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2013-2018

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EDITORIAL

What is the purpose of launching *World Journal of Meta-Analysis*?

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Abstract

The exponential growth of scientific evidence (*i.e.*, primary research) and the ongoing development of methods to summarize such evidence, such as meta-analyses and mixed treatment comparisons (*i.e.*, secondary research), make the worldwide dissemination of high-quality meta-analyses and pertinent articles a key scientific priority. The *World Journal of Meta-Analysis* will apply an electronic open access publishing approach combined with a timely and thorough peer-review of submitted manuscripts, weighing more on quality than priority, in order to improve the dissemination of systematic reviews and meta-analyses, as well as novelties and advancements in methods related to them, focusing on clinical medicine, but spanning all biomedical, epidemiological, and psychological research fields.

Key words: Evidence-based medicine; Meta-analysis; Meta-regression; Review; Systematic review

Core tip: The exponential growth of scientific evidence and the ongoing development of meta-analyses make the worldwide dissemination of the latter study type a key scientific priority. The *World Journal of Meta-Analysis* will apply an electronic open access publishing approach, in order to improve the dissemination of systematic reviews and meta-analyses, focusing on clinical medicine, but spanning all biomedical, epidemiological, and psychological research fields.

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INTRODUCTION

The scientific literature includes thousands of journals on a extremely wide variety of topics, stemming from scientific methods (*e.g.*, *Bayesian Analysis*) or techniques (*e.g.*, *Magnetic Resonance Imaging*) to specific clinical topics (*e.g.*, *Stroke*). In an era dominated by online bibliometric resources and fast dissemination and accrual of scientific evidence, it is becoming increasingly difficult to remain abreast of the most recent scholarly developments. This is one of the main reasons for the success of secondary research, *i.e.*, any form of scholarly activity which aims to appraise and summarize specific research publications (*i.e.*, primary research)[1,2].

Within the context of secondary research, qualitative reviews, defined as viewpoints summarizing the evidence base on a specific scientific topic, conducted without any explicit or validated method, are commonplace. Conversely, systematic reviews are based on explicit and, when possible, validated means to search, select, appraise and summarize the evidence base on a specific scientific topic. Meta-analysis is the method by which primary data, given appropriate methodological approaches, can be summarized, and it is best undertaken in the context of a sys-

tematic retrieval of the literature[3]. Finally, more advanced types of secondary research endeavors include meta-regression analyses, cumulative meta-analyses, individual patient-level meta-analyses, overview of systematic reviews, and mixed treatment comparisons. The latter study type, also known as network meta-analyses, appears very promising and, despite obvious methodological limitations which still require ample research, capable of powerful evidence synthesis[4-8].

The success of reviews, systematic reviews, and meta-analyses is well testified by the fact that this research design has grown exponentially in recent decades, outpacing, at least in relative terms, all other research designs, and it is the most likely to be quoted once published[9-11]. Despite such ongoing success and impact among both researchers and readers, until recently journals devoted specifically to publishing systematic reviews and meta-analyses were lacking. However, with the creation of *Systematic Reviews* in February 2012[12], and the birth of the *World Journal of Meta-Analysis* (*World J Meta-Anal*, *WJMA*, ISSN 2308-3840, DOI: 10.13105) today, accessibility and retrieval of important, and peer-reviewed meta-analyses are set to improve. The *WJMA* Editorial Board has now been established and consists of 402 distinguished experts from 41 countries.

It is not casual that both journals are seeing their light within the electronic open access publication framework. This novel approach, unheard of just a decade ago, is revolutionizing the way evidence is created and disseminated, by putting increasing emphasis on readers downloading, using and commenting on articles, in addition to other researchers later studying and quoting them, rather than on peer-reviewers and editors, who are used to appraise them before full publication. This paradigm shift is well exemplified by the ongoing success of *PLOS ONE*, an open access journal published without any editorial regard for priority. In such scenario, we strongly believe that meta-analyses and similar scholarly efforts to summarize scientific evidence will become more and more important, and thus merit a specific and protected scholarly haven. This is what we, as Editors-in-Chief of the *WJMA*, strive to do.

Among the key advantages of meta-analyses are the cost-effectiveness, ability to maximize statistical power, bolster external validity, appraise clinical and statistical consistency, and explore effect modifiers or moderators, including small study effects (*e.g.*, publication bias) and important patient or study features[13,14]. Despite such important pros, meta-analyses have been criticized as well, citing among the potential disadvantages the inability to correct flaws already present in the original studies, the risks of ecological fallacy and spurious precision, and the fact that an average effect estimate may not be easily applicable to the individual case which is faced in real-world practice[15]. Despite these important drawbacks, it is clear that researchers and readers worldwide trust meta-analyses as a reasonably sound and rigorous research design, and the ongoing accumulation of new methods and refinements in the underlying statistical methods will improve them further, bolstering our optimism concerning their current and future scholarly role.

AIM AND SCOPE

WJMA is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians, with a specific focus on meta-analysis, systematic review, mixed-treatment comparison, meta-regression, and overview of reviews.

The primary task of *WJMA* is to rapidly publish high-quality basic research, clinical studies, methodology or scientific theory in diverse areas of biomedical sciences, Editorial, Frontier, Field of Vision, Minireviews, Review, Topic Highlight, Medical Ethics, and Meta-Analysis. *WJMA* covers a variety of clinical medical fields including allergy, anesthesiology, cardiac medicine, clinical genetics, clinical neurology, critical care, dentistry, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology and hepatology, geriatrics and gerontology, hematology, immunology, infectious diseases, internal medicine, obstetrics and gynecology, oncology, ophthalmology, orthopedics, otolaryngology, pathology, pediatrics, peripheral vascular disease, psychiatry, radiology, rehabilitation, respiratory medicine, rheumatology, surgery, toxicology, transplantation, and urology and nephrology, while maintaining its unique dedication to systematic reviews and meta-analyses.

WJMA is dedicated to become an influential and prestigious journal in meta-analysis, to promote the development of the above disciplines, and to improve the diagnostic and therapeutic skills and expertise of clinicians.

WJMA is edited and published by Baishideng Publishing Group (BPG). BPG has a strong professional editorial team composed of science editors, language editors and electronic editors. BPG currently publishes 42 open access clinical medical journals, and is one of the leading medical publishers, with first-class editing and publishing capacity and production.

CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJMA* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the study is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

COLUMNS

The columns in the issues of *WJMA* will include: (1) Editorial: The editorial board members are invited to make

comments on an important topic in their field in terms of its current research status and future directions to lead the development of this discipline; (2) Frontier: The editorial board members are invited to select a highly cited cutting-edge original paper of his/her own to summarize major findings, the problems that have been resolved and remain to be resolved, and future research directions to help readers understand his/her important academic point of view and future research directions in the field; (3) Field of Vision: The editorial board members are invited to write commentaries on classic articles, hot topic articles, or latest articles to keep readers at the forefront of research and increase their levels of clinical research. Classic articles refer to papers that are included in Web of Knowledge and have received a large number of citations (ranking in the top 1%) after being published for more than 2 years, reflecting the quality and impact of papers. Hot topic articles refer to papers that are included in Web of Knowledge and have received a large number of citations after being published for no more than 2 years, reflecting cutting-edge trends in scientific research. Latest articles refer to the latest published high-quality papers that are included in PubMed, reflecting the latest research trends. These commentary articles should focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions. Basic information about the article to be commented will be provided as well (including authors, article title, journal name, year, volume, and inclusive page numbers; (4) Minireviews: The editorial board members are invited to write short reviews on recent advances and trends in research to provide readers; (5) Review: To make a systematic review to focus on the status quo of research, the most important research topics, the problems that have now been resolved and remain to be resolved, and future research directions; (6) Topic Highlight: The editorial board members are invited to write a series of articles (7-10 articles) to comment and discuss a hot topic; (7) Meta-Analysis: Covers the systematic review, mixedtreatment comparison, meta-regression, and overview of reviews, in order to summarize a given quantitative effect, *e.g.*, the clinical effectiveness and safety of clinical treatments by combining data from two or more randomized controlled trials, thereby providing more precise and externally valid estimates than those which would stem from each individual dataset if analyzed separately from the others; (8) Medical Ethics: The editorial board members are invited to write articles about medical ethics to increase readers' knowledge of medical ethics. The topic covers international ethics guidelines, animal studies, clinical trials, organ transplantation, *etc.*; (9) Letters to the Editor: To discuss and make reply to the contributions published in *WJMA*, or to introduce and comment on a controversial issue of general interest; (10) Book Reviews: To introduce and comment on quality monographs; and (11) Autobiography: The editorial board members are invited to write their autobiography to provide readers with stories of success or failure in their scientific research career. The topic covers their basic personal information and information about when they started doing research work, where and how they did research work, what they have achieved, and their lessons from success or failure.

THE CASE FOR THE *WJMA*

So, who would benefit from submitting a manuscript to the *WJMA* and who should read it? Anyone reporting a meta-analysis, systematic review, mixed-treatment comparison, meta-regression, overview of reviews, or network meta-analysis in any medical-related field is invited to submit his or her work to the *WJMA*. This holds also true for anyone wishing to publish the protocol of any of the above studies, but also for all authors who want to discuss meta-analyses published elsewhere, or exploit meta-analytic methods to appraise other important scientific issues, such as is done in meta-epidemiologic enquiries. Manuscripts focusing on meta-analytic methods are also welcome as developments and improvements in the way meta-analyses are conducted and reported occur with increasing frequency. Indeed, our mission is also to make presentation of results of meta-analyses more easily understandable by the reader. This goal might be achieved by explicitly publishing technical papers, which could also be in the form of simple and clear education papers. While the Editors-in-Chief are skilled and practice routinely clinical medicine and epidemiology, the *WJMA* aims for a broader scope, which build upon its key interest in clinical medicine to include also all biomedical, epidemiological, and psychological research fields.

Accordingly, anyone interested in meta-analyses or important novelties or advancements related to them within the context of clinical medicine, as well as biomedical, epidemiological, and psychological topics, should read regularly the *WJMA*. Moreover, this journal will prove useful also for anyone wanting a high-quality synthesis of information, such that they do not need to trawl the literature themselves as it will already be summarized for them. As Editors-in-Chief, we will surely enjoy our involvement in this exciting editorial effort, and make a formal oath that thorough yet timely external peer-review will be the rule to all manuscripts received, and that quality will always have the upper hand on priority in shaping the editorial decision.

CONCLUSION

In conclusion, the *WJMA* aims to provide for both authors and readers a friendly yet authoritative scholarly framework for the dissemination of meta-analyses and important scientific advancements related to them within the field of medicine, as well as all ancillary disciplines, in keeping with the comprehensive effort of improving dissemination of high-quality science by BPG.

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EDITORIAL

Meta-analyses in the wonderland of neurology

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Abstract

Meta-analyses are often misused and underused in neurology. This editorial provides some comments on the role of meta-analyses in neurological research. Recently, a huge increase in the number of meta-analyses and systematic reviews has been observed in neurological journals. The major strengths of meta-analyses are the increase of statistical power. However, as for any other investigative tool, meta-analytic research is a research method itself which can produce severe shortcomings. Specifically, the issues of search terms, time periods of published studies, databases used for searching, the definitions of inclusion and exclusion criteria for papers (which greatly affect clinical heterogeneity), publication bias; and the statistical methods used, dramatically influence the results of meta-analyses. The main problem of meta-analyses is that they cannot be expected to overcome the limitations of the studies they include (the so-called "garbage in, garbage out" phenomenon). Furthermore, most systematic reviews in the neurological literature lead to the unsatisfying and clinically frustrating statement "further studies are needed". However it is much more frustrating to see how the gaps in scientific knowledge identified by meta-analyses have not been translated into serious efforts to fill them. Besides their role in evaluating efficacy and tolerability of drugs, meta-analyses may be used to assess diagnostic values of debatable clinical findings, as they represent powerful tools to try to answer questions not posed by individual studies and to settle controversies arising from conflicting claims.

Key words: Clinical evaluation; Epilepsy; Meta-analysis; Migraine; Neurology

Core tip: Besides their role in evaluating efficacy and tolerability of drugs, meta-analyses may be used to assess diagnostic values of debatable clinical findings, as they represent powerful tools to try to answer questions not posed by individual studies and to settle controversies arising from conflicting claims.

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META-ANALYSES AND THE NEUROLOGICAL UNANSWERED QUESTIONS

It is both astonishing and frustrating to consider how much meta-analyses are misused and underused in neurological research.

As a young neurology resident, I used to consider experienced neurologists as enlightened, trustworthy and

truth holding people. After gaining some clinical experience in neurology and in evidence-based practice, I learnt to mistrust self assured people without worries, as I realized that truth does not exist in medicine, as it is an asymptotic process[1], not a divine revelation. Similarly, certainty in medicine does not exist, only probability does.

Neurology is probably the field of medicine most burdened with dilemmas on several crucial aspects of pathophysiology, diagnosis, and treatment of a number of diseases. Consider for instance the pathophysiological mechanisms involved in Alzheimer's disease, the questionable therapeutical strategies against multiple sclerosis, and the endless discussions on cortical excitability in migraine or epilepsy. Questions in neurology seem to be much more than answers and as for the Holy Grail, the quest for definite conclusions is hard to be achieved but nevertheless remains an urgent need.

NEUROLOGICAL META-ANALYSES: REASONS FOR SUCCESS

Recently, a huge increase in the number of meta-analyses and systematic reviews has been observed in neurological journals. For instance, the number of articles published in four major neurological journals (*Brain*; *Annals of Neurology*; *Neurology*; and *Journal of Neurology, Neurosurgery, and Psychiatry*) increased from only 53 (1993-2002) to 187 (2003-2012)!

Such a great proliferation of meta-analyses may be easily understood: because of its inflated sample size, meta-analyses can detect treatment effects with greater statistical power, estimating these effects with greater precision than any single study.

SOME PITFALLS OF META-ANALYSES

However, improper use of meta-analyses may lead to erroneous conclusions regarding treatment efficacy. In fact, as for any other investigative tool, meta-analysis is a research method itself which can produce severe shortcomings.

Specifically, the issues of search terms, time periods of published studies, databases used for searching, the definitions of inclusion and exclusion criteria of papers (which greatly affect clinical heterogeneity), publication bias; and the statistical methods used, dramatically influence the results of meta-analyses.

Readers should be well aware of these pitfalls. After all, meta-analyses are human constructs, and as such they are fallible. All that glitters isn't gold!

The main problem of meta-analyses is that they cannot be expected to overcome the limitations of the studies they include (the so-called "garbage in, garbage out" phenomenon). Furthermore, most systematic reviews in neurological literature lead to the unsatisfying and clinically frustrating statement "further studies are needed". However, it is much more frustrating to see how the gaps in scientific knowledge identified by meta-analyses have not been translated into serious efforts to fill them.

ROLE OF META-ANALYSES IN NEUROLOGICAL RESEARCH: SOME PERSONAL EXAMPLES

Despite the above mentioned risks of pitfalls, how can meta-analyses help neurologists in their quest for answers?

As a neurologist dealing with epilepsy and clinical neurophysiology I learnt to use meta-analyses as powerful tools to try to answer questions not posed by individual studies and to settle controversies arising from conflicting claims.

Meta-analyses allowed me not only to evaluate efficacy and tolerability of some neurological treatments[2,3], but also to better understand the diagnostic utility of some debatable clinical findings such as tongue biting, urinary incontinence or eye closure in the differential diagnosis of seizures[4-6]. Meta-analyses helped me to shed further light on the role of cortical excitability in the pathophysiology of migraine or idiopathic generalized epilepsies[7-10].

Finally, meta-analysis prompted me to consider the one single point of view of the view of one single point.

Dear neurologists, if there is no answer, just look for it! And may meta-analyses give you a hand!

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MINIREVIEW

Sirturo (Bedaquiline): The first new anti tubercular drug in decades

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Abstract

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis* and is one of the world's deadliest diseases. Multidrug resistant TB (MDR-TB) is a serious form of TB and it implies resistance for at least two essential first-line agents like, Isoniazid and Rifampicin. The US Food and Drug Administration (FDA) granted accelerated approval to Janseen Therapeutics "Sirturo (Bedaquiline)", a diarylquinoline anti mycobacterial drug on December 28, 2012 as part of combination therapy in adults (≥ 18 years) to treat MDR-TB when other alternatives are not available. The FDA also granted Sirturo fast track designation, priority review and orphan-product designation. Bedaquiline inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*.

Key words: Multidrug resistant tuberculosis; Bedaquiline; Sirturo

Core tip: The US Food and Drug Administration granted accelerated approval to Janseen Therapeutics "Sirturo (Bedaquiline)", a diarylquinoline anti mycobacterial drug on December 28, 2012 as part of combination therapy in adults (≥ 18 years) to treat multidrug resistant tuberculosis when other alternatives are not available.

Undela K. Sirturo (Bedaquiline): The first new anti tubercular drug in decades. *World J Meta-Anal* 2013; 1(1): 8-9 Available from: URL: http://www.wjgnet.com/2308-3840/full/v1/i1/8.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i1.8

INTRODUCTION

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis* and is one of the world's deadliest diseases. According to the Centers for Disease Control and Prevention, nearly 9 million people around the world and 10528 people in the United States became sick with TB in 2011.

Multidrug resistant TB (MDR-TB) is a serious form of TB and it implies resistance for at least two essential first-line agents, like Isoniazid and Rifampicin. MDR-TB is a possibly fatal disease that affects as many as 630000 people worldwide who cannot be cured with existing therapies alone and it is considered an orphan disease in the US, with 98 reported patients in 2011. The World Health Organisation estimates more than two million people will develop MDR-TB between 2011 and 2015.

The US Food and Drug Administration (FDA) granted accelerated approval to Janseen Therapeutics "Sirturo (Bedaquiline)"[1], a diarylquinoline anti mycobacterial drug on December 28, 2012 as part of combination therapy in adults (≥ 18 years) to treat MDR-TB when other alternatives are not available and it leads to the approval of the first TB therapy in 40 years with a new mechanism of action. The FDA also granted Sirturo fast track designation, priority review and orphan-product designation (Figure 1)[2].

MECHANISM OF ACTION

Bedaquiline inhibits mycobacterial ATP (adenosine 5'-tri-

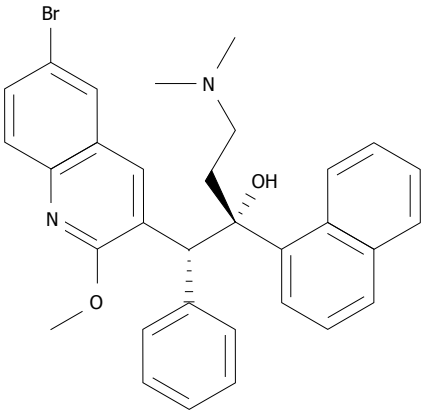

Figure 1 Chemical constitution of "Sirturo (Bedaquiline)".

phosphate) synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*.

MECHANISMS OF RESISTANCE

Mycobacterial resistance mechanisms that affect Bedaquiline include modification of the atpE target gene. Not all isolates with increased minimum inhibitory concentrations have atpE mutations, suggesting the existence of at least one other mechanism of resistance.

SPECTRUM OF ACTIVITY

Bedaquiline has been shown to be active against most isolates of *Mycobacterium tuberculosis*.

SAFETY AND EFFECTIVENESS

Bedaquiline's safety and effectiveness were established in 440 patients in two phase 2 clinical trials. Patients in the first trial were randomly assigned to be treated with Sirturo plus other drugs used to treat MDR-TB (Sirturo treatment group) (n = 79), or a placebo plus other drugs used to treat MDR-TB (placebo treatment group) (n = 81); the other drugs used to treat MDR-TB consisted of a combination of five other antimycobacterial drugs (ethionamide, kanamycin, pyrazinamide, ofloxacin and cycloserine/terizidone or available alternative). Sirturo was administered as 400 mg once daily for the first 2 wk and as 200 mg three times per week for the following 22 wk. After the 24 wk study drug (Sirturo or placebo) treatment phase, patients continued to receive their other drugs used to treat MDR-TB until total treatment duration of 18 to 24 mo was achieved, or at least 12 mo after the first confirmed negative culture. All patients in the second trial, which is ongoing, received Sirturo plus other MDR-TB drugs. In both studies, the primary endpoint was time to sputum culture conversion (SCC), defined as the interval in days between the first dose of the study drug and the date of the first of two consecutive negative sputum cultures collected at least 25 d apart during treatment.

Results from the first trial showed that patients treated with Sirturo combination therapy achieved SCC in a median time of 83 d, compared with 125 d in patients treated with placebo combination therapy. According to these results, 77.6% of patients in the treatment group reached treatment success after 24 wk compared with 57.6% of those in the placebo group. Results from the second trial showed the median time to SCC was 57 d, supporting the efficacy findings of the first trial.

ADVERSE DRUG REACTIONS

Sirturo carries a boxed warning, alerting patients and health care professionals that the drug can affect the heart's electrical activity (QT prolongation) and also notes that an increased risk of death was seen in the Sirturo treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Sirturo should only be used when an effective treatment regimen cannot otherwise be provided.

The most common adverse reactions reported in > 10% of patients treated with Sirturo are nausea, arthralgia and headache. Additional adverse events reported in ⩾ 10% of patients treated with Sirturo and with a higher frequency than the placebo treatment group are hemoptysis and chest pain. More hepatic-related adverse drug reactions were reported with the use of Sirturo plus other drugs used to treat TB compared to other drugs used to treat TB without the addition of Sirturo.

The safety and efficacy of Sirturo for the treatment of drug-sensitive TB has not been established. In addition, there is no data on the treatment with Sirturo of extrapulmonary TB (*e.g.*, central nervous system).

Sirturo was discovered by researchers at "Janssen" and is currently under review by three regulatory bodies, including the European Medicines Agency (European Union), State Food and Drug Administration (China) and Medicines Control Council (South Africa).

