there were six articles in which we could not identify a single disease.

Evidence of effectiveness

Table 4 presents a brief summary of 21 SRs. Five studies (ie, schizophrenia for global and mental state and social functioning,[18] Parkinson's disease for gait and related activities,[29] depressive symptoms,[32] sleep quality,[36] and serious mental disorders for global and social functioning[37]) concluded that there are effects of the intervention.

Ten studies with a meta-analysis (ie, cancer for anxiety, pain, mood, and QoL,[19] advanced life-limiting illness for QoL,[20] mechanically ventilated patients for heart rate, respiratory rate, and anxiety,[22] multiple pain for intensity level and opioid requirement,[23] acquired brain injury for gait parameters,[24] autistic spectrum disorders for communicative skills,[25] cesarean section for heart rate and birth satisfaction,[26] coronary heart disease for blood pressure,

Table 3 International classification of target diseases in each article

Chapter	ICD code	Classification	Study (detail ICD code)
1	A00–B99	Certain infectious and parasitic diseases	
2	C00–D48	Neoplasms	Bradt et al[19] (unidentification about neoplasm type)
3	D50–D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	
4	E00–E90	Endocrine, nutritional and metabolic diseases	Irons et al[34] (E84.9)
5	F00–F99	Mental and behavioral disorders	Sinha et al[17] and Gold et al[25] (F84.0); Mossler et al[18] (F21, F22); Vink et al[21] (F00–03); Maratos et al[28] (F30–33); Cogo-Moreira et al[30] (F81.0); Chan et al[32] (F30–33); and de Niet et al[36] (G47)
6	G00–G99	Diseases of the nervous system	Bradt et al[24] (G46) and de Dreu et al[29] (G20–21)
7	H00–H59	Diseases of the eye and adnexa	
8	H60–H95	Diseases of the ear and mastoid process	
9	I00–I99	Diseases of the circulatory system	Bradt and Dileo[27] (I20–25)
10	J00–J99	Diseases of the respiratory system	Bradt et al[22] (J44) and Irons et al[35] (J47)
11	K00–K93	Diseases of the digestive system	
12	L00–L99	Diseases of the skin and subcutaneous tissue	
13	M00–M99	Diseases of the musculoskeletal system and connective tissue	
14	N00–N99	Diseases of the genitourinary system	
15	O00–O99	Pregnancy, childbirth and the puerperium	Laopaiboon et al[26] (O60)
16	P00–P96	Certain conditions originating in the perinatal period	
17	Q00–Q99	Congenital malformations, deformations and chromosomal abnormalities	
18	R00–R99	Symptoms, signs and abnormal clinical and laboratory finding not elsewhere classified	
19	S00–T98	Injury, positioning and certain other consequences of external causes	
20	V00–Y98	External causes of morbidity and mortality	
21	Z00–Z99	Factors influencing health status and contact with health services	
22	U00–U99	Code for special purpose	
–	Unidentification	Because many illnesses were mixed, we could not identify it	Bradt and Dileo,[20] Cepeda et al,[23] Drahota et al,[31] Naylor et al,[33] and Gold et al[37]

Abbreviation: ICD, International Classification of Diseases.