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Ascorbic acid and low-volume polyethylene glycol for bowel preparation prior to colonoscopy: A meta-analysis

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Abstract

AIM: To evaluate the benefits of low-volume polyethylene glycol (PEG) with ascorbic acid compared to full-dose PEG for colonoscopy preparation.

METHODS: MEDLINE, Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, CINAHL, PubMed, and recent abstracts from major conferences were searched (January 2012). Only randomized-controlled trials on adult subjects comparing low-volume PEG (2 L) with ascorbic acid *vs* full-dose PEG (3 or 4 L) were included. Meta-analysis for the efficacy of low-volume PEG with ascorbic acid and full-dose PEG were analyzed by calculating pooled estimates of number of satisfactory bowel preparations as well as adverse patient events (abdominal pain, nausea, vomiting). Separate analyses were performed for each main outcome by using OR with fixed and random effects models. Heterogeneity was assessed by calculating the I^2 measure of inconsistency. RevMan 5.1 was utilized for statistical analysis.

RESULTS: The initial search identified 242 articles and trials. Nine studies (n = 2911) met the inclusion criteria and were analyzed for this meta-analysis with mean age range from 53.0 to 59.6 years. All studies were randomized controlled trials on adult patients comparing large-volume PEG solutions (3 or 4 L) with low-volume PEG solutions and ascorbic acid. No statistically significant difference was noted between low-volume PEG with ascorbic acid and full-dose PEG for number of satisfactory bowel preparations (OR 1.07, 95%CI: 0.86-1.33, P = 0.56). No statistically significant difference was noted between low-volume PEG with ascorbic acid and full-dose PEG for abdominal pain (OR 1.09, 95%CI: 0.81-1.48, P = 0.56), nausea (OR 0.70, 95%CI: 0.49-1.00, P = 0.05), or vomiting (OR 0.99, 95%CI: 0.78-1.26, P = 0.95). No publication bias was noted.

CONCLUSION: Low-volume PEG with the addition of ascorbic acid demonstrates no statistically significant difference to full-dose PEG for satisfactory bowel preparation and side-effects.

Key words: Polyethylene glycol; Ascorbic acid; Colonoscopy; Meta-analysis; Bowel preparation

Core tip: Optimal visualization of the colon during colonoscopy requires adequate bowel preparation that is effective and tolerable to the patient. Low-volume polyethylene glycol (PEG) preparation coupled with ascorbic acid has been utilized to enhance patient tolerability without affecting the quality of bowel preparation. This

meta-analysis shows that bowel preparation with low-volume PEG with ascorbic acid does not differ from full-dose PEG for quality of bowel preparation or patient tolerability.

Godfrey JD, Clark RE, Choudhary A, Ashraf I, Matteson ML, Puli SR, Bechtold ML. Ascorbic acid and low-volume polyethylene glycol for bowel preparation prior to colonoscopy: A meta-analysis. *World J Meta-Anal* 2013; 1(1): 10-15 Available from: URL: http://www.wjgnet.com/2308-3840/full/v1/i1/10.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i1.10

INTRODUCTION

Colorectal cancer (CRC) is the third-leading cause of cancer and second-leading cause of cancer-related deaths in the United States[1]. In 2012, it is estimated that 143460 new cases of CRC will be diagnosed and 51690 deaths will occur secondary to this disease[1]. Given these estimations, it has become increasingly important to screen for and prevent CRC, ideally detecting the disease in an early stage. Colonoscopy has become a widely available screening test for both preventing and detecting CRC and has been recommended as the preferred CRC prevention test by the American College of Gastroenterology (ACG)[2]. Furthermore, colonoscopy is an important tool in the work-up and management of various other conditions including inflammatory bowel disease, lower-gastrointestinal bleeding, and diarrhea[3-6].

To provide optimal visualization of the colonic mucosa during exam, colonoscopy is dependent on an adequate bowel preparation[7,8]. In order to accomplish this, patients are asked to drink, at times, large volumes of colon preparation solutions[9-11]. This large amount of oral intake prior to a colonoscopy can lead to patient discomfort, nausea, vomiting, and poor patient compliance, which, in turn, leads to a poor colon preparation and increased potential for missed lesions and need for repeat colonoscopy[12-14].

Several bowel cleansing preparations have been developed and used over the years. One of the most common preparations is polyethylene glycol (PEG) which was introduced in 1980[15]. The use of PEG generally requires the ingestion of a large volume of solution (usually 4 L). Several studies have investigated the utility of a low-volume PEG solution (2-3 L) with the addition of adjunct therapy such as a laxative or additive[16-18]. More specifically, some studies have compared a standard PEG preparation to a low-volume PEG preparation coupled with ascorbic acid, acting as an osmotic laxative[19-27]. The low-volume of PEG solution used in these studies has been theorized to decrease patient side-effects and improve patient compliance, resulting in a higher quality of bowel preparation. Therefore, we conducted a meta-analysis to compare low-volume PEG solution with ascorbic acid to standard volume PEG solution for bowel preparation for colonoscopy.

MATERIALS AND METHODS

Study selection criteria

All randomized controlled trials (RCTs) on adult patients comparing large-volume PEG solutions (3 or 4 L) with low-volume PEG solutions and ascorbic acid were included in our analysis.

Data collection and extraction

A three-stage search method was utilized to maximize search results. First, a comprehensive search was performed in MEDLINE, Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, CINAHL, PubMed in January 2012. Second, references of the retrieved articles and reviews were manually searched for any additional articles. Third, a manual search of abstracts submitted to the Digestive Disease Week and the ACG national meetings was performed from 2003-2011. All articles were searched irrespective of language, publication status (articles or abstracts), or results. The search terms used were PEG and ascorbic acid. Only randomized-controlled trials on adult subjects that compared low-volume PEG (2 L) with ascorbic acid *vs* full-dose PEG (3 or 4 L) were included. Standard forms were used to extract data by two independent reviewers. Each study was evaluated by a Jadad score[28] and criteria based on Jüni *et al*[29] to assess the quality of the study.

Statistical analysis

A meta-analysis was performed comparing the efficacy of low-volume PEG with ascorbic acid and full-dose PEG by calculating pooled estimates of number of satisfactory bowel preparations as well as adverse patient events including abdominal pain, nausea, and vomiting. Separate analyses were performed for each main outcome by using OR with fixed and random effects models which was considered significant if $P < 0.05$ and 95%CI does not include 1. Heterogeneity among studies was assessed by calculating I^2 measure of inconsistency which was considered significant if $P < 0.10$ or $I^2 > 50\%$. If heterogeneity was statistically significant, a study elimination analysis was utilized to examine for heterogeneity when certain studies were excluded from the analysis. RevMan 5.1 was utilized for statistical analysis. Publication bias was assessed by funnel plots.

RESULTS

The initial search identified 242 articles and trials (Figure 1). Nine studies satisfied the inclusion criteria ($n = 2911$) with a mean age range from 53.0 to 59.6 years. Table 1 shows a summary of the details for each study including the low-volume and full-dose preparations. All studies used 2 L PEG with ascorbic acid *vs* 3 or 4 L PEG solutions.

Bowel preparations

Eight studies examined the number of satisfactory bowel

Table 1 Details of studies included in the meta-analysis

Author	Type of study	Blinding	Location	No. of patients	Low-volume bowel preparation	Full-dose bowel preparation	Jadad Score
Clark *et al*[27] 2007	RCT Abstract	Single	Not specified	294	2 L PEG with ascorbic acid	4 L PEG	1
Ell *et al*[24] 2008	RCT	Single	Germany	308	2 L PEG with ascorbic acid	4 L PEG	3
Lee *et al*[26] 2008	RCT Abstract	Single	Not specified	56	2 L PEG with ascorbic acid	4 L PEG	1
Corporaal *et al*[22] 2010	RCT	Single	Netherlands	307	2 L PEG with ascorbic acid	4 L PEG	2
Marmo *et al*[23] 2010	RCT	Single	Italy	433	2 L PEG with ascorbic acid	4 L PEG	3
Pontone *et al*[19] 2011	RCT	Single	Italy	130	2 L PEG with ascorbic acid	4 L PEG with Simethicone	3
Jansen *et al*[21] 2011	RCT	Single	Netherlands	370	2 L PEG with ascorbic acid +/- Simethicone	4 L PEG +/- Simethicone	3
González-Méndez *et al*[25] 2011	RCT Abstract	Single	Spain	681	2 L PEG with ascorbic acid + Bisacodyl	3 L PEG + Bisacodyl	1
Valiante *et al*[20] 2012	RCT	Single	Italy	332	2 L PEG with ascorbic acid	4 L PEG	3

PEG: Polyethylene glycol; RCT: Randomized controlled trial.

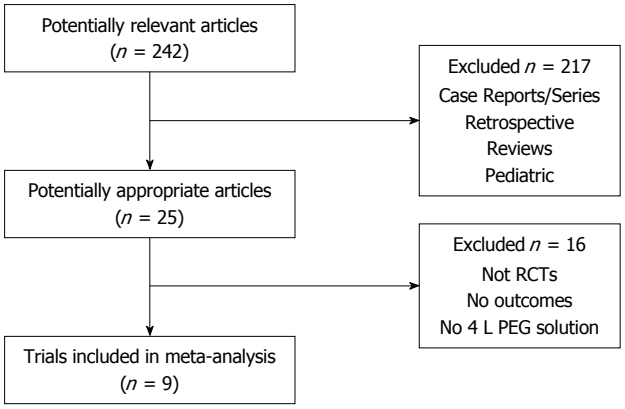

Figure 1 Article search results for this meta-analysis. PEG: Polyethylene glycol; RCT: Randomized controlled trial.

preparations (n = 2478)[19-22,24-27]. Among these 2478 patients, it was found that 1891 had a satisfactory bowel preparation with 950 in the 2 L PEG with ascorbic acid group and 941 in the full-dose PEG group. No statistically significant difference between the two groups was found when evaluating for satisfactory bowel preparation (OR 1.07, 95%CI: 0.86-1.33, P = 0.56). Figure 2 shows the Forest plot for satisfactory bowel preparations. No statistically significant heterogeneity was observed (I^2 = 42%, P = 0.10).

Five studies examined the number of poor bowel preparations (n = 1447)[19-22,24]. Figure 3 shows the Forest plot for these results. There was no significant difference for poor bowel preparation (OR 0.73, 95%CI: 0.48-1.11, P = 0.14) between the two groups. No significant heterogeneity was noted in the poor bowel preparation group (I^2 = 0%, P = 0.64).

Gastrointestinal side effects

Gastrointestinal side effects including abdominal pain[19-24] (n = 1880), nausea[19,20,22-24] (n = 1510), and vomiting[19,20,22-25] (n = 2191) were analyzed. No statistically significant difference was found for abdominal pain (OR 1.09, 95%CI: 0.81-1.48, P = 0.56) or vomiting (OR 0.99, 95%CI: 0.78-1.26, P = 0.95) (Table 2). A trend was noted for less nausea in the 2 L with ascorbic acid as compared to full-dose PEG; however, no statistical significance was reached (OR 0.70, 95%CI: 0.49-1.00, P = 0.05).

Table 2 Outcomes of side effects analyzed between low-volume polyethylene glycol with ascorbic acid and full-dose polyethylene glycol before colonoscopy

Side effect	OR	95%CI	*P*-value	Significance
Abdominal pain	1.09	0.81-1.48	0.56	NS
Nausea	0.70	0.49-1.00	0.05	NS
Vomiting	0.99	0.78-1.26	0.95	NS

NS: Not significant.

Publication bias

No statistically significant publication bias was noted (Figure 4).

DISCUSSION

Colonoscopy is a widely available and highly useful diagnostic tool for evaluating colonic and terminal ileal disease. Its success largely depends on an adequate bowel preparation to allow a thorough examination of the colonic and ileal mucosa. Various bowel preparations have been developed over the years under the premise that an ideal bowel preparation is one that is palatable to the patient, effective in cleansing quality, relatively small in volume, and tolerated well by patients with minimal adverse gastrointestinal symptoms.

One of the most commonly used bowel preparations has been 4 L of PEG solution. While effective, it requires the patient to consume a large amount of volume over a short period of time, resulting in some that are unable to tolerate the preparation. Due to this large volume, several recent studies, including a meta-analysis, have evaluated the effectiveness of administering the PEG solution in a split-dose with half given the evening before and half given the morning of the procedure[30]. While this study showed an improvement in bowel cleansing and decrease in some gastrointestinal side effects, patients still need to

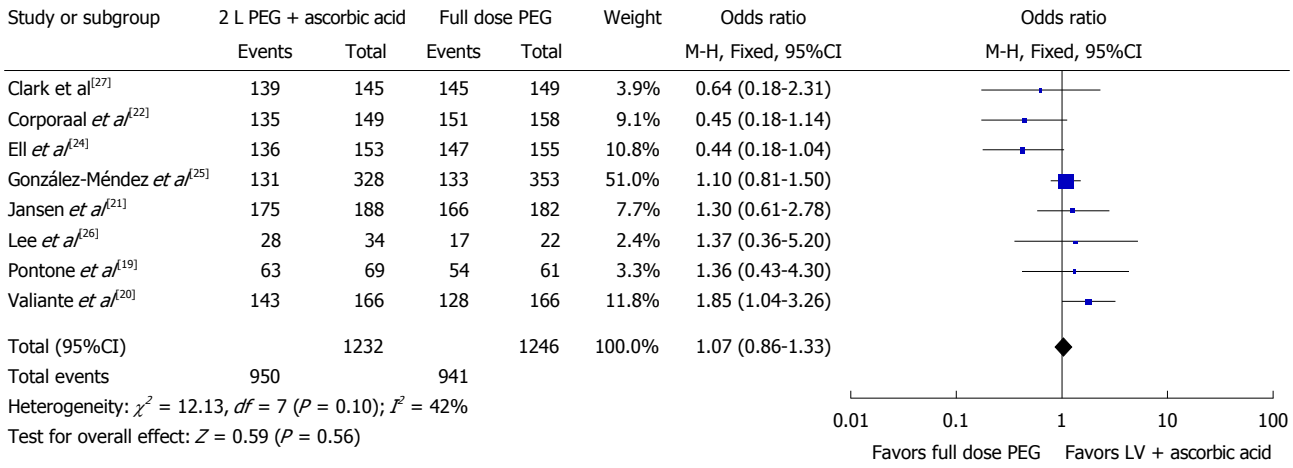

Figure 2 Forest plot for satisfactory bowel preparations between low-volume polyethylene glycol with ascorbic acid compared to full-dose polyethylene glycol. PEG: Polyethylene glycol.

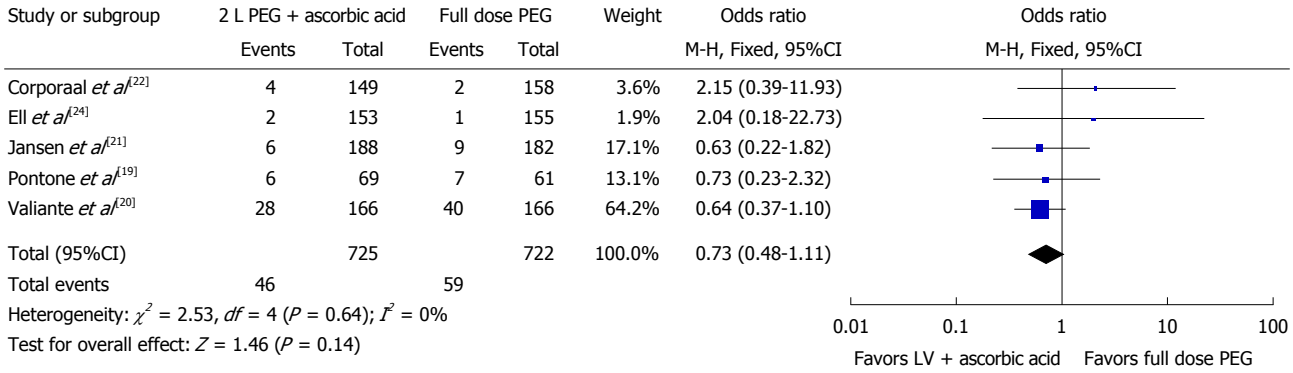

Figure 3 Forest plot for poor bowel preparations between low-volume polyethylene glycol with ascorbic acid compared to full-dose polyethylene glycol. PEG: Polyethylene glycol.

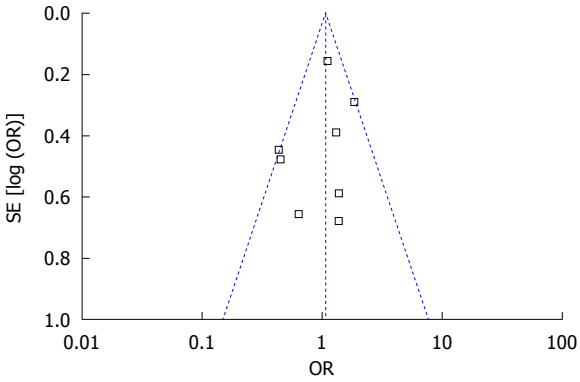

Figure 4 Funnel plot demonstrating no publication bias.

consume 4 L of PEG solution. Other studies have used lower-volume 2 L PEG solutions with various adjuncts including senna, bisacodyl, or magnesium citrate. These studies showed an improvement in tolerability but suggested a decrease in efficacy[16-18]. More recently, several studies have been conducted to evaluate the effectiveness and tolerability of a low-volume 2 L PEG solution with ascorbic acid as compared to full-dose 4 L PEG. These studies suggested that the reduced volume solution is effective in bowel cleansing but may not offer any advantages in reducing potential gastrointestinal side-effects.

Our meta-analysis was conducted to clarify the overall effects of a low-volume 2 L PEG solution with ascorbic acid compared to full-dose 4 L PEG solution. Only RCTs in adult patients were evaluated and used in this study. Based on our findings, low-volume PEG with ascorbic acid was equally effective in producing a satisfactory bowel preparation during colonoscopy, suggesting this to be a reasonable alternative to full-dose 4 L PEG solution with comparable bowel cleansing properties. However, patients receiving the low-volume 2 L PEG solution with ascorbic acid showed a similar pattern in gastrointestinal side effects including abdominal pain, nausea, and vomiting when compared to full-dose 4 L PEG solution, offering no overt advantage. One possible explanation for this is that patients receiving the 2 L PEG solution with ascorbic acid are required to consume an additional 500 mL of clear liquids after each 1 L of solution, totaling 3 L of liquid volume consumed during this preparation. One could argue that this still requires patients to ingest a moderate-to-large amount of fluid during a short period of time.

The strengths of our meta-analysis include the use of RCTs in various populations and end-points that are

significant to clinical practice. This also represents the first meta-analysis performed on this subject. However, a few limitations to this meta-analysis do exist. First, uniformity between the studies in using only 2 L PEG with ascorbic acid and full-dose PEG solution was not consistent among all studies. González-Méndez *et al*[25] used a 3 L PEG solution rather than the typical 4 L PEG solution. This could alter the results as patients ingested an equal volume of liquid (3 L) in both groups. However, if this study was eliminated, the overall results were similar (Satisfactory prep: OR 1.04, 95%CI: 0.75-1.43, P = 0.82). Additionally, a few studies utilized other adjuncts such as bisacodyl[25] and simethicone[19,21]. Given that simethicone is not a laxative, its addition in these studies likely had little impact on the quality of bowel cleansing. However, although bisacodyl is a laxative, it was given to both arms of the study, negating its overall effect. Second, a limited number of studies were used in this meta-analysis; however, all studies to-date were included in this meta-analysis using an extensive search protocol. Third, the quality of the studies was not ideal. As in most bowel preparation studies, it is very difficult to blind the patient. Therefore, these RCT's were single-blinded to the colonoscopist, which is the optimal format for these studies. Also, three of the studies were abstracts with no data regarding method of randomization or blinding, leading to a lower Jadad score. However, these abstract studies were single-blinded randomized trials and due to word limits on abstracts, may not have presented their randomization and blinding techniques, which does not make them any less quality than other bowel prep studies. Finally, slightly different bowel prep rating systems were utilized among studies. However, all studies specifically defined satisfactory or unsatisfactory bowel preparations based upon their specific scale.

In conclusion, our meta-analysis found that a low-volume 2 L PEG solution with ascorbic acid administered for bowel preparation prior to colonoscopy provided equal bowel cleansing when compared to a full-dose 4 L PEG solution. However, the reduced volume of the 2 L PEG solution with ascorbic acid did not provide any benefit when comparing gastrointestinal side-effects including abdominal pain, nausea, and vomiting. Therefore, the low-volume 2 L PEG solution with ascorbic acid can be considered as an appropriate and equally effective bowel preparation prior to colonoscopy but does not appear to offer any advantage over the traditional 4 L PEG solution. Further studies are required to compare the 2 L with ascorbic acid to the newer 4 L split-dose bowel preparation.

COMMENTS

Background

Colorectal cancer (CRC) is a major cause of cancer-related deaths worldwide. Colonoscopy has become a widely available screening test for both preventing and detecting CRC. However, colonoscopy requires an adequate bowel preparation for complete visualization which may induce unwanted side effects and patient discomfort.

Research frontiers

Several studies have compared the standard bowel preparation of 4 L polyethylene glycol (PEG) to a 2 L PEG solution with ascorbic acid. This study is a meta-analysis comparing the above mentioned bowel preparations with regards to adequacy of the bowel preparation as well as patient side-effects during ingestion of the bowel preparation.

Innovations and breakthroughs

This is the first meta-analysis comparing 2 L PEG solution with ascorbic acid to 4 L PEG solution. We found that the 2 L PEG solution with ascorbic acid provided equal bowel cleansing when compared to a full-dose 4 L PEG solution. However, the reduced volume of the 2 L PEG solution with ascorbic acid did not provide any benefit when comparing gastrointestinal side-effects including abdominal pain, nausea, and vomiting.

Applications

The low-volume 2 L PEG solution with ascorbic acid can be considered as an appropriate and equally effective bowel preparation prior to colonoscopy but does not appear to offer any advantage over the traditional 4 L PEG solution.

Terminology

PEG is a common bowel cleansing solution that was first introduced in 1980. Standard bowel preparation using PEG typically involves ingestion of 4 L of solution prior to colonoscopy.

Peer review

This is an interesting study, and a well written paper.

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META-ANALYSIS

Smoking increases risk of tooth loss: A meta-analysis of the literature

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Abstract

AIM: To quantitatively evaluate the impact of smoking on tooth loss.

METHODS: We performed a PubMed search to identify published articles that investigated the risk of tooth loss by smoking, from which RRs and their variance with characteristics of each study were extracted. The random-effects models were used to derive a pooled effect across studies. Potential sources of heterogeneity on the characteristics of the study and their influence on the pooled effect size were investigated using meta-regression models.

RESULTS: We identified 24 studies containing a total of 95973 participants for analysis. The pooled RR of ever-smokers compared with never- smokers was 1.73 (95%CI: 1.60-1.86, $P < 0.001$). In meta-regression analysis, only the mean age of participants alone was identified as a statistically significant source of heterogeneity. The effect of smoking on tooth loss was stronger when the mean age of study participants was higher, indicating possible enhancement of tooth loss due to aging by smoking. RR was significantly lower in former smokers (1.49, 95%CI: 1.32-1.69, $P < 0.001$) than in current smokers (2.10, 95%CI: 1.87-2.35, $P < 0.001$), indicating the substantial benefit of smoking cessation for reducing the risk of tooth loss.

CONCLUSION: Smoking is an independent risk factor for tooth loss regardless of many other confounders. Smoking cessation may attenuate this effect.

Key words: Meta-analysis; Oral health; Relative risk; Smoking; Tooth loss

Core tip: Smoking is known to be a major cause of tooth loss. However, it has never been known how it quantitatively attributes to tooth loss or whether smoking cessation counteracts or not. This study clarified that ever smoking increases risk of tooth loss by 73%. In addition, smoking cessation substantially attenuates this effect.

Sato F, Sawamura M, Ojima M, Tanaka K, Hanioka T, Tanaka H, Matsuo K. Smoking increases risk of tooth loss: A meta-analysis

of the literature. *World J Meta-Anal* 2013; 1(1): 16-26 Available from: URL: http://www.wjgnet.com/2308-3840/full/v1/i1/16.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i1.16

INTRODUCTION

The World Health Organization Global Oral Health Program works to increase awareness of oral health worldwide as an important component of general health and quality of life[1]. A number of studies have investigated the association between tooth loss and cardiovascular diseases, including stroke, atherosclerosis and hypertension[2-8]. Several reviews outlined a possible role for tooth loss in carcinogenesis, independent of other known risk factors[9,10]. Tooth loss is one of the main impediments to oral health; and by affecting the patient's ability to chew and thus altering food choices and the digestive process, may lead to malnutrition[11,12]. The impact of tooth loss can be even more severe, impairing taste, phonetics, and aesthetics, often resulting in limited social and personal interaction[13,14]. A systematic review provided fairly strong evidence that tooth loss is associated with the impairment of oral health-related quality of life[15].

The etiology of tooth loss is complex, and includes factors such as age; sex; body mass index; physical activity; systemic disease, such as osteoporosis and diabetes; socioeconomic status (SES); and oral hygiene behavior[16-21]. Smoking is considered an important risk factor for tooth loss[16,18,19,22-26]. Although numerous studies have consistently reported a positive association, attempts to quantify the association have been hampered by their variation in background factors, such as country of the study, study design, age of participants, sex, and oral hygiene behavior.

The present study aims to: (1) confirm the association between smoking and tooth loss, and to quantify the impact systematically; (2) to confirm the difference in the impact of smoking on tooth loss between former and current smokers; and (3) to investigate the difference in the impact of smoking on tooth loss by the factors above. To our knowledge, this study is the first meta-analysis to quantify the impact of smoking on tooth loss.

MATERIALS AND METHODS

Search strategy

The initial literature search was conducted through PubMed using the free text search term: (tooth loss OR missing tooth OR oral health OR oral hygiene) AND (smoking OR smoke OR cigarette), with publication period updated to July 2010.

We selected candidate studies based on the following inclusion criteria: original article published in English; and the availability of RRs estimates of smoking for tooth loss in the article, namely hazard ratio, risk ratio, or odds ratio, with the reference group consisting of never smokers, and with adjustment for age at least, and their 95%CIs. Two investigators (FS and MS) independently reviewed all potentially relevant articles, and disagreements were resolved by discussion. The reference lists of the studies identified through this process were also checked.

Data extraction

Characteristics extracted from the articles included name of the first author, year of publication, country of study, study design (cohort or cross-sectional study), base population, sex distribution, number of participants, mean age of study population, measure of association (hazard ratio, risk ratio, or odds ratio), point estimate and its 95%CI of RR, adjustment for SES (yes or no), adjustment for behavior associated with oral health (yes or no), and definition of the number of teeth lost.

Data synthesis

For inclusion in quantitative analysis, studies had to provide sufficient data to allow calculation of an effect-size measure and its corresponding measure of variability. Because we extracted multiple estimates from several studies (*e.g.*, using pack-year units or stratified analysis), we pre-pooled RRs to derive one overall RR for each study using fixed-effects estimates weighted by the inverse of their variance as the RR for ever-smokers relative to never-smokers. All analyses were performed on the natural log scale. Because of the widely different methodological approaches used to examine the relationship in the individual studies, we used the random-effects models of DerSimonian-Laird[27] to derive a pooled effect across studies, in which the between-study variance was estimated in addition to the specified within-variance component. We investigated potential sources of heterogeneity on the characteristics of the study and their influence on the pooled effect size using meta-regression models. We examined heterogeneity using Cochrane's Q-test and the I^2 statistic[28]. I^2 can be interpreted as the proportion of the total variation in the estimated slopes for each study due to heterogeneity between studies. Variables considered as potential sources of heterogeneity were the country in which the study was conducted [United States (reference), Japan, Nordic, and others as dummy variables], study design (cohort or cross-sectional), base population (general population or other), sex included in the study (male, female, or both, as dummy variables), mean age of the study population (continuous), adjustment by SES, adjustment by behavior associated with oral health, and definition of the number of teeth lost (continuous).

Publication bias was assessed by a funnel plot with the fitted line corresponding to the regression test for funnel-plot asymmetry proposed by Egger *et al*[29].

All analyses were conducted using the *metan* and *metareg* commands in STATA ver 10.1 (Stata Corporation, College Station, Texas, USA) and were two-sided. Tests were considered statistically significant when the P value were less than 0.05, except in meta-regression analysis, for which we defined a threshold P value of less than 0.1.

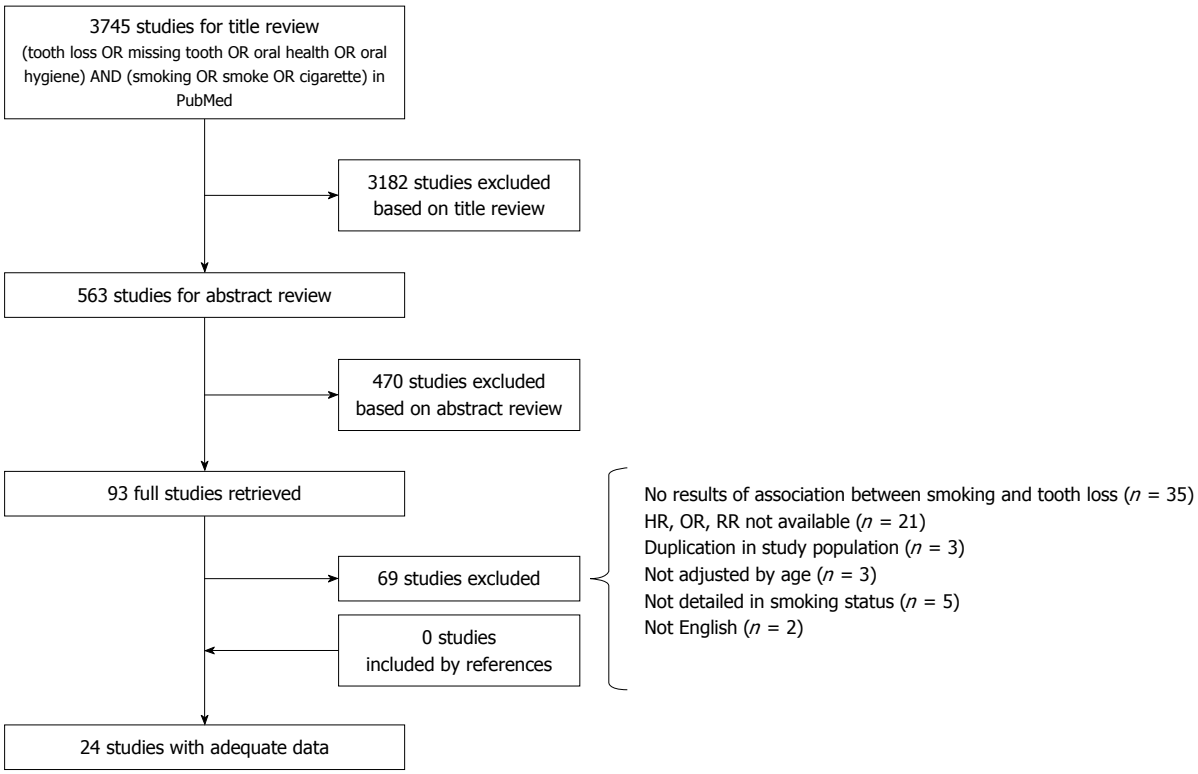

Figure 1 Selection of literature.

RESULTS

Search results

A total of 3745 potentially relevant reports were identified. Of these, 93 full papers were obtained based on title and abstract review (Figure 1), of which 24 with a total of 95973 participants were identified as having sufficient data for inclusion[16-26,30-42].

Table 1 shows the baseline characteristics of participants from each study. By country, seven papers were from the USA, six from Japan, three each from Brazil and Finland, and one each from Sweden, Norway, Germany, Italy, and Australia. Of these, five were cohort studies, with a mean follow-up of 9.4 years; 16 were conducted in general populations; 16 were conducted in both sexes; 15 investigated the risk of tooth loss in current and former *vs* never- smokers; nine investigated the risk of tooth loss in ever- *vs* never-smokers; 15 were adjusted by SES; and 15 were adjusted by behavior associated with oral health. The studies varied in study size (range, 166-8409 for cross-sectional studies, 693-43112 for cohort studies), mean age of the study population (21.5-81.0 years), and definition of the number of teeth lost as a dependent variable. All studies used multivariate analysis to calculate the RR of tooth loss by smoking.

Association between smoking history and risk of tooth loss

Results for the meta-analysis of RRs of tooth loss in ever- *vs* never-smokers are shown in Figure 2. A forest plot of the random-effects model analysis showed that four of the five earliest studies[16-18,30,31] tended to show a higher RR of tooth loss in ever-smokers than those published later. Pooled RR as estimated by the random-effects model was 1.73 (95%CI: 1.60-1.86). Significant heterogeneity was seen between studies, with a P value of < 0.001 and I^2 of 67.4%.

Modifiable factors in smoking history and risk of tooth loss

We used meta-regression analysis to investigate sources of heterogeneity for the relationship between smoking and tooth loss (Table 2). In univariate meta-regression analysis, mean age of the study population ($P = 0.009$) and definition of the number of teeth lost ($P = 0.040$) were identified as potential sources of heterogeneity. Figure 3A and B show the results of meta-analyses sorted by mean age of study population and definition of the number of teeth lost. In multivariate meta-regression with significant modifiers detected by these two variables, mean age of the study population remained as the potentially strongest source of heterogeneity ($P = 0.030$).

Publication bias

We also assessed potential publication bias in selected studies. A funnel plot (Figure 4) shows the distribution of log-transformed RR and standard error in each study, with the fitted line corresponding to the regression test for funnel-plot asymmetry (solid line). Studies with large standard errors with weaker associations seemed less reported; however, the association remained significant even after exclusion of studies with large standard errors greater

Table 1 Baseline characteristics of patients of the 24 included studies

Author (yr)	Country	Study design	Base population	Sex	*n*	Mean age (yr) of subjects	Measure of association	Pattern of comparison (*vs* never smokers)	Relative risk	Adjustment for socioeconomic status	Adjustment for behavior associated with oral health[3]	Definition, No. of tooth loss
Eklund *et al*[16] (1994)	United States	Cohort	General population	M/F	2207	42.0	RR	Ever	1.88 (1.04-3.38)[1]	Yes	Yes	Incidence of tooth loss
Norlén *et al*[18] (1996)	Sweden	Cross-sectional	General population	M	483	68.0	OR	Former	2.60 (1.34-5.03)	Yes	Yes	> 16 loss
								Current	3.02 (1.50-6.07)			
								Ever	2.79 (1.73-4.52)[2]			
Slade *et al*[30] (1997)	Australia	Cohort	General population	M/F	693	73.0	RR	Former	2.55 (1.48-4.40)	No	Yes	Incidence of tooth loss
								Current	2.06 (0.92-4.62)			
								Ever	2.39 (1.52-3.74)[2]			
Suominen-Taipale *et al*[31] (1999)	Finland	Cross-sectional	General population	M/F	213	40.0	OR	Ever	1.4 (1.0-2.0)	Yes	No	28 loss
Xie *et al*[17] (1999)	Finland	Cross-sectional	General population	M/F	293	81.0	OR	Ever	3.12 (1.56-6.23)	No	No	28 loss
Yoshida *et al*[33] (2001)	Japan	Cross-sectional	Petroleum chemical plant employees	M	2015	39.5	OR	Former	1.27 (0.89-1.81)	No	Yes	> 1 loss
								Current	1.54 (1.20-1.96)			
								Ever	1.45 (1.18-1.77)[2]			
Randolph *et al*[32] (2001)	United States	Cross-sectional	General population	M/F	3050	74.1	OR	Former	1.26 (1.04-1.54)	Yes	No	> 14 loss
								Current	1.69 (1.31-2.20)			
								Ever	1.40 (1.20-1.63)[2]			
Ylöstalo *et al*[19] (2004)	Finland	Cross-sectional	General population	M/F	8409	31.0	OR	Ever	1.73 (1.39-2.15)[2]	Yes	Yes	> 6 loss
Cunha-Cruz *et al*[22] (2004)	Brazil	Cross-sectional	University employees	M/F	3840	40.0	OR	Ever	1.62 (1.35-1.96)	Yes	Yes	> 26 loss
Klein *et al*[34] (2004)	United States	Cross-sectional	General population	M/F	2794	65.0	OR	Former	1.57 (1.25-1.98)	Yes	No	> 1 loss
								Current	4.04 (2.52-6.49)			
								Ever	1.88 (1.53-2.31)[2]			
Tanaka *et al*[35] (2005)	Japan	Cross-sectional	Hospital	F	1002	29.8	OR	Former	1.42 (0.91-2.20)	Yes	No	> 1 loss
								Current	1.56 (1.18-2.06)[2]			
								Ever	1.52 (1.20-1.93)[2]			
Susin *et al*[20] (2005)	Brazil	Cross-sectional	General population	M/F	974	48.7	OR	Ever	1.50 (1.18-1.90)[2]	No	No	> 7 loss
Susin *et al*[37] (2006)	Brazil	Cross-sectional	General population	M/F	612	21.5	OR	Ever	1.30 (1.02-1.66)[2]	Yes	No	> 1 loss
Okamoto *et al*[36] (2006)	Japan	Cross-sectional	Hospital	M	1332	43.5	OR	Former	1.11 (0.68-1.85)	No	No	> 1 loss
								Current	1.59 (1.21-2.08)[2]			
								Ever	1.46 (1.15-1.85)[2]			
Krall *et al*[23] (2006)	United States	Cohort	People who received dental care	M	789	49.0	HR	Former	1.3 (0.9-1.7)	Yes	Yes	Incidence of tooth loss
								Current	2.1 (1.5-3.1)			
								Ever	1.7 (1.3-2.2)[2]			
Ojima *et al*[40] (2007)	Japan	Cross-sectional	General population	M/F	1314	30.0	OR					
				Total				Former	0.80 (0.45-1.43)[2]	No	Yes	> 1 loss
								Current	1.91 (1.41-2.59)[2]			
								Ever	1.58 (1.21-2.07)[2]			
				M				Former	1.25 (0.55-2.86)			
								Current	2.21 (1.40-3.50)			
								Ever	1.93 (1.30-2.88)[2]			
				F				Former	0.52 (0.23-1.18)			
								Current	1.70 (1.13-2.55)			
								Ever	1.34 (0.93-1.93)[2]			

Mundt *et al*[24] (2007)	Germany	Cross-sectional	General population	M/F	2501	49.5	OR	Former	1.71 (1.27-2.30)	Yes	Yes	> 26 loss
								Current	2.58 (2.03-3.27)			
								Ever	2.19 (1.82-2.64)[2]			
Dietrich *et al*[25] (2007)	United States	Cohort	Health professional	M	43112	56.0	HR	Former	1.57 (1.53-1.62)[2]	Yes	Yes	Incidence of tooth loss
								Current	2.25 (2.14-2.37)[2]			
								Ever	1.75 (1.69-1.80)[2]			
Hanioka *et al*[38] (2007)	Japan	Cross-sectional	General population	M/F	3999	60.0	OR					
				Total				Former	1.18 (0.87-1.59)	No	Yes	> 20 loss
								Current	2.19 (1.71-2.80)			
								Ever	1.70 (1.40-2.05)[2]			
				M				Former	1.29 (0.92-1.80)			
								Current	2.22 (1.61-3.06)			
								Ever	1.72 (1.36-2.17)[2]			
				F				Former	0.86 (0.46-1.60)			
								Current	2.14 (1.45-3.15)			
								Ever	1.66 (1.19-2.31)[2]			
Musacchio *et al*[39] (2007)	Italy	Cross-sectional	General population	M	1226	76.8	OR	Former	3.42 (2.42-4.82)	Yes	No	28 loss
								Current	4.01 (2.59-6.20)			
								Ever	3.64 (2.77-4.77)[2]			
Haugejorden *et al*[26] (2008)	Norway	Cross-sectional	General population	M/F	1092	47.9	OR	Ever	2.2 (1.3-3.7)	Yes	Yes	> 20 loss
Cunha-Cruz *et al*[41] (2008)	United States	Cohort	People who received dental care	M/F	12631	51.0	RR	Former	1.3 (1.1-1.4)	No	Yes	Incidence of tooth loss
								Current	2.3 (2.0,2.6)			
								Ever	1.8 (1.6-2.0)[2]			
Moedano *et al*[21] (2009)	United States	Cross-sectional	Hospital	M/F	166	69.1	OR	Ever	1.19 (0.49-2.87)	Yes	No	> 10 loss
Yanagisawa *et al*[42] (2010)	Japan	Cross-sectional	General population	M	1088	59.6	OR	Former	1.35 (0.94-1.94)	No	Yes	> 8 loss
								Current	1.67 (1.12-2.50)			
								Ever	1.49 (1.14-1.94)[2]			

[1]Relative risk was calculated from coefficient and standard error; [2]Within-study summary estimate by meta-analysis with fixed effect model; [3]Behaviors associated with oral health include tooth brushing frequencies, existence of periodontal disease at the baseline survey, use of floss, frequency of dental clinic visit and reason for visit and occupation (dentist or not), use of interdental brush, self-check of teeth and gum a using mirror, and experience of tooth brushing instruction. M: Male; F: Female.

than 0.2 (Figure 5). Egger's test also excluded the possibility of publication bias in estimating summary statistics ($P = 0.968$).

Difference in risk of tooth loss between former and current smokers

The potential difference in tooth loss events between former and current smokers was examined by stratified analysis (Figure 6). Nine studies were excluded from analysis because they did not assess the risk in former and current smokers separately. The meta-analysis revealed summary estimates of 1.49 (95%CI: 1.32-1.69) and 2.10 (95%CI: 1.87-2.35) for former and current smokers, respectively, indicating that former smokers have a significantly lower probability of tooth loss than current smokers.