Table 4 Brief summary of 21 systematic reviews

Study	Published year	Intervention type	Meta-analysis	Object disease or symptom	Having effect or not	Adverse events
Sinha et al[17]	2011	Auditory integration therapy and other sound therapies that involved listening to music modified by filtering (attenuating sounds at selected frequencies) and modulating (random alternating high and low sound)	Not performed	Autism spectrum disorders	Unclear	No study reported specific deterioration.
Mossler et al[18]	2011	Music therapy (a systematic process of intervention wherein the therapist helps the client to promote health, using music experiences and the relationships that develop through them as dynamic forces of change)	Performed	Schizophrenia and schizophrenia-like disorders	Effective; improving their global state, mental state (including negative symptoms), and social functioning	No study reported specific deterioration.
Bradt et al[19]	2011	All types of music therapy or music medicine	Performed	Cancer	May be effective; improving anxiety, pain, mood, and QoL	No study reported specific deterioration.
Bradt and Dileo[20]	2010	All types of music therapy or music medicine	Performed	Advanced life-limiting illness	May be effective; improving QoL	No study reported specific deterioration.
Vink et al[21]	2003	All types of music therapy or music medicine	Performed	Dementia	Unclear	No study reported specific deterioration.
Bradt et al[22]	2010	All types of music therapy or music medicine	Performed	Mechanically ventilated patients	May be effective; improving heart rate, respiratory rate, and anxiety	No study reported specific deterioration.
Cepeda et al[23]	2006	Listening to music (as defined by the investigator)	Performed	Acute, chronic, neuropathic, cancer, or experimental pain	May be effective; reducing pain intensity levels and opioid requirements	No study reported specific deterioration.
Bradt et al[24]	2010	All types of music therapy or music medicine	Performed	Acquired brain injury	May be effective; improving gait parameters	No study reported specific deterioration.
Gold et al[25]	2006	Music therapy delivered by a professional	Performed	Autistic spectrum disorders in children	May be effective; improving communicative skills	No study reported specific deterioration.
Laopaiboon et al[26]	2009	All types of music therapy or music medicine	Performed	Cesarean section	May be effective; improving heart rate and birth satisfaction score	No study reported specific deterioration.
Bradt and Dileo[27]	2009	Any form of participation in music (eg, listening to music, singing, and playing music)	Performed	Coronary heart disease	May be effective; improving blood pressure, heart rate, respiratory rate, anxiety, and pain	No study reported specific deterioration.
Maratos et al[28]	2008	Music therapy provided by a certificated professional	Not performed	Depression	May be effective; accepted by people with depression and improving mood	No study reported specific deterioration.
de Dreu et al[29]	2012	Music-based movement therapy (the form of individual gait training or in a group, partnered dance)	Performed	Parkinson's disease	Effective; improving gait and gait-related activities	No study reported specific deterioration.
Cogo-Moreira et al[30]	2012	Music education (individual or group music lessons or musical training)	No studies	Dyslexia	No evidence	Non-information due to no studies included in the review
Drahota et al[31]	2012	Music listening	Performed	Hospital patients	May be effective; improving patient-reported outcomes such as anxiety	No study reported specific deterioration.

(*Continued*)

Table 4 (*Continued*)

Study	Published year	Intervention type	Meta-analysis	Object disease or symptom	Having effect or not	Adverse events
Chan et al[32]	2011	Listening to music via any form of music device or live music, without the active involvement of a music therapist	Performed	Depressive symptoms	Effective; reducing depressive symptoms	No study reported specific deterioration.
Naylor et al[33]	2011	Music as an intervention or therapy, regardless of delivery mode (ie, by a trained music therapist)	Performed	Various clinical condition	May be effective; improving health outcomes in children with learning and developmental disorder	No study reported specific deterioration.
Irons et al[34]	2010	All types of music therapy or music medicine	No studies	Cystic fibrosis	No evidence	Non information due to no studies included in the review
Irons et al[35]	2010	All types of singing programs	No studies	Bronchiectasis	No evidence	Non information due to no studies included in the review
de Niet et al[36]	2009	Listening to music (CD/DVD)	Performed	Sleep complaints	Effective; improving sleep quality	No study reported specific deterioration.
Gold et al[37]	2009	Music therapy (a systematic process of intervention wherein the therapist helps the client to promote health, using music experiences and the relationships that develop through them as dynamic forces of change)	Performed	Serious mental disorders	Effective; improve global state, symptoms, and functioning	No study reported specific deterioration.

Abbreviation: QoL, quality of life

heart rate, respiratory rate, anxiety, and pain,[27] hospital patients for self-reported outcomes such as anxiety,[31] and various clinical conditions for health outcomes in children with learning and developmental disorder[33]) concluded that there might be an effect of the intervention. An SR without a meta-analysis of depression reported that there might be an effect of the intervention.[28]

Two studies (ie, autism spectrum[17] and dementia[21]) described that the effect of intervention is unclear. There was no evidence for three studies (ie, dyslexia,[30] cystic fibrosis,[34] and bronchiectasis[35]) because they were not RCTs.

Adverse events

There were no specific adverse events in any of the studies.

Quality assessment

We evaluated eleven items from the AMSTAR checklist in more detail (Table 5). Inter-rater reliability metrics for the quality assessment indicated substantial agreement for all 231 items (percentage agreement 95.3% and κ=0.825). As a whole, the quality of the articles was very good.

Discussion

This is the first SR of SRs of the effectiveness of cure based on music interventions in studies with RCT designs. Our study is unique because it summarized the evidence for each target disease according to ICD-10 classification. We assume that this study will be helpful to researchers who want to grasp an effect of MT comprehensively and could provide information that is indispensable for the organization that is going to make the guidelines according to each disease.

Twenty-one SRs based on RCTs were identified, and music intervention was clearly effective for five diseases (ie, schizophrenia for global and mental state and social functioning, Parkinson's disease for gait and related activities, depressive symptoms, sleep quality, and serious mental disorders for global and social functioning).

A review of all SRs showed that there was no special adverse effect or harm associated with MT.