DISCUSSION

This study is the first meta-analysis of the impact of smoking on tooth loss, and includes the difference in impact between former and current smokers. We found an approximately 70% greater risk of tooth loss in ever- than never-smokers. Moreover, we found that former smokers had a statistically significantly lower risk of tooth loss than current smokers, with current smokers showing a 110% increase in risk compared with 49% in former smokers. We also evaluated potential sources of heterogeneity by factors thought

Table 2 Source of heterogeneity by meta-regression analysis

Factors	Univariate			Multivariate		
	Coefficient	SE	*P* value	Coefficient	SE	*P* value
Published year	-0.0063553	0.01429	0.661	-	-	-
Country (*vs* United States)						
Japan	-0.0922341	0.11903	0.447	-	-	-
Finland, Norway, Sweden	0.1485642	0.14826	0.328	-	-	-
Other countries	0.1828302	0.12939	0.173	-	-	-
Study design (cohort *vs* cross-sectional)	0.0667818	0.12342	0.594	-	-	-
Base Population of Study (general population *vs* others)	-0.0761659	0.10297	0.467			
Sex (male *vs* female)						
Male	0.0739773	0.11212	0.517	-	-	-
Female	-0.1176073	0.24732	0.639	-	-	-
Mean age of study population	0.0080805	0.00284	0.009	0.0067276	0.00288	0.030
Adjustment for socioeconomic status (Yes *vs* No)	-0.0723939	0.10375	0.493	-	-	-
Adjustment for behavior associated with oral health (Yes *vs* No)	-0.0054823	0.10733	0.960	-	-	-
Definition number of tooth loss in the study (range: 1-28)	0.0093892	0.00430	0.040	0.0065434	0.00414	0.129

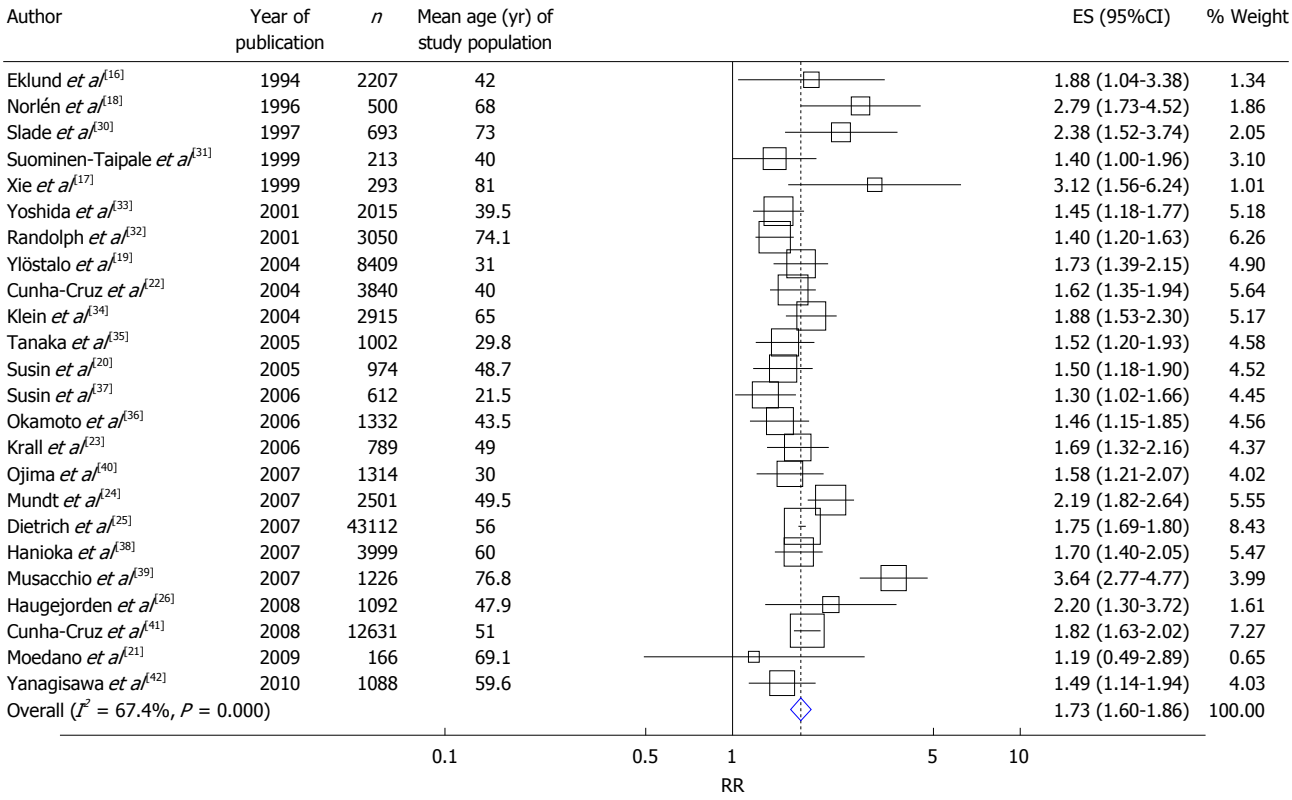

Figure 2 Forest plots of relative risk. The size of the squares corresponds to the weight of the study in the meta-analysis. Combined relative risk was calculated using the random-effects model. Weights are from random effects analysis.

to influence the effect of smoking on tooth loss. Results showed no statistically significant heterogeneity by country (included in the present study), study design, sex, oral health behavior, or SES except age. Although the risk of tooth loss by smoking showed heterogeneity by participant age, RRs of all studies were significantly higher in ever-smokers than in never-smokers, except for one study, which had the smallest number of participants of all studies analyzed[21].

Several mechanisms have been hypothesized to explain the association between smoking and tooth loss. Systemic effects of smoking include dysfunction of gingival fibroblasts, a decrease in microcirculatory function and immune system deficiency *via* effects of chemicals included in tobacco smoke[10,43]. Bacterial organisms in periodontal region are reported to contribute to tissue destruction among smokers[44-46]. These lines of evidences are consistent with findings in this study and are suggestive of importance of implementation of smoking cessation in the dental field[47].

We speculate that several factors might explain why the effect of smoking on tooth loss was modified by age.

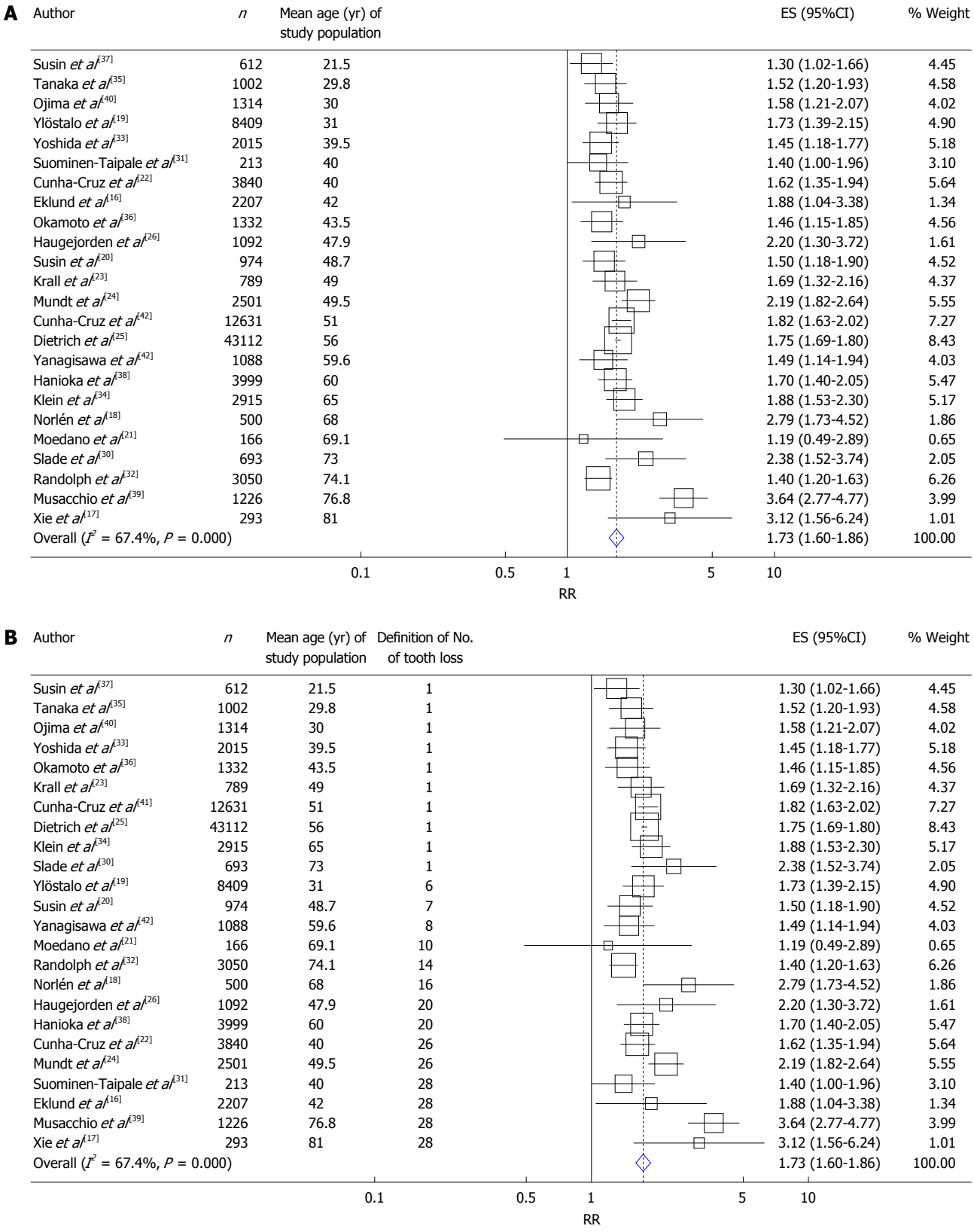

Figure 3 Forest plots of relative risk sorted by mean age of the study population (A) and by the number of teeth lost defined as representing a case (B). A: The size of the squares corresponds to the weight of the study in the meta-analysis. Combined relative risk was calculated using the random-effects model; B: The studies with definition of 1 means those losing one or more teeth were defined as cases. The size of the squares corresponds to the weight of the study in the meta-analysis. Combined relative risk was calculated using the random-effects model. Weights are from random effects analysis.

First, because we did not include data on smoking dose and duration, we could not exclude confounding by these factors. Some studies have indicated that the effect of smoking is dose- and duration-dependent[19,24,25,36]. Par-

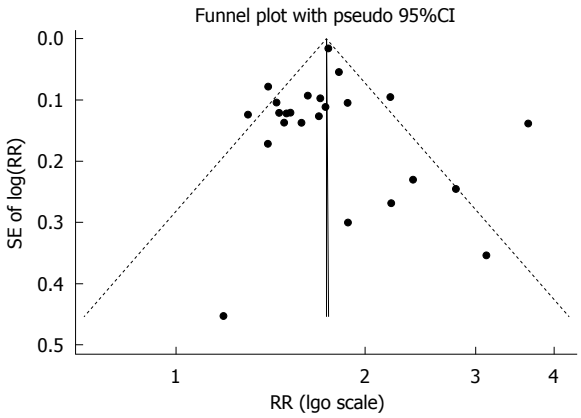

Figure 4 Funnel plot of included studies for the evaluation of publication bias.

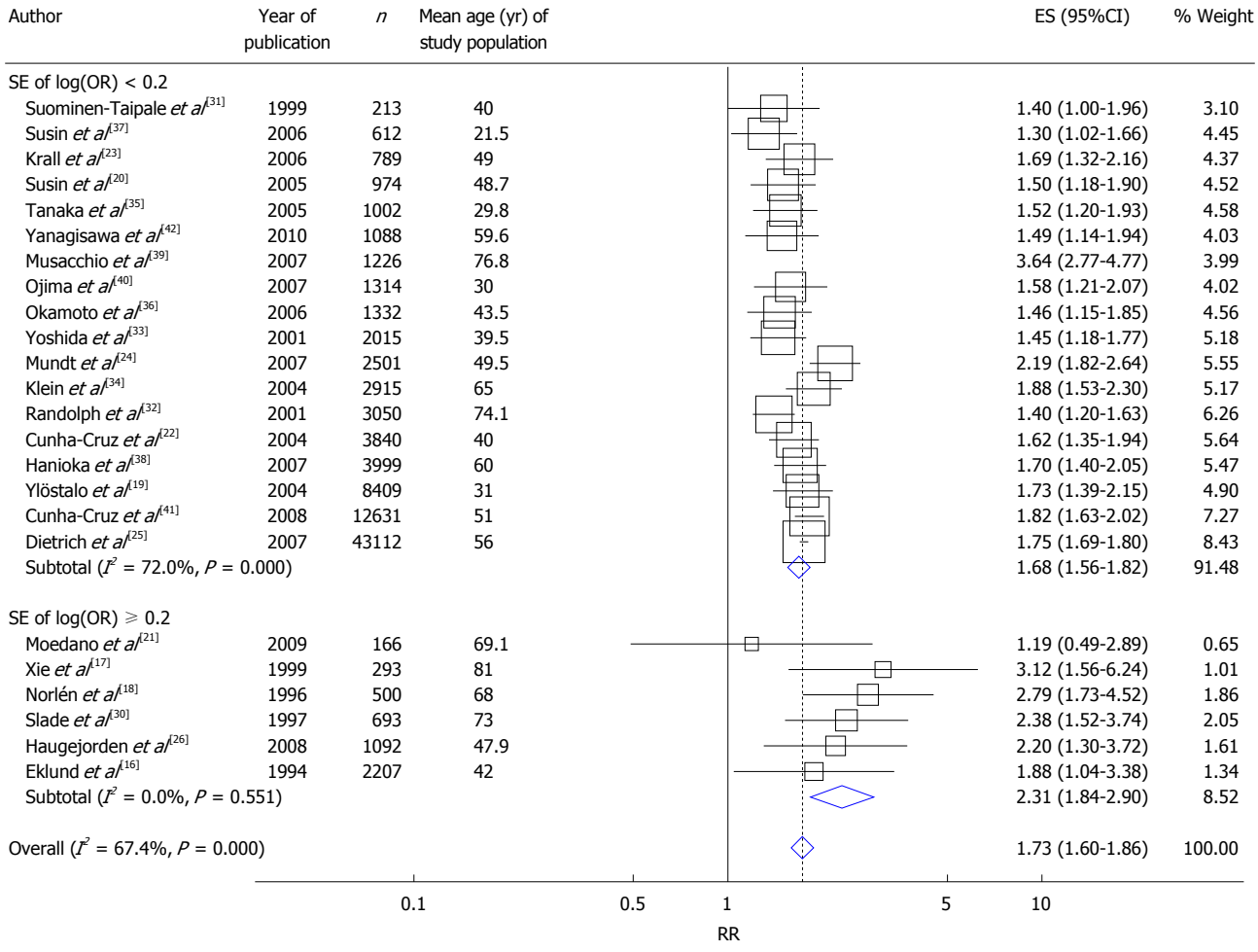

Figure 5 Subset-analysis according to the precision of studies. Weights are from random effects analysis.

ticularly among current smokers, older smokers may also have a lower daily consumption. Second, because tooth loss is a cumulative and irreversible event, older subjects may tend to have fewer teeth than younger smokers, and might therefore tend to be defined as case subjects. Third, chronic diseases such as diabetes and osteoporosis, which are considered as risk factors for tooth loss, may be more prevalent in older than younger people[17,21].

Several technical limitations of this meta-analysis warrant mention. One major limitation is the data source we used. Analyses were based on abstracted rather than individual patient data (IPD). In general, an IPD-based meta-analysis would allow a more robust estimation of the association. Second, the validity of meta-analyses is significantly threatened by potential publication bias. Although we detected no evidence of publication bias using

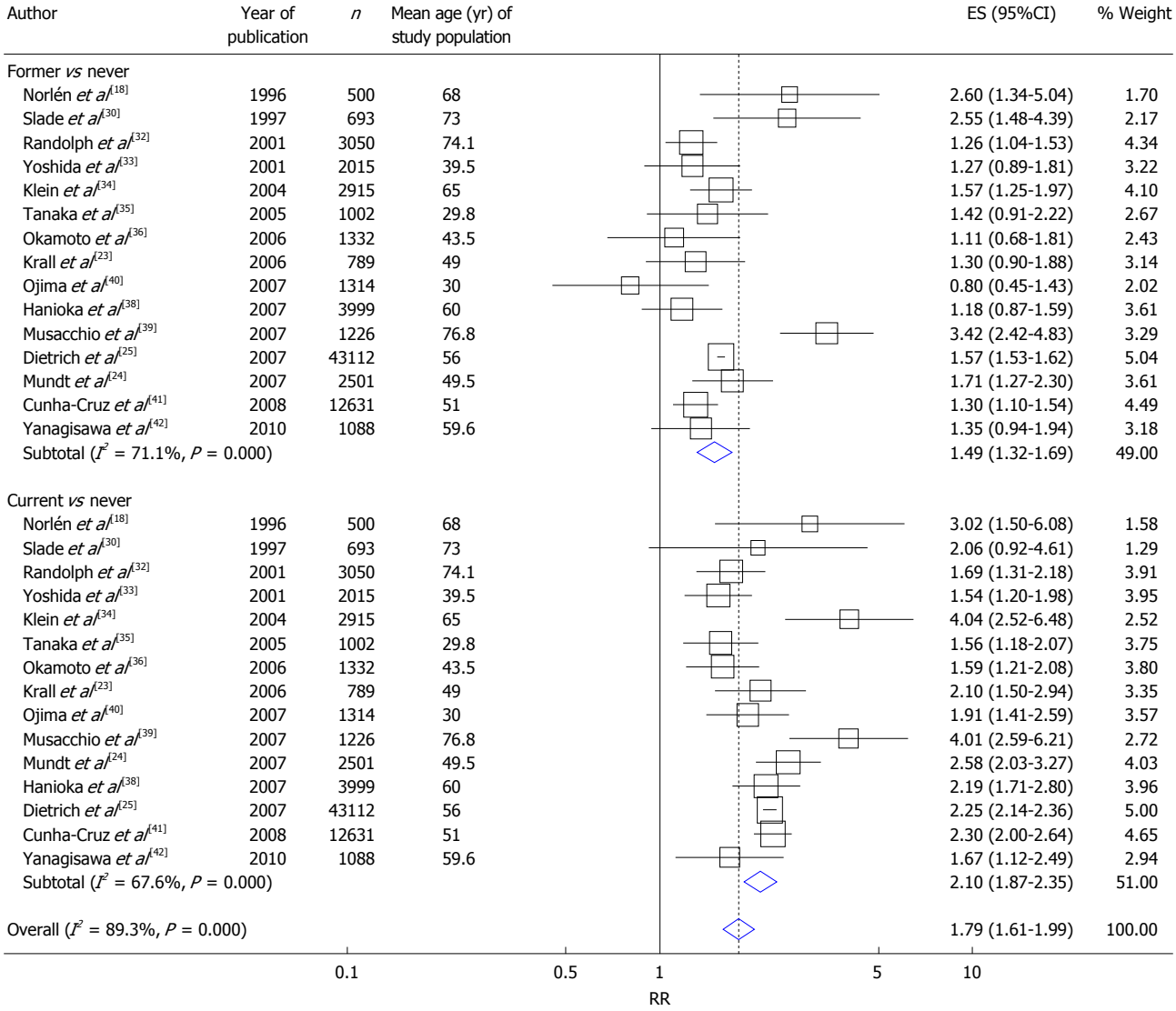

Figure 6 Subset meta-analysis according to smoking status. Weights are from random effects analysis.

graphical and statistical methods, it is difficult to completely rule out this possibility. A third limitation might be potential heterogeneity across studies, although we applied a random-effect model. Further, although we evaluated as many candidate characteristics as possible, unmeasured potential sources of heterogeneity might have remained. Although we tried to evaluate the different impact of smoking between former and current smokers, we did not directly compare two groups because RRs directly comparing two groups were not available in most of the studies. There have been discussions on how to precisely estimate the pooled estimates of RRs combining several levels of groups with strong correlations[48-50], we chose Greenland and Longnecker's methods[48] instead of Hamling's method[49] based on a recent study by Orsini *et al*[50] reporting negligible difference in estimation. Finally, we abstracted data only from English-language articles, and we only used PubMed search results because of lack of access. Therefore, bias might have occurred in our search strategy. However, given the nature of the studies we were looking for, namely clinical studies of adequate quality, we consider our search within MEDLINE to be sufficient.

In conclusion, we demonstrated that smoking is a risk factor for tooth loss regardless of many other confounders, and that smoking cessation has a protective effect against tooth loss. Although our conclusions should be interpreted cautiously, our results nevertheless raise a critical point regarding the long-standing debate on whether smoking is a risk factor for tooth loss. Implementation of smoking cessation in the dental field is encouraged.

COMMENTS

Background

The World Health Organization Global Oral Health Program works to increase awareness of oral health worldwide as an important component of general health and quality of life. Number of tooth loss is one of the main impediments to oral health and smoking behavior could be the one of the modifiable causes of tooth loss, therefore, quantitative evaluation of the impact of smoking on tooth loss is needed.

Research frontiers

Smoking behavior is a risk factor for the risk of tooth loss, however, the effects of confounders such as sex, age, and other comorbidity on tooth loss have

limited its interpretability among population. Therefore, more quantitative evaluation of the association between smoking and tooth loss is essential.

Innovations and breakthroughs

Previous studies have suggested that smoking behavior could be a risk of tooth loss, however, it has not been quantitatively evaluated. This meta-analysis of the literatures clarified that (1) ever-smoking increased the risk by 73% relative to non-smokers; and (2) risk increase among former smokers was different from that in current smokers (49% and 110%, compared to non-smokers). The latter suggests that it is important to consider smoking cessation to reduce the risk of tooth loss among smokers.

Applications

The study results suggest that the smoking increased the risk of tooth loss. Smoking cessation might be recommended to reduce the risk of tooth loss.

Peer review

This is a good quantitative study in which authors analyzed the impact of smoking on number of teeth loose with consideration of potential heterogeneity of studies. The results are interesting and suggest that smoking behavior should be considered in the oral health policy and practice.

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Effectiveness of rehabilitation based on recreational activities: A systematic review

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Abstract

AIM: To summarize the evidence from randomized controlled trials (RCTs) on the rehabilitation effects of recreational activities.

METHODS: Studies were eligible if they were RCTs. Studies included one treatment group in which recreational activity was applied. We searched the following databases from 1990 to May 31, 2012: MEDLINE *via* PubMed, CINAHL, Web of Science, and Ichushi-Web. We also searched all Cochrane Databases and Campbell Systematic Reviews up to May 31, 2012.

RESULTS: Eleven RCTs were identified, which included many kinds of target diseases and/or symptoms such as stroke, dementia, Parkinson's disease, acquired brain injury, chronic non-malignant pain, adolescent obesity, high-risk pregnancy, and the frail elderly. Various intervention methods included gaming technology, music, dance, easy rider wheelchair biking, leisure education programs, and leisure tasks. The RCTs conducted have been of relatively low quality. A meta-analysis (pooled sample; n = 44, two RCTs) for balance ability using tests such as "Berg Balance Scale" and "Timed Up and Go Test" based on game intervention revealed no significant difference between interventions and controls. In all other interventions, there were one or more effects on psychological status, balance or motor function, and adherence as primary or secondary outcomes.

CONCLUSION: There is a potential for recreational activities to improve rehabilitation-related outcomes, particularly in psychological status, balance or motor function, and adherence.

Key words: Recreation activities; Randomized controlled trial; Rehabilitation effect

Core tip: This is the first systematic review of the effectiveness of rehabilitation based on recreational ac-

tivities. There is a potential for recreational activities to improve rehabilitation-related outcomes, particularly in psychological status (depression, mood, emotion, and power), balance or motor function, and adherence (feasibility and attendance). To most effectively assess the potential benefits of recreational activities for rehabilitation, it will be important for further research to utilize (1) randomized controlled trials methodology (person unit or cluster unit) when appropriate; (2) an intervention dose; (3) a description of adverse effects and withdrawals; and (4) the cost of recreational activities.

Kamioka H, Tsutani K, Yamada M, Park H, Okuizumi H, Honda T, Okada S, Park SJ, Kitayuguchi J, Handa S, Mutoh Y. Effectiveness of rehabilitation based on recreational activities: A systematic review. *World J Meta-Anal* 2013; 1(1): 27-46 Available from: URL: http://www.wjgnet.com/2308-3840/full/v1/i1/27.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i1.27

INTRODUCTION

Recreational activity is anything that is stimulating and rejuvenating for an individual. Some people may enjoy nature hikes, others may enjoy playing the guitar. The idea behind these activities is to expand the mind and body in a positive, healthy way. The best reason to take part in these activities is that they will slow the aging process by helping to lessen or eliminate stress[1]. A dictionary describes "recreation" as "the fact of people doing things for enjoyment, when they are not working"[2]. However, there are various views about what constitutes a recreational activity and there is no fixed consensus.

A systematic review (SR) of randomized controlled trials (RCTs) based on recreational and leisure activity reported some beneficial effects such as improvement in quality of life, as well as health-promoting, educational and therapeutic effects[3]. Three RCTs adopted for this review evaluated appreciation of performed music[4], entertainment using an easy rider wheelchair bike[5], and leisure tasks[6] as the intervention method. In the present study, we assumed that recreational activity is defined broadly as a physical activity with a strong element of pleasure or enjoyment.

Stroke is a disease that typically requires rehabilitation and has been described as a worldwide epidemic[7]. Many stroke patients suffer from sensory, motor and cognitive impairment as well as a reduced ability to perform self care and to participate in social and community activities[8]. Standardized repetitive task training has been shown to be effective in some aspects of rehabilitation, such as improving walking distance and speed[9]. Over the years, virtual reality (VR) and interactive video gaming (IVG) have emerged as new treatment approaches in stroke rehabilitation. In particular, commercial gaming consoles are being rapidly adopted in clinical and nursing settings. A recent SR of stroke rehabilitation studies reported that the use of VR and IVG may be beneficial in improving arm function and activities of daily living (ADL) function when compared with the same dose of conventional therapy, although there was insufficient evidence to reach a conclusion about the effect of VR and IVG on grip strength or gait speed[10].

The current study has shown that even a short duration of Wii play can provide an effective adjunct to standard rehabilitation for fall prevention, although a "Wii only" training approach is not being advocated[11]. The "enjoyment" factor is an important one that may aid adherence to training for rehabilitation[12].

Low back pain is also a disease that requires rehabilitation and is the most common reason for use of complementary and alternative medicine in the United States[13]. A SR of RCTs into alternative therapy (*i.e.,* spa and balneotherapy) targeting the relief of lower back pain reported that even though the data are scarce, there was encouraging evidence suggesting that these therapies may be effective[14].

Over the years, recreational activity and relaxation in a forest environment called "forest therapy" or "Shinrin-yoku" (forest-air bathing and forest-landscape watching, walking, *etc.*), have become a kind of climate therapy or nature therapy and are popular methods for many urban people with mentally stressful situations[15]. The fields of preventive and alternative medicine have also shown an interest in the therapeutic effects of forest therapy[16]. A study reported that forest environments may contribute to the maintenance of health and well-being by, for example reducing hostility and depression which are risk factors for coronary heart diseases, or by improving overall emotions, particularly among populations with poor mental health[17]. In addition, a recent study reported that forest bathing trips increase natural killer (NK) cell activity, which was mediated by increases in the number of NK cells and by the levels of intracellular anti-cancer proteins and phytoncides released from trees. The decreased production of stress hormones may also partially contribute to the increased NK cell activity[18].

It is well known in research design that evidence grading is highest for a SR with meta-analysis of RCTs. Although many studies have reported the rehabilitation effects of recreational activities, there is no SR of evidence based on RCTs. The objective of this review was to summarize the evidence from RCTs on the rehabilitation effects of recreational activities.

MATERIALS AND METHODS

Criteria for considering studies included in this review

Types of studies: Studies were eligible if they were RCTs.

Types of participants: There was no restriction on patients.

Types of intervention and language: Studies included

at least one treatment group in which recreation activity was applied. The definition of the recreational activity is complex, but, in this study, it describes a specific exercise item. Specifically, any kind of recreational activity (not only dynamic activities but also musical appreciation or playing, painting, hand-craft, *etc.*) was permitted and defined as an intervention. However, we excluded comprehensive exercise interventions such as walking, jogging, Tai chi, Yoga, stretching, and strength training. There was no restriction on the basis of language.

Types of outcome measures: We focused on rehabilitation effects. The World Health Organization states that rehabilitation of people with disabilities is a process aimed at enabling them to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels[19]. Rehabilitation provides disabled people with the tools they need to attain independence and self-determination. In this study, beneficial outcome measures included cognitive function, physical function, and pain-relief. We did not specify secondary outcomes but instead estimated items as primary outcomes if an article treated them as rehabilitation effects.

Search methods for studies identification

Bibliographic database: We searched the following databases from 1990 to May 31, 2012: MEDLINE *via* PubMed, CINAHL, Web of Science, Ichushi Web (in Japanese), and the Western Pacific Region Index Medicus (WPRIM). The International Committee of Medical Journal Editors (ICMJE) recommended uniform requirements for manuscripts submitted to biomedical journals in 1993. We selected articles published (that included a protocol) since 1990, because it appeared that the ICMJE recommendation had been adopted by the relevant researchers and had strengthened the quality of reports.

We also searched the Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), the Cochrane Central Register of Controlled Trials (Clinical Trials or CENTRAL), the Cochrane Methodology Register (Methods Studies), the Health Technology Assessment Database (Technology Assessments), the NHS Economic Evaluation Database (Economic Evaluations), About The Cochrane Collaboration databases (Cochrane Groups) and Campbell Systematic Reviews (the Campbell Collaboration), and the All Cochrane all up to May 31, 2012.

All searches were performed by two specific searchers (hospital librarians) who were qualified in medical information handling, and who had sophisticated skills in the searching of clinical trials.

Search strategies: The special search strategies contained the elements and terms for MEDLINE, CINAHL, Web of Science, Ichushi Web, WPRIM, All Cochrane databases, and Campbell Collaboration (Table 1). Only keywords about interventions were used for the searches. First, titles and abstracts of identified published articles were reviewed in order to determine the relevance of the articles. Next, references in relevant studies and identified RCTs were screened.

Registry checking: We searched the International Clinical Trials Registry Platform (ICTRP), Clinical Trials.gov, the University Hospital Medical Information Network-Clinical Trials Registry (UMIN-CTR), the Japan Pharmaceutical Information Center-Clinical Trials Information (Japic CTI), and the Japan Medical Association-Center for Clinical Trials (JMACCT CTR), all up to May 31, 2012. ICTRP and the WHO Registry Network meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration. Primary registries meet the requirements of the ICMJE. Clinical Trials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world. UMIN-CTR, Japic CTI, and JMACCT CTR are registries of clinical trials conducted in Japan and around the world.

Handsearching, reference checking, *etc.*: We handsearched abstracts published on recreation activities in relevant journals in Japan. We checked the references of included studies for further relevant literature.

Review methods

Selection of trials: In order to make the final selection of studies for the review, all criteria were applied independently by five authors (*e.g.,* Honda T, Kitayuguchi J, Okada S, Park SJ) to the full text of articles that had passed the first eligibility screening (Figure 1). Disagreements and uncertainties were resolved by discussion with other authors (*e.g.*, Mutoh Y, Okuizumi H, Park H).

Studies were selected when (1) the design was an RCT; and (2) one of the interventions was a form of recreational activity. Rehabilitation effects were used as a primary outcome measure. Trials that were excluded are presented with reasons for their exclusion (Table 2).

Quality assessment of included studies

In order to ensure that variation was not caused by systematic errors in the study design or execution, seven review authors (Okuizumi H, Mutoh Y, Okada S, Park SJ, Honda T, Handa S, and Honda T) independently assessed the quality of articles. A full quality appraisal of these papers was made using the combined tool based on the "CONSORT 2010"[20] and the "CONSORT for non-pharmacological trials"[21], developed to assess the methodological quality of non-pharmacological RCTs. These checklists were not originally developed to use as a quality assessment instrument, but we used them because they are the most important tools related to the internal and external validity of trials.

Each item was scored as "present" (p), "absent" (a), "unclear or inadequately described" (?), or "not appli-

Table 1 The special search strategies

1 MEDLINE
#1 Search "Recreation" [MeSH Major Topic]
#2 Search "Recreation Therapy" [MeSH Major Topic]
#3 Search "Rehabilitation" [MeSH Major Topic]
#4 Search "Treatment Outcome" [MeSH Terms]
#5 Search (#1) OR #2
#6 Search (#3) OR #4
#7 Search (#5) AND #6
#8 Search (#5) AND #6 Filters: Publication date from 1990-01-01 to 2012-04-30
#9 Search (#5) AND #6 Filters: Publication date from 1990-01-01 to 2012-04-30; Humans
#10 Search (#5) AND #6 Filters: Publication date from 1990-01-01 to 2012-04-30; Humans; Randomized Controlled Trial
2 CINHAL
#1 TX recreation
#2 (MH "Recreation+") OR (MH "Recreational Therapy")
#3 #1 or #2
#4 TX rehabilitation
#5 (MH "Rehabilitation+")
#6 (MH "Treatment Outcomes+") OR (MH "Outcome Assessment")
#7 #4 or #5 or #6
#8 #3 and #7
#9 #3 and #7
#10 #3 and #7
#11 #3 and #7
3 Web of Science
#1 Recreation
#2 Leisure
#3 #1 OR #2
#4 Rehabilitation
#5 "Quality of life"
#6 Outcome
#7 #4 OR #5 OR #6
#8 #3 AND #7
#9 Randomized OR randomised
#10 (#8 AND #9) AND Article time span = 1990-2012
4 Ichushi Web (Originally in Japanese)
#1 Recreation/TH or recreation/AL or recreational/AL or recreation/AL or Rikuryeshon/AL or recreation/AL
#2 Rehabilitation/HL or rehabilitation/AL or rehabilitation/ALAL
#3 #1 and #2
#4 (#3) and (DT = 1990:2012 PT = original papers CK = person)
#5 (#4) and (RD = randomized controlled trials, quasi-randomized controlled trials, comparative studies)
#6 (#4) and (RD = randomized controlled trials)
5 WPRIM
#1 recreation
6 All Cochrane
#1 MeSH descriptor Recreation explode all trees
#2 (recreation): ti, ab, kw
#3 MeSH descriptor Rehabilitation explode all trees
#4 MeSH descriptor Randomized Controlled Trials as Topic explode all trees
#5 (Randomized controlled trial): ti, ab, kw
#6 (#1 OR #2)
#7 (#4 OR #5)
#8 (#3 AND #6 AND #7), from 1990 to 2012
7 Campbell Collaboration
#1 Recreation
8 ICTRP
#1 Recreation
9 Clinical Trials.gov
#1 Recreation OR recreational
10 UMIN-CTR (Originally in Japanese)
#1 Recreation
11 Japic CTI (Originally in Japanese)
#1 Recreation
12 JMACCT CTR (Originally in Japanese)
#1 Recreation

ICTRP: International Clinical Trials Registry Platform; UMIN-CTR: University Hospital Medical Information Network-Clinical Trials Registry; Japic CTI: Japan Pharmaceutical Information Center-Clinical Trials Information; JMACCT CTR: Japan Medical Association-Center for Clinical Trials.

cable" (n/a). Depending on the study design, some items were not applicable. The "n/a" studies were excluded from calculation for quality assessment. We displayed the percentage of present description in all 47 checked items for the quality assessment of articles. Then, based on the percentage of risk of poor methodology and/or bias, each item was assigned to the following categories: good description (80%-100%), poor description (50%-79%), very poor description (0%-49%). Disagreements and uncertainties were resolved by discussion with other authors (*e.g.,* Okuizumi H, Okada S and Kamioka H). Inter-rater reliability was calculated on a dichotomous scale using percentage agreement and Cohen's κ coefficient (*k*).

Summary of studies and data extraction: Seven review authors (Okuizumi H, Mutoh Y, Okada S, Park SJ, Honda T, Handa S and Kamioka H) described the summary from each article based on the recommended structured abstracts[22,23].

Benefit, harm, and withdrawals

The GRADE Working Group[24] reported that the balance between benefit and harm, quality of evidence, applicability, and the certainty of the baseline risk were all considered in judgments about the strength of recommendations. Adverse events, withdrawals, and cost for intervention were especially important information for researchers and users of clinical practice guidelines, and we have presented this information with the description of each article.

Analysis

Pre-planned stratified analyses were: (1) trials comparing recreational activities with no treatment or waiting list controls; (2) trials comparing different types of general rehabilitation method [*e.g.,* physical therapy, occupational therapy (OT), *etc.*]; and (3) trials comparing recreational activities with other intervention(s) (*e.g.,* musical appreciation *vs* singing). We planned to express the results of each RCT, when possible, as relative risk with corresponding 95%CI for dichotomous data, and as standardized or weighted mean differences (SMD) with 95%CI for continuous data. However, heterogeneous results of studies that met inclusion criteria were not combined. All analyses were computed with the "R version 2.15.1", a free software environment for statistical computing and graphics (URL:http://www.r-project.org/), which compiles and runs on a wide variety of UNIX platforms, Windows.

Table 2 References to studies excluded in this review

Excusion No.	Ref.	Title	Reason of exclusion
1	Green *et al*[48]	Physiotherapy for patients with mobility problems more than 1 year after stroke: a randomised controlled trial	Not recreation activity
2	Kobayashi *et al*[49]	Effects of a fall prevention program on physiacal activities of elderly people living in a rural region: an interventional trial	Community-dwelling healthy elderly
3	Das *et al*[50]	The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: A randomized controlled trial	Cross-over design
4	Hurwitz *et al*[51]	Effects of recreational physical activity and back exercises on low back pain and psychological distress: Findings from the UCLA low back pain study	Observational study
5	Matsuo[52]	The influence of the exercise using a video game on the physical function and brain activities	Cross-over design
6	Saposnik *et al*[53]	Effectiveness of virtual reality exercises in stroke rehabilitation: rationale, design, and protocol of a pilot randomized clinical trial assessing the Wii gaming system	Research protocol
7	Mitsumura *et al*[54]	Effect on physical and mental function of a group rhythm exercise for elderly persons certified under the less severe grades of long-term care insurance	Exercise training
8	Fraga *et al*[55]	Aerobic resistance, functional autonomy and quality of life of elderly women impacted by a recreation and walking program	Community-dwelling healthy elderly
9	Watanabe *et al*[56]	Effects of congnitive rehabilitation with computer training on neurophychological function in schizophrenia	Not recreation activity
10	Hsu *et al*[57]	A "Wii" bit of fun: The effects of adding Nintendo Wii Bowling to a standard exercise regimen for residents of long-term care with upper extremity dysfunction	Cross-over design
11	Kwok *et al*[58]	Evaluation of the Frails' Fall Efficacy by Comparing Treatments on reducing fall and fear of fall in moderately frail older adults: study protocol for a randomised control trial	Research protocol

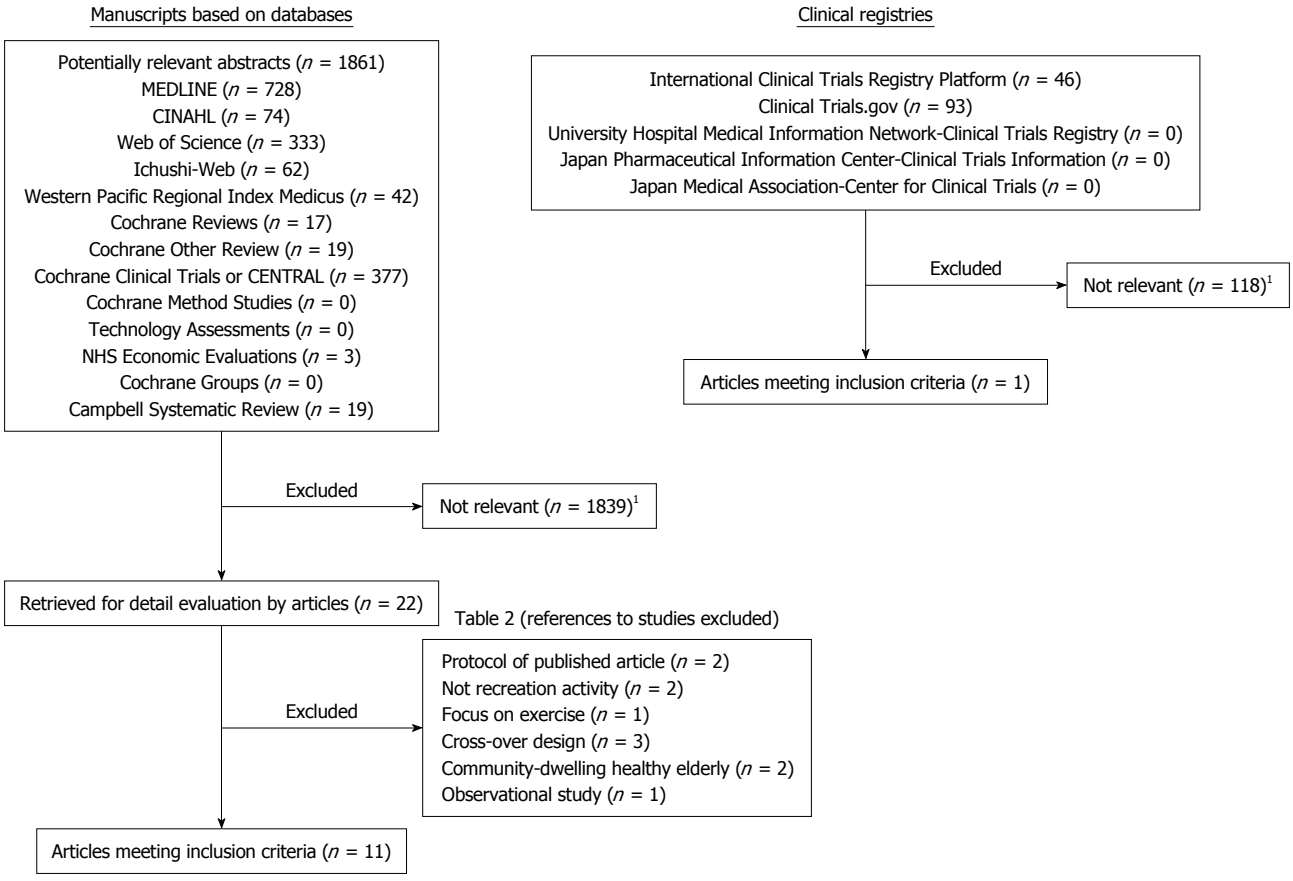

Figure 1 Flowchart of trial process. [1]Reduplication.

Research protocol registration

We submitted and registered our research protocol to the PROSPERO database (No. CRD42012002381)[25]. This is an international database of prospectively registered SRs in health and social care. Key features from the review protocol are recorded and maintained as a permanent record in PROSPERO. This will provide a comprehensive listing of SRs registered at inception, and enable compar-

ison of reported review findings with what was planned in the protocol. PROSPERO is managed by CRD and funded by the UK National Institute for Health Research. Registration was recommended because it encourages full publication of the review's findings and transparency in changes to methods that could bias findings[26].

RESULTS

Study selection

The literature searches based on databases included 1861 potentially relevant articles (Figure 1). Abstracts from those articles were assessed and 22 papers were retrieved for further evaluation (checks for relevant literature). Eleven publications were excluded because they did not meet the eligibility criteria (Table 2). Eleven studies[4-6,27-34] met all inclusion criteria (Figure 1).

Study characteristics

The language of all eligible publications was English. Target diseases and/or symptoms (Table 3) were stroke,[6,29,33,34] depression[5], Parkinson's disease[32], acquired brain injury[28], chronic non-malignant pain (CNMP)[4], adolescent obesity[31], high-risk pregnancy[30], and the frail elderly[27]. Intervention methods were gaming technology[27-29,31,33], music[4,30], dance[32], easy rider wheelchair biking[5], leisure education programs[34], and leisure tasks[6].

For gaming technology intervention, Szturm *et al*[27] reported that dynamic balance exercises on fixed and compliant sponge surfaces could be coupled to interactive video game-based tasks in frail community-dwelling older adults. Gil-Gómez *et al*[28] reported that virtual treatment with game exercises promotes improvement in the dynamic balance of patients with acquired brain injury. Saposnik *et al*[29] reported that VR Wii gaming technology represents a safe, feasible, and potentially effective alternative to facilitate rehabilitation therapy and promote motor recovery after stroke. Adamo *et al*[31] reported that cycling to music was superior to interactive video game cycling in promoting attendance and intensity of exercise expenditure for obese adolescent people, indicating that investment in the more expensive GameBike may not be worth the cost. Yavuzer *et al*[33] reported that Playstation EyeToy Games combined with a conventional stroke rehabilitation program have the potential to enhance upper extremity-related motor functioning in subacute stroke patients.

Siedliecki *et al*[4] reported that nurses could help patients with CNMP identify and use music they enjoy as a self-administered complementary intervention to facilitate feelings of power, and to decrease perceptions of pain, depression and disability. Bauer *et al*[30] reported that single session music and recreational therapy interventions effectively alleviate antepartum-related distress among high-risk women experiencing antepartum hospitalization and should be considered as valuable additions to any comprehensive antepartum program.

Concerning dance intervention, Hackney *et al*[32] reported that the tango may target deficits associated with Parkinson's disease more than the waltz/foxtrot, but both dances may benefit balance and locomotion.