Tendency of target disease and outcome

The most commonly reported target diseases were "Mental and behavioural disorders (F00-99)",[17,18,21,25,28,30,32,36] and the effect of MT on these diseases was improved mental health (eg, anxiety and mood), pain, QoL, and communication skills. The main reason given in these articles for improved mental health was that the beauty and rhythm of the music tone allowed the

Table 5 AMSTAR is a measurement tool created to assess the methodological quality of systematic reviews

	Total evaluation	N (%)
1. Was an "a priori" design provided?	☐ Yes	20 (95%)
The research question and inclusion criteria should be established before the conduct of the review.	☐ No	0 (0%)
	☐ Can't answer	1 (5%)
	☐ Not applicable	0 (0%)
2. Was there duplicate study selection and data extraction?	☐ Yes	21 (100%)
There should be at least two independent data extractors and a consensus procedure for disagreements	☐ No	0 (0%)
should be in place.	☐ Can't answer	0 (0%)
	☐ Not applicable	0 (0%)
3. Was a comprehensive literature search performed?	☐ Yes	21 (100%)
At least two electronic sources should be searched. The report must include years and databases used	☐ No	0 (0%)
(eg, CENTRAL, EMBASE, and MEDLINE). Keywords and/or MeSH terms must be stated and where feasible	☐ Can't answer	0 (0%)
the search strategy should be provided. All searches should be supplemented by consulting current contents,	☐ Not applicable	0 (0%)
reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing		
the references in the studies found.		
4. Was the status of publication (ie, grey literature) used as an inclusion criterion?	☐ Yes	14 (67%)
The authors should state that they searched for reports regardless of their publication type.	☐ No	6 (28%)
The authors should state whether or not they excluded any reports (from the systematic review),	☐ Can't answer	0 (0%)
based on their publication status, language etc.	☐ Not applicable	1 (5%)
5. Was a list of studies (included and excluded) provided?	☐ Yes	17 (81%)
A list of included and excluded studies should be provided.	☐ No	4 (19%)
	☐ Can't answer	0 (0%)
	☐ Not applicable	0 (0%)
6. Were the characteristics of the included studies provided?	☐ Yes	18 (85%)
In an aggregated form such as a table, data from the original studies should be provided on the participants,	☐ No	1 (5%)
interventions and outcomes. The ranges of characteristics in all the studies analyzed, eg, age, race, sex,	☐ Can't answer	0 (0%)
relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Not applicable	2 (10%)
7. Was the scientific quality of the included studies assessed and documented?	☐ Yes	19 (90%)
"A priori" methods of assessment should be provided (eg, for effectiveness studies if the author(s)	☐ No	0 (0%)
chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment	☐ Can't answer	0 (0%)
as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Not applicable	2 (10%)
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	☐ Yes	18 (85%)
The results of the methodological rigor and scientific quality should be considered in the analysis	☐ No	2 (10%)
and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Can't answer	0 (0%)
	☐ Not applicable	1 (5%)
9. Were the methods used to combine the findings of studies appropriate?	☐ Yes	16 (76%)
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity	☐ No	0 (0%)
(ie, chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or	☐ Can't answer	0 (0%)
the clinical appropriateness of combining should be taken into consideration (ie, is it sensible to combine?).	☐ Not applicable	5 (24%)
10. Was the likelihood of publication bias assessed?	☐ Yes	15 (71%)
An assessment of publication bias should include a combination of graphical aids	☐ No	0 (0%)
(eg, funnel plot, other available tests) and/or statistical tests (eg, Egger regression test).	☐ Can't answer	0 (0%)
	☐ Not applicable	6 (29%)
11. Was the conflict of interest stated?	☐ Yes	20 (95%)
Potential sources of support should be clearly acknowledged in both the systematic review	☐ No	0 (0%)
and the included studies.	☐ Can't answer	0 (0%)
	☐ Not applicable	1 (5%)

Abbreviations: CENTRAL, Cochrane Central Register of Controlled Trials; MeSH, Medical Subject Headings; Can't, can not.

patient to be comfortable. In studies about the effects of MT on anxiety, discomfort, fear, and pain, MT has been variably applied as an accessory treatment for persons with addictions,[6] and as evasion of direct discomfort for undergoing medical device procedures such as colonoscopy,[8] colposcopy[9] and dental procedures.[7]

The second most frequently reported target diseases were "Diseases of the nervous system (G00-99)",[24,29] and the effects of MT on these diseases showed commonly gait parameters. MT is expected to improve gait and related activities such as rehabilitation in diseases of the central nervous system. There were also several

studies that identified "Diseases of the respiratory system (J00-99)."[22,35] Improvements seen in these studies were mainly due to effects of singing on breathing function, such as respiratory rate, and on the circulation function, such as heart rate.

Validity of overall evidence based on quality assessment

We performed an evaluation of all SRs by the AMSTAR checklist developed to assess the methodological quality of SRs. There were no serious problems with the conduct and reporting of all target studies. This study included 16 Cochrane Reviews.[17–28,30,31,34,35] In the Cochrane Reviews, the eligibility criteria for a meta-analysis are strict, and for each article, heterogeneity and low quality of reporting are to first be excluded. Therefore, we assumed that the conclusion of each SR had enough validity.

Overall evidence

Most importantly, a specific adverse effect or harmful phenomenon did not occur in any study, and MT was well tolerated by almost all patients. MT treatment has positive effects for the following: schizophrenia and/or serious mental disorders for global and social functioning, Parkinson's disease for gait and related activities, depressive symptoms, and sleep quality. We assume that the direct effects of MT are generally improvement of mental health and sense of rhythm, and reduction of pain. In addition, we assume that communication with other people improves through music, the sense of isolation disappears, and QoL rises.

Although further accumulation of RCT data is necessary, MT may be effective treatment for the following diseases and symptoms: cancer and/or advanced life-limiting illnesses affecting mental state and QoL, mechanically ventilated patients with impaired respiratory function and mental state, chronic pain requiring opioid treatment, acquired brain injury affecting gait parameters, autistic spectrum disorders involving communicative skills, cesarean section effects on heart rate and birth satisfaction, coronary heart disease effects on circulatory, respiratory function, and mental state, and self-reported outcomes for hospitalized patients and other patients with various clinical conditions. These SRs describe the need for additional high quality RCTs to assess the effect of MT.

Future research agenda to build evidence

Table 6 shows the future research agenda for studies on the treatment effect of MT. Because only SRs of RCTs were included in this study, their characteristic study designs limited our results to the assessment of short-term effects. Even if a study is not an RCT design, it is necessary to evaluate the long-term effects.

Table 6 Future research agenda to build evidence of music therapy

Item
1. Long-term effect
2. Consensus of the intervention framework such as type, frequency, time for each disease*
3. Dose–response relationship
4. Description of cost
5. Development of the original checklist for music therapy**

Notes: *Reporting guidelines for intervention on each disease; **reporting guideline for research methodology on study plan, implementation, and description.

Because studies of intervention using music vary in design, a consensus of the framework is necessary.[10] In this study, examination according to a detailed intervention method was not possible, but it would be important for future studies to define MT. Furthermore, studies to assess dose–response relationships according to each disease are clearly necessary.[18]

Bowen et al[38] suggested that public health is moving toward the goal of implementing evidence-based intervention. However, the feasibility of possible interventions and whether comprehensive and multilevel evaluations are needed to justify them must be determined. It is at least necessary to show the cost of such interventions. We must introduce an interventional method based on its cost-benefit, cost-effectiveness, and cost-utility.

In addition, MT as an intervention is unique and completely different than pharmacological or traditional rehabilitation methods. Therefore, it may be necessary to add some original items like herbal intervention,[39] aquatic exercise,[40] and balneotherapy[41] to the CONSORT 2010 checklist as alternative or complementary medicines.

Strength and limitations

This review has several strengths: 1) the methods and implementation registered high on the PROSPERO database; 2) it was a comprehensive search strategy across multiple databases with no data restrictions; 3) there were high agreement levels for quality assessment of articles; and 4) it involved detailed data extraction to allow for collecting all articles' content into a recommended structured abstract.

This review also had several limitations that should be acknowledged. Firstly, some selection criteria were common across studies, as described above; however, bias

remained due to differences in eligibility for participation in each original RCT. Secondly, publication bias was a limitation. Although there was no linguistic restriction in the eligibility criteria, we searched studies with only English and Japanese keywords. Thirdly, in order to be specific to SRs based on RCTs, it ignores some excellent results of primary research by other research designs. Fourthly, as a point of terminology for MT, because we applied a broad definition to the use of music in medicine, it may be more confusing or a bit misleading in the cultural context of Western health care.

In addition, since this review focused on summaries of effects of MT for each disease, we did not describe all details on quality and quantity such as type of MT, frequency of MT, and time on MT. Moreover, we could not follow standard procedures as estimates of the effects of moderating variables. Finally, because we broadly defined MT as music appreciation, musical instrument performance, and singing, we could not assess a specific intervention.