Fitzsimmons[5] reported that easy rider wheelchair biking contributed to the body of knowledge regarding options for the treatment of depression in older adults, and provided encouraging findings that psychosocial interventions might be effective in reducing depression.

Desrosiers *et al*[34] reported that the results for leisure education programs indicated their effectiveness in improving participation in leisure activities, improving satisfaction with leisure and reducing depression in people with stroke.

Parker *et al*[6] reported that additional OT treatments did not show a clear beneficial effect on mood, leisure activity or independence in ADL measured at 6 or 12 mo.

Quality assessment

We evaluated 47 items from the CONSORT 2010 and the "CONSORT for non-pharmacological trials" checklists in more detail (Table 4). Inter-rater reliability metrics for the quality assessment indicated substantial agreement for all 517 items (percentage agreement 97% and k = 0.953).

This assessment evaluated the quality of how the main findings of the study were summarized in the written report. There was a remarkable lack of description in the studies of the methods, results, discussion, and other information in general. The items for which the description was lacking (very poor; < 50%) in many studies were as follows (present ratio; %): "in the abstract, description of the experimental treatment, comparator, care providers, centers, and blinding status" (36%); "important changes to methods after trial commencement" (36%); "details of how the interventions were standardized" (40%); "details of how adherence of care providers with the protocol was assessed or enhanced" (11%); "any changes to trial outcomes after the trial outcomes after the trial commenced" (25%); "how sample size was determined" (45%); "when applicable, explanation of any interim analyses and stopping guidelines" (22%); "when applicable, details of whether and how the clustering by care providers or centers was addressed" (11%); "type of randomization" (29%); "when applicable, how care providers were allocated to each trial group" (29%); "who generated the random allocation sequence, who enrolled participants, and who assigned participants to intervention" (45%); "whether or not those administering co-interventions were blinded to group assignment" (0%); "if blinded, method of blinding and description of the similarity of interventionist" (18%); "methods for additional analyses, such as subgroup analyses and adjusted analyses" (38%); "when applicable, details of whether and how the clustering by care providers or centers was addressed" (38%); "for binary outcomes, presentation of both absolute and relative effect sizes is recommended"

Table 3 Brief summary of articles based on structured abstracts and additional elements

Ref. Citation	Szturm *et al*[27] *Phys Ther* 2011; 91: 1449-1462	Gil-Gómez *et al*[28] *J Neuroeng Rehabil* 2011; 8: 30	Saposnik *et al*[29] *Stroke* 2010; 41: 1477-1484
Title	Effects of an interactive computer game exercise regimen on balance impairment in frail community-dwelling older adults: a randomized controlled trial	Effectiveness of a Wii balance board-based system (eBaViR) for balance rehabilitation: a pilot randomized clinical trial in patients with ABI	Effectiveness of virtual reality using Wii gaming technology in stroke rehabilitation: a pilot randomized clinical trial and proof of principle
Aim/objective	To examine the feasibility and benefits of physical therapy based on a task-oriented approach delivered *via* an engaging, interactive video game paradigm. The intervention focused on performing targeted dynamic tasks, which included reactive balance controls and environmental interaction	To evaluate the efficacy of the eBaViR system as a rehabilitation tool for balance recovery in patients with ABI	To examine the feasibility and safety the VR Nintendo Wii gaming system (VRWii) compared with RT in facilitating motor function on the upper extremity required for activities of daily living among patients with subacute stroke receiving standard rehablitation
Setting/place	A geriatric day hospital (Winnipeg, Manitoba, Canada)	Hospital NISA Valencia al Mar y Sevilla A ljarafe, Spain	Toronto Rehabilitation Institute
Participants	Thirty community-dwelling and ambulatory older adults. Inclusion Criteria; age: 65-85 yr, MMSE score > 24, English-speaking with the ability to understand the nature of the study and provide informed consent, independent in ambulatory functions, with or without an assistive device (cane or walker). without a disability and medical conditions (cancer, kidney disease, fracture, uncontrolled diabetes or seizure disorder, cardiovascular-related problems, stroke, multiple sclerosis, late-stage Parkinson disease, fainting, or dizzy spells)	Twenty participants. Inclusion criteria were: (1) age ⩾ 16 yr and < 80 yr; (2) chronicity > 6 mo; (3) absence of cognitive impairment (MMSE > 23); (4) able to follow instructions; and (5) ability to walk 10 m indoors with or without technical orthopaedic aids	Participants (n = 22) who are 18 to 85 yr of age (mean age 61.3 yr) having a first-time ischemic or hemorrhagic stroke
Intervention	The control group received the typical rehabilitation program such as strengthening and balance exercise at the day hospital. The experimental group received a program of dynamic balance exercises coupled with computer-based video game play, using a center-of-pressure position signal as the computer mouse. The tasks were performed while standing on a fixed floor surface, with progression to a compliant sponge pad. Each group received 16 sessions, scheduled 2/wk, with 45 min	Each patient participated in a total of 20 1-h-sessions of rehabilitation and accomplished a minimum of 3 sessions and a maximum of 5 sessions per week. During control sessions, traditional rehabilitation exercises that focused on balance training were practiced either individually or in a group. The sessions of the trial group were programmed according to the three games of the system (Simon, Balloon Breaker and Air Hockey) with a system based on the eBaViR. The eBaViR using Nintendo system had a significant improvement in static and/or standing balance (BBS and Anterior Reaches Test) compared to patients who underwent traditional therapy. The patients reported having had fun during the treatment without suffering from cyber side effects, which implies additional motivation and adhesion level to the treatment	Participants received an intensive program consisting of 8 interventional sessions of 60 min each over a 14-d period. Intervention group conducted a virtual reality Wii gaming, and the control group did a RT such as card game
Main and secondary outcomes	BBS, TUG, ABC	BBS, Brunel Balance Assessment, and ART	Feasibility and safety were set as the main outcome, and the efficiency was a secondary outcome in this study
Randomisation	Group assignment codes were placed in envelopes and sealed. Each individual who agreed to enter the study randomly selected an envelope	The randomization schedule was computer generated using a basic random number generator	The randomization schedule was computer generated using a basic random number generator
Blinding/masking	Assessors were blinded to the participant group assignments. The participant names of the GaitRite data files were coded	Program specialsits and assessors were blinded to the patients group assignments	Only caregivers were blinded (single blinding)
Numbers randomised	Experimental group (n = 15) and Control group (n = 15)	Trial group (n = 10) and Control group (n = 10)	Virtual Reality Therapy (n = 11) and Recreation Therapy (n = 11)

Recruitment	Thirty community-dwelling and ambulatory older adults who were attending the Riverview Health Center Day Hospital for treatment of limitations were recruited to participate in this study	"Seventy-nine hemiparetic patients who had sustained an ABI and were attending a rehabilitation program were potential candidates for participation in this study"	110 potential candidates were screened to participate in EVREST (the Effectiveness of Virtual Reality Excercises in Stroke Rehabiritation), and a total of 88 patients were excluded
Numbers analysed	Experimental group (n = 14) and Control group (n = 13)	Trial group (n = 9) and Control group (n = 8)	Virtual Reality Therapy (n = 10) and Recreation Therapy (n = 10) on the primary end point
Outcome	Finding demonstrated significant improvements in posttreatment balance performance scores for both group, and change scores were significantly greater in the experimental group compared with the control group (BBS; P = 0.001, ABC; P = 0.02). No significant treatment effect was observed in either group for the TUG or spatiotemporal gait variables	Patients using eBaViR had a significant improvement in static balance (P = 0.011 in BBS and P = 0.011 in ART) compared to patients who underwent traditional therapy. Regarding dynamic balance, the results showed significant improvement over time in all these measures, but no significant group effect or group-by-time interaction was detected for any of them, which suggest that both groups improved in the same way	Feasibility (time tolerance) and safety (intervention-related adverse event) did not show significant difference between groups. In contrast, the intervention group showed a significant improvement in mean motor function (Wolf Motor Function Test) compared to the control group (-7.4 s; 95%CI: -14.5--0.2)
Harm	No description	No adverse events	No adverse events
Conclusion	Dynamic balance exercises on fixed and compliant sponge surfaces were feasibly coupled to interactive video game-based exercise. This coupling, in turn, resulted in a greater improvement in dynamic standing balance control compared with the typical exercise program. However, there was no transfer of effect to gait function	The results suggest that eBaViR represents a safe and effective alternative to traditional treatment to improve static balance in the ABI population	Virtual reality Wii gaming technology represents a safe, feasible, and potentially effective alternative to facilitate rehabilitation therapy and promote motor recovery after stroke
Trial registration	Clinical Trials.gov (NCT01381237)	No registration	No description
Found	Grant from the Riverview Health Centre Foundation, Winnipeg, Manitoba, Canada: The Fund provided the space at their facility and access to their day hospital program clients for assessment and treatment of the control group	Ministerio de Educación y Ciencia Spain, Projects Consolider-C (SEJ2006-14301/ PSIC), "CIBER of Physiopathology of Obesity and Nutrition, an initiative of ISCIII" and the Excellence Research Program PROMETEO	This study was supported by a grant from the Ministry of Health and Long Term Care through the Ontario Stroke System, administered by Heart and Stroke Foundation of Ontario
Cost of intervention	No description	No description	No description
Ref.	Bauer *et al*[30]	Adamo *et al*[31]	Hackney *et al*[32]
Citation	*J Womens Health* (Larchmt) 2010; 19: 523-531	*Appl Physiol Nutr Metab* 2010; 35: 805-815	*J Rehabil Med* 2009; 41: 475-481
Title	Alleviating distress during antepartum hospitalization: a randomized controlled trial of music and recreation therapy	Effects of interactive video game cycling on overweight and obese adolescent health	Effects of dance on movement control in PD: a comparison of Argentine tango and American ballroom
Aim/objective	To examine the efficacy of a single session music or recreation therapy intervention to reduce antepartum-related distress among women with high-risk pregnancies extended antepartum hospitalizations	To examine the efficacy of interactive video game stationary cycling (GameBike) in comparison with stationary cycling to music on adherence, energy expenditure measures, submaximal aerobic fitness, body composition, and cardiovascular disease risk markers in overweight and obese adolescents, using a randomized controlled trial design	To compare the effects of tango, waltz/foxtrot and no intervention on functional motor control in individuals with PD
Setting/place	Midwestern, suburban teaching hospital with a regional Perinatal Center with 26 private rooms on the antepartum unit	The Endocrinology clinic at the Children's Hospital of Eastern Ontario	No description
Participants	Participants (n = 80) were hospitalized with various high-risk obstetric health issues, including preterm labor, premature rupture of membranes, preeclampsia, and multiple gestations. They were all over the age of 18 (mean age 31 yr), between 24 and 38 wk of gestation	Thirty obese adolescents between ages of 12-17 yr	Fifty-eight participants with idiopathic PD participated. They were at least 40 yr of age, could stand for at least 30 min, and walk independently for ≥ 3 m with or without an assistive device

Intervention	Participants were received a 1-h music or recreation therapy intervention. Music therapists offered a range of interventions for patients, all within the current standards of care of these therapies, included music-facilitated relaxation, active music listening, song writing, music for bonding, and clinical improvisation. Recreation therapy interventions offered included adaptive leisure activities, creative arts, community resource education, and leisure awareness activities	In the experimental group (interactive video game cycling), participants (n = 15) were required to exercise on a GameBike interactive video gaming system that was interfaced with a Sony Play Station 2. Participants were allowed to select from variety of choices, video games to play while cycling and were permitted to switch games during the exercise session. In control group (stationary cycling to music), participants were allowed to listen to music of their choice *via* radio, CD, or personal music device. The instructions given participants and the general protocol for this condition was the same as for video game condition. The 10-wk program consisted of twice weekly sessions lasting a maximum of 60 min per session, respectively	The both dance classes were taught by the same instructor who was an experienced professional ballroom dance instructor and an American Council on Exercise certified personal trainer. Those in the dance groups attended 1-h classes twice a week, completing 20 lessons in 13 wk. Both genders spent equal time in leading and following dance roles. Healthy young volunteers, recruited from physical therapy, pre-physical therapy and pre-medical programs at Washington University and St. Louis University, served as dance partners for those with PD. Volunteers were educated about posture and gait problems associated with PD
Main and secondary outcomes	Antepartum Bedrest Emotional Impact Inventory Scores	Adherence, submaximal aerobic fitness (Peak workload,Time to exhaustion,Peak heart rate), exercise behaviour, body composition, and blood parameters	The Unified Parkinson's Disease Rating Scale Motor Subscale 3 (UPDRS), BBS, TUG, 6MWT, FOG questionnaire, and forward and backward gait (gait velocity, stride length, and single support time)
Randomisation	The groups were assigned by the research coordinator (using a Random Numbers Statistical Table and opaque envelopes containing group membership) to an intervention condition (either a music or recreation therapy) or waitlist control condition	The randomization schedule was computer generated using a basic random number generator	Randomly selecting one of the 3 conditions from a hat
Blinding/masking	Only participants were blinded (single blinding)	No blinding	The first author was not blinded to group assignment. The evaluations were videotaped for a rater who was a specially trained physiotherapy student otherwise not involved in the study (blinded assessor). Participants were not informed of the study hypotheses
Numbers randomised	Music therapy group (n = 19), recreation therapy group (n = 19), and control group (n = 42)	Video game cycling (n = 15) and Music cycling (n = 15)	Waltz/foxtrot (n = 19), Tango (n = 19), and Control (n = 20)
Recruitment	Identified eligible patients through chart review and nursing report during 2003-2005. A total of 136 patients; once enrolled, however, 56 patients were unable to complete the study	Participants were recruited between May 2007 and January 2009 and the final subject assessment was completed in March 2009. A total of 150 families were screened through the Endocrinology clinic at the Children's Hospital of Eastern Ontario to determine Assessed for eligibility. Thirty families me the all inclusion criteria	Participates were recruited from the St. Louis community through advertisement at local support groups and local community events. Most were directly recruited *via* telephone from the Washington University Movement Disorders Center database
Numbers analysed	Music therapy group (n = 19), recreation therapy group (n = 19), and control group (n = 42)	Video game cycling (n = 13) and Music cycling (n = 13)	Waltz/foxtrot (n = 17), Tango (n = 14), and Control (n = 17)
Outcome	Significant association were found between the delivery of music and recreation therapy and reduction of antepartum-related distress in women hospitalized with high-risk pregnancies. These statistically significant reductions in distress persisted over a period of up to 48-72 h (each P < 0.05)	The music group had a higher rate of attendance compared with the video game group (92% *vs* 86%, P < 0.05). Time spent in minutes per session at vigorous intensity (80%-100% of predicted peak heart rate) (24.9 ± 20 min *vs* 13.7 ± 12.8 min, P < 0.05) and average distance (km) pedaled per session (12.5 ± 2.8 km *vs* 10.2 ± 2.2 km, P < 0.05) also favoured the music group. However, both interventions produced significant improvements in submaximal indicators of aerobic fitness as measured by a graded cycle ergometer protocol	Significant improvements were noted in tango and waltz/foxtrot on the BBS, 6MWT and backward stride length when compared with controls (P < 0.05). Control group worsened significantly with respect to disease severity, as measured by the UPDRS, and on time spent in single support during forward and backward walking
Harm	No description	No adverse events	No description

Conclusion	Single session music and recreation therapy interventions effectively alleviate antepartum-related distress among high-risk women experiencing antepartum hospitalization and should be considered as valuable additions to any comprehensive antepartum program	The results supported the superiority of cycling to music and indicated investing in the more expensive GameBike may not be worth the cost	Tango may target deficits associated with PD more than waltz/foxtrot, but both dances may benefit balance and locomotion
Trial registration	No description	Clinical Trials.gov (NCT00983970)	No description
Found	No description	The Canadian Diabetes Association	The American Parkinson's Disease Association and NIH grant K01-048437
Cost of intervention	No description	Participants and their families were reimbursed CAN$10 per visit to the laboratory for parking and transportation costs, and the participants were given a CAN$20 movie theatre gift certificate following trial completion	No description
Ref.	Yavuzer *et al*[33]	Desrosiers *et al*[34]	Siedliecki *et al*[4]
Citation	*Eur J Phys Rehabil Med* 2008; 44: 237-244	*Arch Phys Med Rehabil* 2007; 88: 1095-1100	*J Adv Nurs* 2006; 54: 553-562
Title	''Playstation eyetoy games'' improve upper extremity-related motor functioning in subacute stroke: a randomized controlled clinical trial	Effect of a home leisure education program after stroke: a randomized controlled trial	Effect of music on power, pain, depression and disability
Aim/objective	To evaluate the effects of "Playstation EyeToy games" on upper extremity motor recovery and upper extremity-related motor functioning of patients with subacute stroke	To evaluate the effect of a leisure education program on participation in and satisfaction with leisure activities (leisure-related outcomes), and well-being, depressive symptoms, and quality of life (primary outcomes) after stroke	To test the effect of music levels of power, pain, depression, and disability; to compare the effect of researcher-provided relaxing music choices with subject-preferred music, selected daily based on self-assessment; and to test the relationship between power and the combined dependent variable of pain, depression and disability
Setting/place	Twenty inpatients with hemiparesis after stroke in rehabilitation center from the general hospital, Turkey	Home and community	Pain clinics and chiropractic office in northeast Ohio, United States
Participants	Twenty hemiparetic inpatients with post-stroke. Eligible criteria: (1) first hemiparesis within 12 mo; (2) Brunnstrom stage 1-4 for upper extremity; and (3) no severe cognitive disorders	Sixty-two people (mean age 70 yr) with stroke	Participation of 60 African American and Caucasian people aged 21-65 yr (mean age 49.7 yr) with chronic non-malignant pain CNMP
Intervention	Both the intervention group and the control group participated in a conventional stroke rehabilitation program, 5 d a week, 2-5 h/d for 4 wk. The conventional program is patient-specific and consists of neurodevelopmental facilitation techniques, physiotherapy, OT, and speech therapy. For the same 4-wk of period, the EyeToy group received an additional 30 min of VR therapy program	The experimental participants (n = 33) received the leisure education program (leisure awareness, self-awareness, and competence development) at home once a week for 8 to 12 wk. The recreational therapist was responsible for the intervention whereas the occupational therapist acted as a consultant. The control participants (n = 29) were also visited by the recreation therapist but the topics discussed were unrelated to leisure (*e.g.*, family, cooking, politics, news, everyday life)	Patterning Music (PM; subject-preferred music) group were asked to select upbeat, familiar, instrumental or vocal music to ease muscle tension and stiffness. Standard Music (SM; researcher-provided music) group were offered a choice of one 60-min relaxing instrumental music tape from a collection of five tapes (piano, jazz, orchestra, harp and synthesizer) used in several music and acute pain studies. Each group received their assigned intervention for 1-h a day for 7 consecutive days. Control group received standard care that did not include music intervention, and all participants kept a diary for 7 d
Main and secondary outcomes	Brunnstrom stages and FIM	Minutes of leisure activity per day, number of leisure activities, the Leisure Satisfaction Scale, the Individualized Leisure Profile, the GWBS, the Center for Epidemiological Studies Depression Scale, and the SA-SIP30	Power (characterize power: awareness, choices, freedom, and a personal involvement in creating change), pain, depression, and disability
Randomisation	The randomization schedule was computer generated using a basic random number generator	The randomization schedule was computer generated using a basic random number generator	The random allocation sequence using the Min-8 program
Blinding/masking	Assessor was blinded to the group allocation of the subject. Patients and physical therapist were not blinded	Only assessor was blinded	No description
Numbers randomised	Intervention group (n = 10) and Control group (n = 10)	Experimental participants (n = 33) and Control participants (n = 29)	PM group (n = 18), SM group (n = 22), and Control group (n = 20)

Recruitment	"Inpatients with hemiparesis after stroke"	A total of 62 people entered the trial carried out in 2002 and 2003. Authors recruited them after a review of medical charts of people (n = 230) who were previously admitted with stroke to a rehabilitation or acute care facility up to 5 yr before the study	64 patients with CNMP was recruited over a 24-mo period from 2001 to 2003 from pain clinics and a chiropractic office in northeast Ohio
Numbers analysed	Intervention group (n = 10) and Control group (n = 10)	Experimental participants (n = 29) and Control participants (n = 27)	PM group (n = 18), SM group (n = 22), and Control group (n = 20),
Outcome	The mean change score (95%CI) of the FIM self-care score [(5.5 (2.9-8.0) *vs* 1.8 (0.1-3.7), P = 0.018] showed significantly more improvement in the EyeToy group compared to the control group. No significant differences were found between the groups for the Brunnstrom stages for hand and upper extremity	There was a statistically significant difference in change scores between the groups for satisfaction with leisure with a mean difference of 11.9 points (95%CI: 4.2-19.5) and participation in active leisure with a mean difference of 14.0 min (95%CI: 3.2-24.9). There was also a statistically significant difference between groups for improvement in depressive symptoms with a mean difference of -7.2 (95%CI: -12.5--1.9). Differences between groups were not statistically significant on the SA-SIP30 (0.2; 95%CI: -1.3-1.8) and GWBS (2.2; 95%CI: -5.6-10.0)	The music groups had more power and less pain (P = 0.002), depression (P = 0.001) and disability (P = 0.024) than the control group, but there were no statistically significant differences between the two music interventions. The model predicting both a direct and indirect effect for music was supported
Harm	No adverse events	No description	No description
Conclusion	"Playstation EyeToy Games" combined with a conventional stroke rehabilitation program have a potential to enhance upper extremity-related motor functioning in subacute stroke patients	The results indicate the effectiveness of the leisure education program for improving participation in leisure activities, improving satisfaction with leisure and reducing depression in people with stroke	Nurses can help patients with CNMP identify and use music they enjoy as a self-administered complementary intervention to facilitate feelings of power, and to decrease perceptions of pain, depression and disability
Trial registration	No description	No description	No description
Found	No description	The Canadian Institutes of Health Research (MOP-49526)	The Frances Payne Bolton Alumni Association, Case Western Reserve University, Cleveland Ohio; Sigma Theta Tau, Delta Omega Research Grant; NRSA (NINR; NIH#1F31nro7565)
Cost of intervention	No description	No description	No description
Ref.	Fitzsimmons[5]	Parker *et al*[6]	
Citation	*J Gerontol Nurs* 2001; 27: 14-23	*Clin Rehabil* 2001; 15: 42-52	
Title	Easy rider wheelchair biking. A nursing-recreation therapy clinical trial for the treatment of depression	A multicentre randomized controlled trial of leisure therapy and conventional occupational therapy after stroke. TOTAL Study Group. Trial of Occupational Therapy and Leisure	
Aim/objective	To determine if participation in a therapy biking program had an effect on the degree of depression in older adults living in a long-term facility in upstate New York	To evaluate the effects of leisure therapy and conventional OT on the mood, leisure participation and independence in ADL of stroke patients 6 and 12 mo after hospital discharge	
Setting/place	The New York State Home for Veterans (Veterans' Home)	Five UK centres: Aintree Fazakerley Hospital, Bristol Southmead Hospital, Edinburgh Western General Hospital, Glasgow Royal Infirmary and Nottingham University Hospital	
Participants	Thirty-nine older adults (mean age 80 yr) with depression living a long-term facility	Four hundred and sixty-six stroke patients (mean age 72 yr)	
Intervention	Ease rider Program (Therapy program) intervention. The experimental groups received the therapeutic biking program for 1 h a day, 5 d a week, for 2 wk	Two treatment groups (ADL group and Lisure group) received OT interventions at home for up to 6 mo after recruitment. The protocol specified a minimum of 10 sessions lasting not less than 30 min each. The treatment goals set in the ADL group were in term of improving independence in self-care tasks and therefore treatment involved practising these task (such as preparing a meal or walking outdoor). For the leisure group, goals were set in term of leisure activity and so interventions included practising the leisure task as well as any ADL tasks necessary achieve the leisure objective. Control group received no OT treatment within the trial	