Conclusion

This comprehensive summary of SRs demonstrates that MT treatment improved the following: global and social functioning in schizophrenia and/or serious mental disorders, gait and related activities in Parkinson's disease, depressive symptoms, and sleep quality. MT may have the potential for improving other diseases, but there is not enough evidence at present. Most importantly, a specific adverse effect or harmful phenomenon did not occur in any of the studies, and MT was well tolerated by almost all patients.

To most effectively assess the potential benefits of MT, it will be important for future research to explore 1) long-term effects, 2) a consensus of the framework of music intervention, 3) dose–response relationships, 4) the cost of the intervention, and 5) development of the original check item in MT.

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Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. All authors took part in drafting the article or revising it critically for important intellectual content.

Ethical approval

No ethical approval was required.

Data sharing

No additional data are available.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 References to studies excluded in this review

First author. Journal (Year)	Title	Reason for exclusion
Standley J. *Neonatal Netw* (2012)	Music therapy research in the NICU: an updated meta-analysis	Not SR based on RCTs
Wittwer JE. *Disabil Rehabil* (2012)	Rhythmic auditory cueing to improve walking in patients with neurological conditions other than Parkinson's disease – what is the evidence?	Not SR based on RCTs
Hurkmans J. *Aphasiology* (2012)	Music in the treatment of neurological language and speech disorders: a systematic review	Not SR based on RCTs
Burns DS. *J Music Ther* (2012)	Theoretical rationale for music selection in oncology intervention research: an integrative review	Not SR based on RCTs
Fredericks S. *Clin Nurs Res* (2012)	Anxiety, depression, and self-management: a systematic review	Not SR based on RCTs
Galaal K. *Cochrane Database Syst Rev* (2011)	Interventions for reducing anxiety in women undergoing colposcopy	Not treatment or rehabilitation
Pittman S. *Int Nurs Rev* (2011)	Music intervention and preoperative anxiety: an integrative review	Not SR based on RCTs
Cogo-Moreia H. *Cochrane Database Syst Rev* (2011)	Music education for improving reading skills in children and adolescents with dyslexia	Updated or replacement SR
Schmid W. *BMC Health Serv Res* (2010)	Home-based music therapy – a systematic overview of settings and conditions for an innovative service in healthcare	Not SR based on RCTs
Renner RM. *Contraception* (2010)	Pain control in first-trimester surgical abortion: a systematic review of randomized controlled trials	Not music therapy
de Niet GJ. *Int J Evid Based Healthc* (2009)	Review of systematic reviews about the efficacy of non-pharmacological interventions to improve sleep quality in insomnia	Not music therapy
Engwall M. *J Perianesth Nurs* (2009)	Music as a nursing intervention for postoperative pain: a systematic review	Not treatment or rehabilitation
Harting L. *Arch Dis Child Fetal Neonatal Ed* (2009)	Music for medical indications in the neonatal period: a systematic review of randomised controlled trials	Not treatment or rehabilitation
Bechtold ML. *Dig Dis Sci* (2009)	Effect of music on patients undergoing colonoscopy: a meta-analysis of randomized controlled trials	Not treatment or rehabilitation
Klassen JA. *Ambul Pediatr* (2008)	Music for pain and anxiety in children undergoing medical procedures: a systematic review of randomized controlled trials	Not treatment or rehabilitation
Tam WW. *World J Gastroenterol* (2008)	Effect of music on procedure time and sedation during colonoscopy: a meta-analysis	Not treatment or rehabilitation
Gillen E. *Int J Evid Based Healthc* (2008)	Effects of music listening on adult patients' pre-procedural state anxiety in hospital	Not treatment or rehabilitation
Dileo C. *Cochrane Database Syst Rev* (2008)	Music for preoperative anxiety	Protocol
Mays KL. *Subst Abus* (2008)	Treating addiction with tunes: a systematic review of music therapy for the treatment of patients with addictions	Not SR based on RCTs
Klassen JA. *Ambul Pediatr* (2008)	Music for pain and anxiety in children undergoing medical procedures: a systematic review of randomized controlled trials	Not treatment or rehabilitation
Galaal K. *Cochrane Database Syst Rev* (2007)	Interventions for reducing anxiety in women undergoing colposcopy	Not treatment or rehabilitation
Rudin D. *Endoscopy* (2007)	Music in the endoscopy suite: a meta-analysis of randomized controlled studies	Not treatment or rehabilitation
Richards T. *Medsurg Nurs* (2007)	The effect of music therapy on patients' perception and manifestation of pain, anxiety, and patient satisfaction	Not SR based on RCTs
Vanderboom T. *J Radiol Nurs* (2007)	Does music reduce anxiety during invasive procedures with procedural sedation? An integrative research review	Not SR based on RCTs
Lim PH. *Int Nurs Rev* (2006)	Music as nursing intervention for pain in five Asian countries	Not SR based on RCTs
Ostermann T. *Expert Rev Neurother* (2006)	Music therapy in the treatment of multiple sclerosis: a comprehensive literature review	Not SR based on RCTs
Dileo C. *J Soc Integr Oncol* (2006)	Effects of music and music therapy on medical patients: a meta-analysis of the research and implications for the future	Not SR based on RCTs
Sung HC. *J Clin Nurs* (2005)	Use of preferred music to decrease agitated behaviors in older people with dementia: a review of the literature	Not SR based on RCTs

(*Continued*)

Table S1 *(Continued)*

First author. Journal (Year)	Title	Reason for exclusion
Pelletier CL. *J Music Ther* (2004)	The effect of music on decreasing arousal due to stress: a meta-analysis	Not SR based on RCTs
Whipple J. *J Music Ther* (2004)	Music in intervention for children and adolescents with autism: a meta-analysis	Not SR based on RCTs
Wilkins MK. *Evid Based Nurs* (2004)	Music intervention in the intensive care unit: a complementary therapy to improve patient outcomes	Not SR based on RCTs
Gold C. *J Child Psychol Psychiatry* (2004)	Effects of music therapy for children and adolescents with psychopathology: a meta-analysis	Not SR based on RCTs
Silverman MJ. *J Music Ther* (2003)	The influence of music on the symptoms of psychosis: a meta-analysis	Not treatment or rehabilitation
Standley JM. *J Pediatr Nurs* (2002)	A meta-analysis of the efficacy of music therapy for premature infants	Not SR based on RCTs
Evans D. *J Adv Nurs* (2002)	The effectiveness of music as an intervention for hospital patients: a systematic review	Not SR based on RCTs
You ZY. *Acta Academiae Med Sinicae* (2002)	Meta-analysis of assisted music therapy for chronic schizophrenia	Reduplication study/ error of selection
You ZY. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* (2002)	Meta-analysis of assisted music therapy for chronic schizophrenia	Updated or replacement SR
Evans D. *Joanna Briggs Institute Evidence Based Nurs Midwifery* (2001)	Music as an intervention for hospital patients: a systematic review	Not SR based on RCTs
Koger SM. *Cochrane Database Syst Rev* (2000)*	Music therapy for dementia symptoms	Updated or replacement SR
Koger SM. *Cochrane Database Syst Rev* (2000)*	Music therapy for dementia symptoms	Updated or replacement SR
Koger SM. *J Music Ther* (1999)	Is music therapy an effective intervention for dementia? A meta-analytic review of literature	Not SR based on RCTs

Note: *Published and reformed in the same year.
Abbreviations: NICU, neonatal intensive care unit; RCT, randomized controlled trial; SR, systematic review.

A modified Essen stroke risk score for predicting recurrent cardiovascular events: development and validation

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Background **The Essen stroke risk score is widely applied to predict the risk of recurrent ischemic stroke. We developed a modified Essen stroke risk score and validated it using a large prospective Effective Vascular Event REduction after STroke (EVEREST) registry including 3588 patients with ischemic stroke in Japan. Patients with cardioembolic stroke were excluded, and follow-up was one-year.**

Methods **The modified Essen stroke risk score was calculated from scores for waist circumference, stroke subtype by etiology, and gender in addition to age, hypertension, diabetes mellitus, previous myocardial infarction, other cardiovascular diseases except myocardial infarction and atrial fibrillation, peripheral artery disease, smoking, and previous stroke or transient ischemic attack. A multiple logistic regression model identified the predictors (each assigned one or two points) and provided c-statistics for the modified Essen stroke risk score. We considered two outcomes, recurrent ischemic stroke and cardiovascular events (defined as the combined outcomes of fatal or nonfatal stroke, myocardial infarction, nonfatal unstable angina, and cardiac death).**

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Results **Recurrent ischemic stroke occurred in 121 patients (3·7%) and cardiovascular events occurred in 133 (4·0%) within a year. The c-statistic (used for discrimination) was 0·632 for recurrent stroke and 0·640 for cardiovascular events. Patients scoring 6 or greater were classified as high risk, otherwise were classified as low risk. Kaplan–Meier analysis revealed that the modified risk score was more predictive than the Essen stroke risk score in both men and women.**

Conclusions **The modified Essen stroke risk score increased the ability of the Essen stroke risk score to predict recurrent cardiovascular events. Patients with a high modified Essen stroke risk score should be candidates for intensified secondary prevention strategies.**

Key words: ischemic stroke, predictive ability, prognosis, risk score, secondary prevention, validation

Introduction

Stroke is an important disabling disease that imposes social burdens such as caregiver expense. According to the Hisayama study conducted in the 1990s, the annual incidence of stroke recurrence is approximately 10% (1). Since the introduction of antihypertensive, lipid lowering, and antiplatelet therapy over 20 years ago, stroke recurrence has been declining. The REduction of Atherothrombosis for Continued Health (REACH) registry study found that stroke recurrence was 3·0% annually in 2009 (2).