Main and secondary outcomes	The short-form Geriatric Depression Scale	For mood, the GHQ/For leisure activity, the Nottingham Leisure Questionnaire/For independence in ADL, the Nottingham Extended ADL Scale
Randomisation	No description	The Collaborative Stroke Audit and Research telephone randomization service was used to allocate patients to one of three group: leisure, ADL and control
Blinding/masking	No description	Only participants were blinded
Numbers randomised	Treatment group (n = 20) and Control group (n = 20)	Leisure group (n = 153), ADL group (n = 156), and Control group (n = 157)
Recruitment	The target population (n = 90) was residents with a diagnosis of or symptoms of depression in the New York State Home for Veterans	Recruitment was conducted at five UK centres: Aintree Fazakerley Hospital, Bristol Southmead Hospital, Edinburgh Western General Hospital, Glasgow Royal Infirmary and Nottingham University Hospital. 1750 patients was registered
Numbers analysed	Treatment group (n = 19) and Control group (n = 20)	Leisure group (n = 113), ADL group (n = 106), and Control group (n = 112)
Outcome	The control groups' GDS pretest means of 7.95 increased slightly at the posttest to 8.65, indicating a slight increase (+0.70) in depression. The treatment groups' pretest 7.68 decreased to 4.21 (-3.47) at the posttest, denoting a marked decrease in depression (P < 0.001)	At 6 mo and compared to the control group, those allocated to leisure therapy had nonsignificantly better GHQ scores (-1.2: 95%CI: -2.9-0.5), leisure scores (+0.7: 95%CI: -1.1-2.5) and Extended ADL scores (+0.4: 95%CI: -3.8-4.5): the ADL group had nonsignificantly better GHQ scores (-0.1: 95%CI: -1.8-1.7) and Extended ADL scores (-1.4: 95%CI: -2.9-5.6) and nonsignificantly worse leisure scores (-0.3: 95%CI: -2.1-1.6). The results at 12 mo were similar
Harm	No adverse events	No description
Conclusion	This study contributes to the body of knowledge of nursing regarding options for the treatment of depression in older adults, and is an encouraging that psychosocial interventions may be effective in reducing depression	In contrast to the findings of previous smaller trials, neither of the additional OT treatments showed a clear beneficial effect on mood, leisure activity or independence in ADL measured at 6 or 12 mo
Trial registration	No description	No description
Found	The NewYork State Dementia Research Grant 2000	NHS Research and Development Programme
Cost of intervention	The cost of a basic bike is approximately $3600 plus shiping	No description

ABI: Acquired brain injury; PD: Parkinson's disease; BBS: Berg Balance Scale; RT: Recreational therapy; MMSE: Mini-Mental State Examination; TUG: Timed "Up and Go" Test; ABC: Activities-specific Balance Condidence Scale; ART: Anterior Reach Test; 6MWT: 6-min walk test; CNMP: Chronic non-malignant pain; OT: Occupational therapy; GWBS: General Well-Being Schedule; SA-SIP30: Stroke-Adapted Sickness Impact Profile; FIM: Functional Independence Measure; ADL: Activities of daily living; GHQ: General Health Questionnaire.

(11%); "results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory" (14%); "all important harmful or unintended effects in each group" (27%); "generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial" (27%); "registration number and name of trial registry" (18%); and "where the full trial protocol can be accessed, if available" (18%).

Meta-analysis of balance ability

Results from RCTs with control groups[27,28] were pooled in a meta-analysis to establish the overall effect of balance ability interventions compared with no-interventions controls (Figures 2 and 3). For the Berg Balance Scale (BBS), the included interventions were sufficiently homogenous (I^2 = 62.8%, P = 0.101), so the fixed effects model was used. This revealed a non-significant difference in balance ability favoring interventions over controls at the last reported assessment (SMD = 3.75; 95%CI: 1.82-5.69; n = 44). For the Timed "Up and Go" (TUG), the interventions were homogenous (I^2 = 69.5%, P = 0.070), so the fixed effects model was also used. This revealed a no significant difference in balance ability favoring interventions over controls (SMD = 0.19; 95%CI: -4.09-4.47; n = 44). A funnel plot to assess publication bias was not generated as fewer than 10 interventions were included in the meta-analysis[35].

Withdrawals and adverse events

Five studies[5,28,29,31,33] reported no adverse events during all interventions but there were no descriptions of adverse events in the other studies (Table 3). Two stud-

Table 4 Evaluation of the quality of randomized controlled trials by using the CONSORT 2010 checklist and the checklist for reporting trials nonpharmacologic treatments

Paper Section/ Topic	ID	CONSORT 2010; items	Checklist for reporting trials of nonpharmacologic treatment: items	Ref.											Present description[1]	
				[27]	[28]	[29]	[30]	[31]	[32]	[33]	[34]	[4]	[5]	[6]	No/sum	Rate (%)
Title and abstract	1a	Identification as a randomised trial in the title		p	p	p	p	a	?	p	p	a	a	p	7/11	64
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)		n/a	n/a	p	p	p	p	p	p	?	?	p	7/9	78
			In the abstract, description of the experimental treatment, comparator, care providers, centers, and blinding status	p	p	p	?	?	?	?	p	?	?	?	4/11	36
Introduction																
Background and objectives	2a	Scientific background and explanation of rationale		p	p	p	p	p	p	?	p	p	p	p	10/11	91
	2b	Specific objectives or hypotheses		p	p	p	p	p	p	p	p	p	p	p	11/11	100
Methods																
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio		p	?	p	p	p	p	p	p	p	p	p	10/11	91
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		p	p	?	p	a	?	p	a	a	a	a	4/11	36
Participants	4a	Eligibility criteria for participants		p	p	p	p	p	p	p	p	p	p	p	11/11	100
	4b	Settings and locations where the data were collected	When applicable, eligibility criteria for centers and those performing the interventions	p	?	p	p	p	?	p	p	p	p	p	9/11	82
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Precise details of both the experimental treatment and comparator	p	p	p	p	?	p	p	?	p	p	p	9/11	82
			Description of the different components of the interventions and, when applicable, descriptions of the procedure for tailoring the interventions to individual participants	a	a	p	p	a	p	a	a	p	p	p	6/11	55
			Details of how the interventions were standardized	a	a	a	p	a	p	n/a	a	p	?	p	4/10	40
			Details of how adherence of care providers with the protocol was assessed or enhanced	a	?	a	n/a	a	p	n/a	a	?	?	?	1/9	11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed		p	p	p	p	p	p	p	p	?	?	p	9/11	82
	6b	Any changes to trial outcomes after the trial commenced, with reasons		p	p	a	n/a	a	n/a	n/a	a	a	a	a	2/8	25
Sample size	7a	how sample size was determined		p	p	a	?	a	?	p	a	a	p	p	5/11	45
	7b	when applicable, explanation of any interim analyses and stopping guidelines		p	a	a	n/a	a	n/a	?	a	a	p	p	3/9	33
			When applicable, details of whether and how the clustering by care providers or centers was addressed	p	a	a	n/a	a	n/a	?	a	?	?	p	2/9	22
Randomisation: Sequence generation	8a	Method used to generate the random allocation sequence		?	p	?	p	p	p	p	p	p	a	p	8/11	73

	8b	Type of randomisation; details of any restriction (such as blocking and block size)		n/a	n/a	p	n/a	?	n/a	p	?	a	a	a	2/7	29
			When applicable, how care providers were allocated to each trial group	n/a	n/a	a	n/a	?	n/a	a	?	p	?	p	2/7	29
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned		a	a	p	p	?	p	p	?	p	a	p	6/11	55
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions		a	a	p	p	?	p	p	?	a	a	p	5/11	45
			Details of the experimental treatment and comparator as they were implemented	a	a	p	p	?	p	p	?	p	?	p	6/11	55
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		p	p	p	p	a	p	p	p	a	a	a	7/11	64
			Whether or not those administering co-interventions were blinded to group assignment	?	?	a	?	a	?	a	?	a	a	a	0/11	0
	11b	if relevant, description of the similarity of interventions	If blinded, method of blinding and description of the similarity of interventionist	?	?	a	p	a	p	a	a	a	a	a	2/11	18
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes		?	?	p	p	p	p	p	p	p	p	p	9/11	82
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		a	a	n/a	n/a	a	n/a	p	a	p	a	p	3/8	38
			when applicable, details of whether and how the clustering by care providers or centers was addressed	a	a	n/a	n/a	a	n/a	a	a	p	p	p	3/8	38
Results																
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center	a	a	p	p	p	?	p	p	p	p	p	8/11	73
	13b	For each group, losses and exclusions after randomisation, together with reasons		?	?	p	p	p	p	p	p	p	p	p	9/11	82
Recruitment	14a	Dates defining the periods of recruitment and follow-up		?	?	p	?	p	?	p	p	p	p	p	7/11	64
	14b	Why the trial ended or was stopped		?	?	p	n/a	p	n/a	p	p	p	a	p	6/9	67
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	When applicable, a description of care providers (case volume, qualification, expertise, *etc*.) and centers (volume) in each group	p	p	p	p	a	p	p	a	a	a	p	7/11	64
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups		p	p	p	p	p	p	p	p	p	p	p	11/11	100
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)		p	p	p	p	a	p	p	p	p	p	p	10/11	91

	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	?	?	p	n/a	a	n/a	a	a	a	a	a	1/9	11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	a	a	n/a	n/a	a	n/a	n/a	a	p	a	a	1/7	14
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	a	p	a	?	p	?	p	a	a	a	a	3/11	27
Discussion															
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	p	p	p	p	a	p	p	p	p	p	a	9/11	82
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	p	p	p	p	?	p	?	?	p	a	a	6/11	55
		In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care provides or centers in each group													
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	p	p	p	p	?	p	p	?	p	?	p	8/11	73
		Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial	?	?	p	p	?	?	?	?	p	?	?	3/11	27
Other information															
Registration	23	Registration number and name of trial registry	p	a	?	?	p	?	?	?	?	?	?	2/11	18
Protocol	24	Where the full trial protocol can be accessed, if available	p	a	p	?	a	?	a	a	a	a	a	2/11	18
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p	?	p	?	a	p	p	p	p	p	p	8/11	73

[1]Present description means present No. and sum except "n/a" and its percentage. a: Absent; ?: Unclear or inadequately described.

ies[29,32] reported no withdrawals (dropouts), nine studies showed some dropouts because of mainly death, death in family, hospitalization, and injuries due to other causes. The reasons preventing patients from recreational activities were not shown.

Costs of intervention

Two studies[5,31] described the costs of intervention (Table 3). Adamo *et al*[31] showed parking and transportation costs, as well as movie theatre gift certificates following the trial completion. Fitzsimmons[5] showed the cost of an easy rider wheelchair bike. There was no information regarding costs of intervention in the other studies.

DISCUSSION

This is the first SR of the effectiveness of rehabilitation based on recreational activities. Eleven RCTs were identified, target diseases and/or symptoms included stroke, dementia, Parkinson's disease, acquired brain injury, CNMP, adolescent obesity, high-risk pregnancy, and the frail elderly. The intervention methods included various approaches such as gaming technology, music, dance, easy rider wheelchair biking, leisure education programs, and leisure tasks. Primary or secondary outcomes were generally psychological status

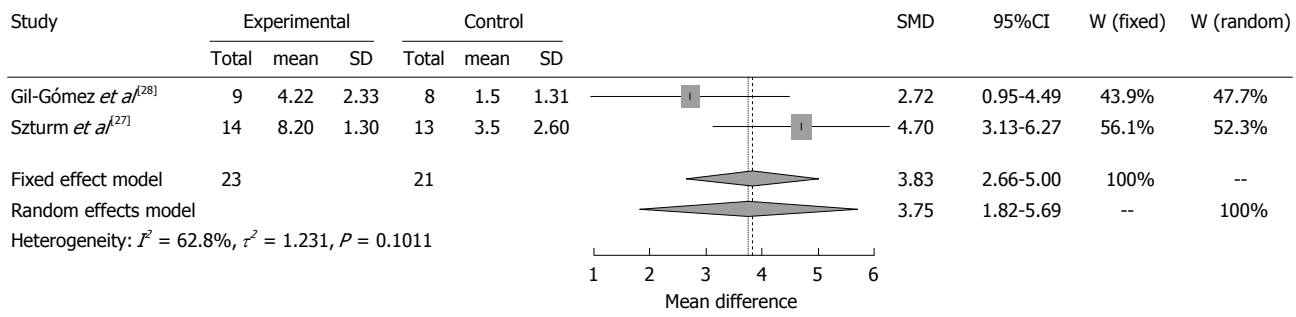

Figure 2 A meta-analysis on the effect of the Berg Balance Scale by gaming intervention. SMD: Standardized mean difference.

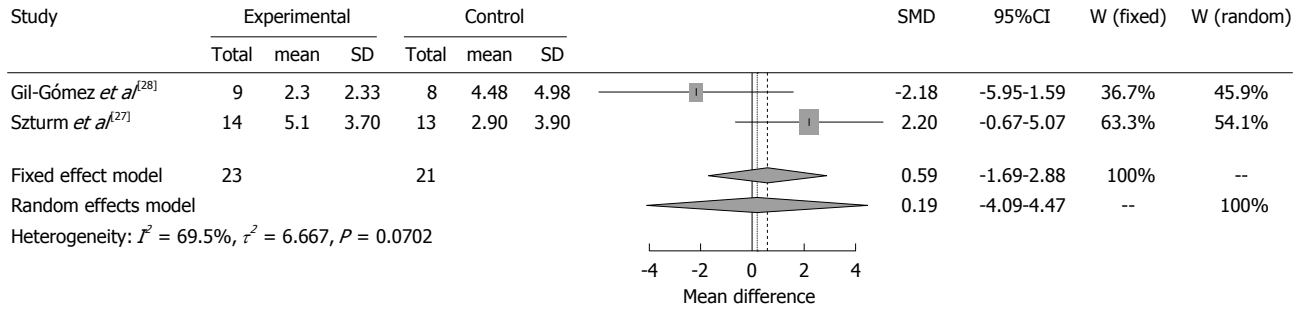

Figure 3 A meta-analysis on the effect of the Timed "Up and Go" Test by gaming intervention. SMD: Standardized mean difference.

(depression, mood, emotion, and power), balance or motor function, and adherence (feasibility and attendance).

Video gaming as new trend of rehabilitation

The trend over the past 10 years towards game interventions by VR is particularly interesting. Basically, sedentary screen time has been shown to be associated with obesity[36] as well as negative health outcomes such as premature death[37,38], independent of physical activity levels[39]. However, one strategy, the term "active video gaming" or "virtual gaming" has been used to describe games in which body movement is necessary or encouraged by the control scheme of each game. Typically, active games use a motion-sensing or motion-encouraging controller rather than a traditional handheld game pad controller. Lyons *et al*[40] reported that dance simulation and fitness games seemed to have the potential to produce moderate-intensity physical activity in physiological experiments. A recent SR[41] without meta-analysis, based on video games reported that there is potential for video games to improve health-related outcomes, particularly in the area of psychological and physical therapy. However, the included RCTs were of relatively low quality. A discussion, including a meta-analysis to clearly demonstrate an effect of the video game, was required.

Meta-analysis of balance ability based on video games

For BBS and TUG as an indicator of balance ability, the interventions were not identical, but the results for both revealed no significant differences in balance ability between interventions and controls. One reason for this was that the pooled sample size was very small (two studies, 44 participants) and we could not, therefore, calculate and describe a funnel plot to assess publication bias. It may be difficult to recruit many patients as participants in rehabilitation studies, although studies (cluster- or multicenter-RCTs depending on the case) with sufficient numbers of subjects are necessary. The second problem may be that the dose-regimen, such as period and frequency of the interventions, was inadequate. The mental and physical burden on participants is increased when there is substantial intervention, although it is expected that the effect of balance ability would rise in a positive relationship with the quantity of intervention. Because a gradual increase in load with recovery is necessary in rehabilitation programs, it is easy to assign settings like "Level" or "Stage" for the game, such as first, second level, *etc*. Therefore, we also expect to understand correctly the results and detailed descriptions of "pragmatic trials"[42] as well as "explanatory trials" for the rehabilitation effects of game intervention.

Non-meta-analysis of other recreation activities

In all other interventions, there wa at least one effect on psychological status, balance or motor function, and adherence as the primary or secondary outcomes. However, it was impossible to perform a meta-analysis and integrate the results since the main outcome measures and interventions were different. Therefore, we recognize the potential for recreational activities to improve rehabilitation effects, but could not provide conclusive evidence of these rehabilitation effects.

Overall evidence and quality assessment

The CONSORT 2010 and the CONSORT for non-phar-

Table 5 Overall evidence and future research agenda to build evidence

Overall evidence in the present	Research agenda
There is potential for effects such as psychological status, balance or motor function, and adherence but overall evidence remains unclear	Structural description of papers based on the CONSORT 2010 and the CONSORT for nonpharmacological trials 1 Satisfactory description and methodology (Method used to generate the random allocation sequence, blinding, care provider, estimated effect size and its precision, harm, external validity, and trial registry with protocol) 2 Description of intervention dose (if pragmatic intervention) 3 Adequate sample size to perform a meta-analysis 4 Description of adverse effects (*e.g.*, dizziness by watching screen) 5 Description of withdrawals 6 Description of cost (*e.g.*, gaming equipment) 7 Development of the original check item in recreation activity

macological trials checklists were not originally developed for use as quality assessment instruments, but we used them as such because they are the most important tools related to the internal and external validity of trials. There were serious problems with the conduct and reporting of the target studies. In particular, our review detected omissions in the following descriptions: methods used to generate the random allocation sequence, blinding, care provider, estimated effect size and its precision, harm, external validity, and trial registry with protocol. Descriptions of these items were lacking (very poor; < 50%) in many studies.

In the Cochrane Review, the eligibility criteria for a meta-analysis are strict, and for each article, heterogeneity and low quality of reporting must first be excluded. Because there was insufficient evidence in the studies of recreational intervention, due to poor methodological and reporting quality as well as heterogeneity, we are unable to offer any conclusions about the effects of rehabilitation by recreational intervention based on RCTs. Both the CONSORT 2010 and the CONSORT for nonpharmacological trials checklists are relatively new, but it was shown that the study protocol description and implementation for recreational studies could be subjected to these checklists.

Overall evidence and future research agenda to build evidence

The results of this study suggest that few RCTs have been conducted in this area, and that the RCTs conducted have been of relatively low quality. Table 5 shows the future research agenda for studies of the rehabilitation effect by recreational activity. There is potential for effects on psychological status, balance or motor function, and adherence, but the overall evidence remains unclear. Therefore, researchers should use the appropriate checklists for research design and intervention method, as this would lead to improvement in the quality of the study, and would contribute to the accumulation of evidence. Researchers should also present not only the efficacy data, but also description of any adverse events or harmful phenomena and withdrawals. Many studies in this review did not describe these factors.

A recent study[43] 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 choose to introduce an interventional method based on its cost-benefit, cost-effectiveness, and cost-utility. In addition, recreational activities as intervention are unique and completely different than pharmacological or traditional rehabilitation methods. Therefore it may be necessary to add some original items such as herbal intervention[44], aquatic exercise[45], and balneotherapy[46] to the CONSORT checklist as alternative or complementary medicines.

Strength and limitations

This review had 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 of an article's content into a recommended structured abstract. The conduct and reporting of this review also aligned with the PRISMA statement[47] for transparent reporting of SRs and meta-analyses.

This review also had several limitations that should be acknowledged. Firstly, although some selection criteria were common across studies, as described above, bias remained due to differences in eligibility for participation in each study. Secondly, publication bias was a limitation. Although there was no linguistic restriction in the eligibility criteria, we searched studies with only English and Japanese key words. In addition, this review reported on a relatively small and heterogeneous sample of studies. Moreover we could not follow standard procedures for estimating the effects of moderating variables. Finally, although we used an original definition of recreation activity because of the lack of a clear worldwide definition, our definition was not universal.