Identification of high-risk patients using risk score models is important for optimizing the cost–benefit relationship in view of tightening health care budgets. The Framingham risk score is the most famous model used to predict coronary heart disease (3). Another one is the $CHADS_2$ score used to predict cardioembolic ischemic stroke after atrial fibrillation (AF) (4,5). Thus, risk prediction models may be used to identify such high-risk patients.

The ABCD and $ABCD_2$ scores were developed for predicting secondary events after transient ischemic attack (TIA) (6,7). The American Heart Association guidelines recommend the use of the $ABCD_2$ score for patients with TIA to identify those patients at high risk for early recurrence. They also advocate immediate hospitalization and emergent diagnostic evaluation for such patients (8). For the secondary prevention of stroke, the Essen stroke risk score (ESRS) may be the most popular in clinical practice. It was developed for use in the CAPRIE (9) study and validated externally by the REACH registry data (10). The ESRS takes into account such predictors as age, hypertension, diabetes mellitus, previous myocardial infarction (MI), other cardiovascular disease except MI and AF, peripheral artery disease (PAD), smoking, and previous TIA or stroke. The ESRS can easily distinguish the low-risk category (score 0–3) from the high-risk category (score 4 or greater). The Systemic Risk Score Evaluation in Ischemic Stroke Patients (SCALA) adds the ankle-brachial index (11). The Stroke Progress Instrument II deals with predictors that are similar to those above as well as congestive heart failure (12).

Although it is useful for the prediction of recurrent ischemic stroke, the ESRS may not perform well enough according to the low c-statistic (10). Waist-to-hip ratio is a significant risk factor for ischemic stroke (13). Stroke subtype is also considered a risk factor because small artery disease (lacunar infarct) seems to be a less severe etiologic subtype of stroke. Men are also considered to be at higher risk than women. We modified the ESRS taking into account waist circumference, stroke subtype, and gender, validated its use in a large registry of Japanese patients known as the Effective Vascular Event REduction after STroke (EVEREST) registry (14), and compared the discriminatory and predictive accuracy of the modified ESRS to that of the original ESRS.

Methods

The EVEREST is a large prospective registry in Japan of 3588 ischemic stroke patients with up to 12 months of follow-up (14). Patients were 45 years or older and had suffered an episode of noncardioembolic ischemic stroke less than six-months earlier; their modified Rankin scale was less than or equal to grade 2. Stable outpatients were recruited consecutively between January 2007 and May 2008 from 313 sites mainly by general practitioners. The study was conducted in accordance with the Declaration of Helsinki. Its protocol was reviewed and approved by the ethics committee of Keio University Hospital, the institution of the principal investigator (N. S.). The data on patients were collected from the physicians of the participating institutions not from the patients directly. In addition, patients were not identifiable because all identifying information, such as the name or initial of the patient, were expunged from the dataset.

The primary outcome in the EVEREST registry was fatal/nonfatal recurrent ischemic stroke. Secondary outcomes were all-cause mortality, MI, stroke, and PAD. In this study, two outcomes: (a) recurrent ischemic stroke within a year after the occurrence of first ischemic stroke and (b) cardiovascular event (a composite of fatal/nonfatal stroke, MI, nonfatal unstable angina and cardiac death within a year after the occurrence of ischemic stroke), were considered.

As in the ESRS, we first considered age, hypertension, diabetes mellitus, previous MI, other cardiovascular diseases except AF or MI, PAD, smoking, previous stroke, or TIA as independent predictors. In the modified ESRS, we further considered waist circumference greater than 90 cm or not, stroke subtype except small vessel occlusion (lacunar infarct) or not, and gender as independent predictors.

Statistical analysis

Continuous variables are presented as mean with standard deviation or median with interquartile range and categorical

variables as frequencies and percentages. The Student's *t*-test was used for comparison of normally distributed continuous data, and Wilcoxon rank sum test was used for comparison of two groups with non-normally distributed variables. Chi-square test and Fisher's exact test were used for comparison of contingency tables. Multiple logistic regression and its accompanying c-statistic was used to test for the relation between various independent variables and the outcome, and to evaluate the discriminatory ability of various prediction models. The c-statistics were obtained by measuring areas under receiver operating characteristic (ROC) curves (15,16). Each risk factor was scored based on the value for the corresponding standardized beta-coefficient of the logistic regression. Calibration was tested using the Hosmer–Lemeshow goodness-of-fit statistics (17). Kaplan–Meier curves were generated for each stratum by the value of the modified ESRS and compared between the strata using a log-rank test. All analyses were performed with SAS software version 9·2 and JMP 9 (SAS Institute Inc., Cary, NC).

Results

Of the 3588 patients assessed for eligibility, 3452 patients who experienced ischemic stroke were included in the analysis of this study (designed to test and validate the use of the modified ESRS). However, additional patients were excluded from analysis due to missing recurrence data ($n = 160$) or cardiovascular event data ($n = 162$). Within a year after the occurrence of ischemic stroke, 121 patients out of 3292 (3·7%) had a recurrence and 133 patients out of 3290 (4·0%) had a cardiovascular event including recurrent ischemic stroke.

Table 1 compares patients with recurrent stroke to patients without it, and patients with a cardiovascular event to patients without an event. As expected, older, obese, diabetic patients tended to be more prone to recurrent ischemic stroke. Similarly, cardiovascular events appeared to be more prevalent in older, obese, diabetic patients with previous MI.

Table 2 shows the standardized coefficients of predictors (identified as significant by multiple logistic regression) that might be used to predict a future event, and shows the assigned scores that might be used in the scoring system. Although some scores (which were based on the standardized coefficients) were discrepant such as the scores for age 65–75 and greater than 75, we adopted the scores used to calculate the original ESRS including the scores for age, hypertension, diabetes mellitus, previous MI, other cardiovascular diseases except MI and AF, smoker, previous stroke, or TIA. As the prevalence of PAD (0·6%) was very low, no events occurred in the PAD group, and the PAD variable was excluded from the prediction model. Similarly, because all the patients in our sample had strokes, previous stroke or TIA was excluded from the model. However, one point each was given for PAD, previous stroke, or TIA as in the original ESRS.

Table 1 Baseline characteristics

	Recurrent ischemic stroke			Cardiovascular events		
Predictor	Present ($n = 121$)	Absent ($n = 3171$)	*P* value	Present ($n = 133$)	Absent ($n = 3157$)	*P* value
Age, years, median (IQR)	71 (67–77)	70 (62–76)	0·006	72 (67–78)	70 (62–76)	0·002
Male gender, *n* (%)	89 (74)	2114 (67)	0·11	96 (72)	2106 (67)	0·19
Waist circumference, cm, median (IQR)	88 (80–93)	85 (78–90)	0·002	87 (80–93)	85 (78–90)	0·001
Waist circumference ≥90 cm, *n* (%)	48 (40)	858 (27)	0·002	52 (39)	854 (27)	0·002
Hypertension, *n* (%)	90 (74)	2395 (76)	0·77	100 (75)	2383 (75)	0·94
Diabetes mellitus, *n* (%)	47 (39)	822 (26)	0·002	52 (39)	817 (26)	0·0007
Previous myocardial infarction (MI), *n* (%)	5 (4)	79 (2)	0·24	8 (6)	76 (2)	0·010
Atrial fibrillation (AF), *n* (%)	1 (1)	71 (2)	0·52	2 (2)	70 (2)	1·00
Other cardiovascular diseases except MI/AF, *n* (%)	3 (2)	85 (3)	1·00	4 (3)	83 (3)	0·78
Peripheral artery disease, *n* (%)	0 (0)	19 (1)	1·00	0 (0)	19 (1)	1·00
Smoker, *n* (%)	32 (26)	700 (22)	0·26	33 (25)	699 (22)	0·47
Stroke subtype on admission, *n* (%)						
Small artery occlusion	45 (37)	1431 (45)	0·23	47 (35)	1427 (45)	0·051
Large artery atherosclerosis	14 (12)	328 (10)		17 (13)	325 (10)	
Other determined etiology	12 (10)	359 (11)		12 (9)	359 (11)	
Undetermined etiology	50 (41)	1052 (33)		57 (43)	1045 (33)	
Modified Rankin scale, *n* (%)						
0	41 (34)	1220 (38)	0·41	44 (33)	1216 (39)	0·27
1	58 (48)	1420 (45)		64 (48)	1413 (45)	
2	21 (18)	530 (17)		24 (18)	527 (17)	
Systolic blood pressure, mmHg, median (IQR)	136 (123–150)	138 (126–150)	0·95	135 (124–150)	138 (126–150)	0·94
Diastolic blood pressure, mmHg, median (IQR)	78 (72–84)	80 (70–87)	0·38	78 (71–84)	80 (70–87)	0·28