In conclusion, this comprehensive SR demonstrates that recreational activities may have the potential for im-

proving rehabilitation in a wide variety of areas, and for a variety of patients and elderly people. To most effectively assess the potential benefits of recreational activities for rehabilitation, it will be important for further research to utilize (1) RCT methodology (person unit or cluster unit) when appropriate; (2) an intervention dose; (3) a description of adverse effects and withdrawals; and (4) the cost of recreation activities.

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COMMENTS

Background

Recreational activity is anything that is stimulating and rejuvenating for an individual. "Enjoyment" is an important factor that may aid adherence to training for rehabilitation.

Research frontiers

Although many studies have reported the rehabilitation effects of recreational activities, there is no systematic review (SR) of the evidence based on randomized controlled trials.

Innovations and breakthroughs

This is the first SR of the effectiveness of rehabilitation based on recreational activities. There were serious problems with the conduct and reporting of the target studies. In particular, this review detected omissions in the following descriptions: methods used to generate the random allocation sequence, blinding, care provider, estimated effect size and its precision, harm, external validity, and trial registry with protocol. Descriptions of these items were lacking (very poor; < 50%) in many studies.

Applications

There is a potential for recreational activities to improve rehabilitation-related outcomes, particularly in psychological status (depression, mood, emotion, and power), balance or motor function, and adherence (feasibility and attendance).

Terminology

For rehabilitation, the World Health Organization explains that rehabilitation of people with disabilities is a process aimed at enabling them to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels. The definition of the recreational activity is complex but, in this study, it distinguishes the specific exercise item. Specifically, any kind of recreation activity (not only dynamic activities but also musical appreciation or play, painting, hand-craft, *etc.*) was permitted and defined as an intervention.

Peer review

The authors have done an excellent job in presenting results, with a format different than that normally employed in works of meta-analysis. This did not include the usual estimates of effect size based on meta-analytical indicators but is likely that this did not lead to major complications, given the number of studies analyzed. It is a good descriptive work, very systematic and ordered.

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Periodontal disease is associated with increased coronary heart disease risk: A meta-analysis based on 38 case-control studies

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Abstract

AIM: To investigate whether periodontal disease (PD) is associated with increasing coronary heart disease (CHD) risk by performing a meta-analysis.

METHODS: Two authors independently searched PubMed and China National Knowledge Infrastructure up to January 10th, 2013 for relevant case-control studies that investigated the association between PD and CHD. After quality assessment using Newcastle-Ottawa Scale and data extraction by two independent authors, the overall and subgroup meta-analyses were performed and publication bias were examined using the Comprehensive Meta-Analysis V2 software. Potential publication bias was assessed using visual inspection of the funnel plots, Egger linear regression test, and trims and fill method.

RESULTS: Finally 38 relevant case-control studies were identified, involving 4950 CHD patients and 5490 controls. Eleven studies were rated low quality and 27 were high quality. Based on random-effects, a significant association was identified between PD and CHD (OR 3.79, 95%CI: 2.23-6.43, $P < 0.001$, $I^2 = 98.59\%$), and sensitivity analysis showed that this result was robust. Subgroup analyses according to adjusted/unadjusted ORs, source of control, methodological quality, end point, assessment of PD/CHD, and ethnicity also indicated a significant association. Publication bias was detected, and the estimated OR including the "missing" studies did not substantially differ from our estimate with adjustment for missing studies (OR 4.15, 95%CI: 2.62-6.54, $P < 0.001$).

CONCLUSION: Based on the meta-analysis, PD is probably associated with CHD risk independently and significantly.

Key words: Periodontal disease; Coronary heart disease; Case-control study; Risk factor; Meta-analysis

Core tip: Growing evidence indicated that periodontal disease (PD) might be associated with coronary heart disease (CHD), however, results from the studies were inconsistent. This meta-analysis based on 38 case-control studies indicated that PD increased a 3.79-fold risk of CHD (OR = 3.79, 95%CI: 2.23-6.43, $P < 0.001$, $I^2 = 98.59\%$). The results showed that PD is probably an independent and significant risk factor for CHD.

Leng WD, Zeng XT, Chen YJ, Zhan ZQ, Yang Y. Periodontal disease is associated with increased coronary heart disease risk: A meta-analysis based on 38 case-control studies. *World J Meta-Anal* 2013; 1(1): 47-56 Available from: URL: http://www.wjgnet.com/2308-3840/full/v1/i1/47.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i1.47

INTRODUCTION

Coronary heart disease (CHD) is one of the major causes of mortality, account for nearly 30% of deaths worldwide[1]. As almost half of all first onset of CHD events occur in asymptomatic patients[2], it is important to seek CHD risk factors and accurately identify high-risk individuals and guide the risk reduction interventions, prevention, and lifestyle changes. CHD is a complex disease, epidemiologic studies have suggested that the etiology of CHD involved interactions of genetics, environmental factors, and gene-gene and gene-environment[3]. Environmental factors (including psychological and social factors)[4,5] are the classical risk factors for CHD, however, these markers do not explain the etiology of CHD to the fullest of its extent. Given the importance of fatal health problem related to CHD, efforts are being made to identify other modifiable risk factors that play a role in the etiology of CHD.

Periodontal disease (PD) is a group of inflammatory diseases which affect the supporting tissues of the tooth, approximately at least 35% dentate adults aged 30-90 years in United States suffer from PD[6], and it also affects up to 90% of the worldwide population[7]. Based on the theory of "focal infection" which emerged at the beginning of the 20th century, many studies have observed a possible role of PD as a risk factor for systemic conditions over the past two decades[8], such as cardiovascular diseases[9], diabetes[10], and chronic obstructive pulmonary disease[11].

Growing evidences indicated that chronic infections and inflammation (such as PD) might play a role in the initiation and progression of CHD[12]. Many epidemiological studies have investigated the link between PD and risk of CHD, and most of them found a positive association, even though some results are varied or even contradictory among studies. There was a published meta-analysis based on 8 cross sectional and 14 case-control studies by Blaizot *et al*[9] in 2009, which identified that there were higher odds of developing CHD in patients with PD (OR 2.35, 95%CI: 1.87-2.96, $P < 0.0001$). However, this meta-analysis did not perform subgroup analyses because of the study design, and adjusted or unadjusted factors. As we know, a cross sectional design is subjected to more confounding and biases than a case-control design, and adjusted data could obtain more precise point estimate than unadjusted data. Up to now, there have been 38 case-control studies[13-50] published in English or Chinese.

An improved understanding of this association may have important public health and clinical implications, for prevention and treatment of PD would reduce the CHD events. This meta-analysis aims to (1) evaluate the inconsistent results from published case-control studies on the association between PD and risk of CHD; (2) gain a more precise estimate association; and (3) provide a general interpretation of the results in the context of other evidences and propose suggestions for the prevention and treatment of the diseases.

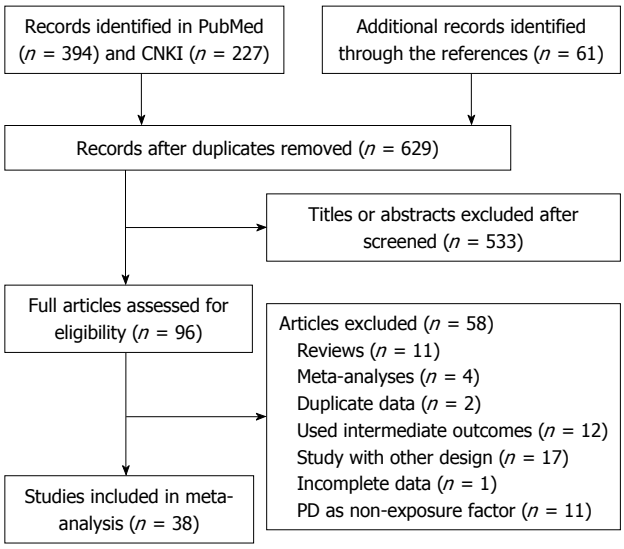

Figure 1 Flow chart of included case-control studies that tested the association between periodontal disease and risk of coronary heart disease. PD: Periodontal disease; CHD: Coronary heart disease; CNKI: China National Knowledge Infrastructure.

MATERIALS AND METHODS

We followed the proposed MOOSE (Meta-Analysis of Observational Studies in Epidemiology)[51] guidelines to report the present meta-analysis.

Literature search

We initially identified published studies that investigated the association between PD and CHD by searching the PubMed and China National Knowledge Infrastructure databases up to January 10th, 2013. The following search terms were used: (1) "PD" or "peridontal disease" or "periodontitis" or "periodontal attachment loss" or "periodontal pocket" or "alveolar bone loss", and (2) "CHD" or "coronary artery disease" or "myocardial infarction (MI)" or "angina pectoris" or "ischemic heart disease". The studies were published in either English or Chinese. We also reviewed the reference lists of retrieved articles, previous meta-analysis, and recent reviews.

Study selection

Any study met all of the following criteria was included: (1) the study was of a case-control design; (2) clear diagnostic criteria for PD and CHD were reported; (3) the association between PD and risk of CHD was investigated, and PD is the exposed factor; and (4) the ORs and the

Table 1 Characteristics and methodological quality of included 38 case-control studies in the meta-analysis

Ref.	Location	Sample size	Age (case/control, yr)	Source of control	Assessment		End points	OR (95%CI)	NOS
					PD	CHD			
Li *et al*[13]	China	88/128	> 60	Hospital-based	PI	C	CHD	1.85 (1.07-3.20)	4
López *et al*[14]	Chile	35/51	42.5 ± 5.7/40.5 ± 6.3	Hospital-based	PPD	ECG	CHD	3.17 (1.31-7.65)[1]	6
Huang *et al*[15]	China	146/136	58.7 ± 8.9	Hospital-based	Q	CAG	CHD	2.27 (1.40-3.68)	5
Liu *et al*[16]	China	216/216	59.4 ± 15.3/57.9 ± 13.7	Population-based	PI	CAG	CHD	5.42 (3.32-8.86)	4
Rutger Persson *et al*[17]	Sweden	80/80	63.4 ± 8.9/61.9 ± 9.1	Population-based	ABL	ECG	MI	14.1 (5.8-34.4)[1]	7
Geerts *et al*[18]	Belgium	108/62	59.2 ± 10.9/57.7 ± 8.7	Hospital-based	PPD	C	CHD	6.50 (1.80-23)[1]	7
Montebugnoli *et al*[19]	Italy	63/50	52.3 ± 4.9/54.5 ± 6.1	Population-based	PPD	CAG	CHD	4.61 (1.00-23.20)[1]	8
Renvert *et al*[20]	Sweden	88/80	62.7 ± 9.1/NA	Hospital-based	PPD	C	MI	7.67 (1.13-51.92)[1]	6
Tang *et al*[21]	China	250/250	⩾ 45	Hospital-based	CPI	C	CHD	1.95 (1.36-2.78)	4
Buhlin *et al*[22]	Sweden	143/50	65.9 ± 8.6/64.5 ± 8.3	Population-based	PPD	CAG	CHD	3.80 (1.68-8.74)[1]	8
Liu *et al*[23]	China	45/40	54.9 ± 8.1/51.2 ± 6.5	Hospital-based	PI	CAG	CHD	18.70 (6.25-55.93)	4
Wang *et al*[24]	China	216/216	59 ± 15/58 ± 14	Population-based	ABL	CAG	CHD	1.76 (1.31-2.36)[1]	7
Andriankaja *et al*[25]	United States	537/800	54.6 ± 8.5/55.0 ± 0.0	Population-based	CAL	C	MI	2.24 (1.60-3.13)[1]	8
Barilli *et al*[26]	Brazil	40/59	49.2 (30-79)	Hospital-based	CPI	C	CHD	61 (17.26-214.86)	5
Briggs *et al*[27]	United Kingdom	92/79	56.7 ± 6.3/58.2 ± 6.7	Population-based	PPD	CAG	CHD	3.06 (1.02-9.17)[1]	8
Geismar *et al*[28]	Denmark	110/140	65/62.6	Hospital-based	ABL	ECG	CHD	2.0 (0.77-5.08)[1]	7
Li *et al*[29]	China	357/305	72.5 ± 8.9	Population-based	PI	CAG	CHD	1.16 (0.91-1.48)	6
Spahr *et al*[30]	Germany	263/526	61.0 ± 7.1/61.0 ± 7.1	Population-based	CPI	CAG	CHD	1.67 (1.08-2.58)[1]	8
Zhang *et al*[31]	China	77/74	50.2 ± 9.6/50.8 ± 9.5	Population-based	PPD	CAG	CHD	2.13 (1.08-4.22)	6
Zhang *et al*[32]	China	277/238	57 ± 11.3/55 ± 10.8	Hospital-based	CAL	CAG	CHD	2.70 (1.52-4.80)[1]	7
Latronico *et al*[33]	Italy	15/19	57.7/55.1	Population-based	ABL	CAG	CHD	5.85 (1.03-33.12)	6
Nonnenmacher *et al*[34]	Germany	45/45	63.5 ± 7.4/63.6 ± 7.4	Hospital-based	CAL	CAG	CHD	3.2 (1.2-9.0)[1]	7
Rech *et al*[35]	Brazil	58/57	59.3/70	Hospital-based	PPD	ECG	MI	1.8 (0.7-4.7)[1]	6
Ge *et al*[36]	China	13/30	55.1 ± 4.8/51.2 ± 4.7	Hospital-based	CAL	CAG	CHD	2.53 (1.01-6.32)[1]	6
Meng *et al*[37]	China	150/150	71.2 ± 4.6/71.9 ± 4.7	Population-based	ABL	C	CHD	2.95 (1.74-5.02)	5
Wu *et al*[38]	China	77/75	53.81 ± 8.25/ 51.14 ± 6.44	Hospital-based	CAL	CAG	CHD	2.18 (1.52-3.13)	5
Zamirian *et al*[39]	Iran	80/80	54.0 ± 8.7/51.9 ± 9.4	Hospital-based	CAL	ECG	MI	3.18 (1.37-7.42)[1]	6
Zhu *et al*[40]	China	98/104	61.34 ± 9.63	Population-based	CAL	C	MI	11.43 (2.59-50.34)	5
Dong *et al*[41]	China	161/162	33-66/30-70	Population-based	ABL	CAG	CHD	5.74 (2.07-15.90)[1]	7
Ma *et al*[42]	China	146/257	45-72	Hospital-based	CAL	CAG	CHD	2.36 (1.49-3.73)	5
Oikarinen *et al*[43]	Kuwait	88/88	48.8 ± 10.0/47.0 ± 11.6	Hospital-based	ABL	C	CHD	19.69 (19.36-20.02)	6
Sun *et al*[44]	China	167/242	68.28 ± 10.53/ 50.18 ± 10.56	Hospital-based	CAL	CAG	CHD	9.10 (0.87-95.07)[1]	7
Willershausen *et al*[45]	Germany	125/125	61.8 ± 10.4/63.4 ± 10.7	Population-based	CAL	ECG	MI	3.65 (2.02-6.56)[1]	7
Bokhari *et al*[46]	Pakistan	45/35	41.67 ± 5.11/ 40.31 ± 6.97	Hospital-based	PPD	CAG	CHD	6.37 (1.26-32.27)	6
Chen[47]	China	46/34	38-68/35-66	Hospital-based	ABL	CAG	CHD	9.87 (3.50-27.82)	4
Sikka *et al*[48]	India	100/100	54.97 ± 7.97/ 55.1 ± 8.08	Population-based	CPI	CAG	CHD	2.66 (1.50-4.71)	7
Ashraf *et al*[49]	Pakistan	145/145	53.3 ± 12.3/51.7 ± 11.6	Hospital-based	CPI	C	CHD	1.20 (0.93-1.55)[1]	7
Zhang *et al*[50]	China	162/162	66.7/66.0	Hospital-based	Q	CAG	CHD	2.16 (1.65-2.83)[1]	6

[1]Adjusted OR and 95%CI. PD: Periodontal disease; CHD: Coronary heart disease; NOS: Newcastle-Ottawa Scale; CAG: Coronary arteriography; ECG: Electrocardiograph; MI: Myocardial infarction; CAL: Clinical attachment loss; PPD: Periodontal pocket depth; ABL: Alveolar bone loss; CPI: Community periodontal index; PI: Periodontal index; Q: Questionnaire; C: Cardiologist.

corresponding 95%CIs, or the number of events were reported. Two authors independently evaluated the eligibility of all retrieved studies; disagreements were resolved by discussion or consultation with a third author.

Methodological quality assessment

The methodological quality of included studies was assessed independently by two authors according to the Newcastle-Ottawa Scale (NOS) for case-control study[52]. The NOS for case-control study consists of 3 parameters of quality: selection, comparability, and exposure assessment. It assigns a maximum of 4 points for selection, a maximum of 2 points for comparability, and a maximum of 3 points for exposure. Therefore, 9 points is the highest score, reflecting the highest quality. We defined overall quality rating scores < 6 as low quality, and ⩾ 6 as high quality. All discrepancies between authors were addressed by a common reevaluation of the original article.

Data extraction

Two authors independently extracted data of each study using a preliminary standardized data collection form. Data extracted included: first author's last name, year of publication, country of study; characteristics of study

Table 2 Adjustments in case-control studies included in this meta-analysis

Ref.	Adjustment
López *et al*[14]	DM, systolic blood pressure, and smoking
Rutger Persson *et al*[17]	Smoking
Geerts *et al*[18]	Age, gender, smoking, DM, hypertension, hyperlipidemia, diet, and alcohol
Montebugnoli *et al*[19]	Age, smoking, DM, hypertension, high/low density lipoprotein, CRP, leukocytes, BMI, social class
Renvert *et al*[20]	Smoking
Buhlin *et al*[22]	Age, gender, smoking, DM, BMI, education, place of birth
Wang *et al*[24]	Gender, age, BMI, smoking, hypertension, DM, blood lipid, CRP, white blood count, and fibrinogen
Andriankaja *et al*[25]	Age, gender, hypertension, cholesterol, DM, and smoking
Briggs *et al*[27]	Smoking, education, alcohol, BMI, exercise, unemployment, hobby, plaque, and CRP
Geismar *et al*[28]	Gender, smoking, DM, and education
Spahr *et al*[30]	Age, sex, BMI, smoking, alcohol, DM, hypertension, hyperlipoproteinemia, education, exercise, and statin intake
Zhang *et al*[32]	Smoking, age, gender, BMI, hypertension, DM, high-density lipoproteincholesterol, total Cholesterol, total glycerin
Nonnenmacher *et al*[34]	Smoking and BMI
Rech *et al*[35]	Age, gender, smoking, DM
Ge *et al*[36]	Blood pressure and BMI
Zamirian *et al*[39]	Smoking and alcohol
Dong *et al*[41]	Smoking, age, and education
Sun *et al*[44]	Age and BMI
Willershausen *et al*[45]	Age, gender, and smoking
Ashraf *et al*[49]	Age, gender, and education
Zhang *et al*[50]	Age, gender, smoking, alcohol, hypertension, and BMI

DM: Diabetes mellitus; BMI: Body mass index; CRP: C-reactive protein.

population and age at baseline; number of participants with PD and CHD, and total number of participants, or ORs and relevant 95%CIs; end points of CHD, ascertainment of PD and CHD; and adjustment for covariates. Any disagreement was resolved by consensus. CHD was defined as MI, angina pectoris, and other ischemic heart diseases (IHD).

Statistical analysis

We pooled the results from single studies which were found to be both clinically and statistically appropriate. We computed pooled ORs and relevant 95%CIs using Comprehensive Meta-Analysis software, Version 2.2 (Biostat, Englewood, NJ, United States)[53], to generate forest plots, determine whether a statistical association between PD and CHD exists, assess the heterogeneity of the selected studies, and detect whether publication bias present. Heterogeneity was quantified using the I^2 statistic[54], with the low, moderate, and high I^2 values of 25%, 50%, and 75%, respectively[55], where I^2 value of 25% or lower indicated no evidence of heterogeneity, we used the fixed-effect model; otherwise, the random-effects model was used.

When heterogeneity existed, we performed subgroup and sensitivity analyses to explore possible explanations for the heterogeneity and examine the influence of various exclusion criteria on the overall risk estimate. We also investigated the influence of single study on the overall risk estimate by sequentially removing each study to test the robustness of the main results.

Potential publication bias was assessed by visual inspection of the funnel plots of overall outcome. The Egger linear regression test was used to examine the association between mean effect estimate and its variance[56]. In addition, to assess the effect of possible publication bias, we calculated the number of unpublished studies which may exist to negate the results, and the pooled OR adjusted for publication bias using the trim and fill method[57].

RESULTS

Study identification

Of 682 records searched initially, 38 case-control studies[13-50] were included in this meta-analysis. A detailed flowchart of the selection process is shown in Figure 1.

Characteristics and quality of studies

Table 1 presents the major characteristics and methodological quality of the 38 case-control studies. These studies focused on CHD only. Sample sizes ranged from 34 to 1337, involving 4950 CHD patients and 5490 controls subjects. Twenty-one studies[14,17-20,22,24,25,27,28,30,32,34-36,39,41,44,45,49,50] were adjusted covariates (Table 2), while there was no adjustment of the other 17 studies[13,15,16,21,23,26,29,31,33,37,38,40,42,43,46-48]. The methodological quality of 11 studies[13,15,16,21,23,26,37,38,40,42,47] according to NOS were rated low quality, and 27 were rated high quality[14,17-20,22,24,25,27-36,39,41,43-46,48-50]. All the CHD patients were confirmed and non-CHD patients were excluded by coronary arteriography (CAG), cardiologists, or electrocardiography (ECG).

PD and risk of CHD

Of all 38 studies, six studies[19,28,29,35,44,49] showed no statistical difference, and all the 38 studies identified significantly increased risk of developing CHD (OR 3.79, 95%CI: 2.23-6.43, $P < 0.001$). Substantial heterogeneity was observed ($I^2 = 98.59\%$, $P < 0.001$). Figure 2 shows the results from the random-effects model pooling the ORs and 95%CIs.

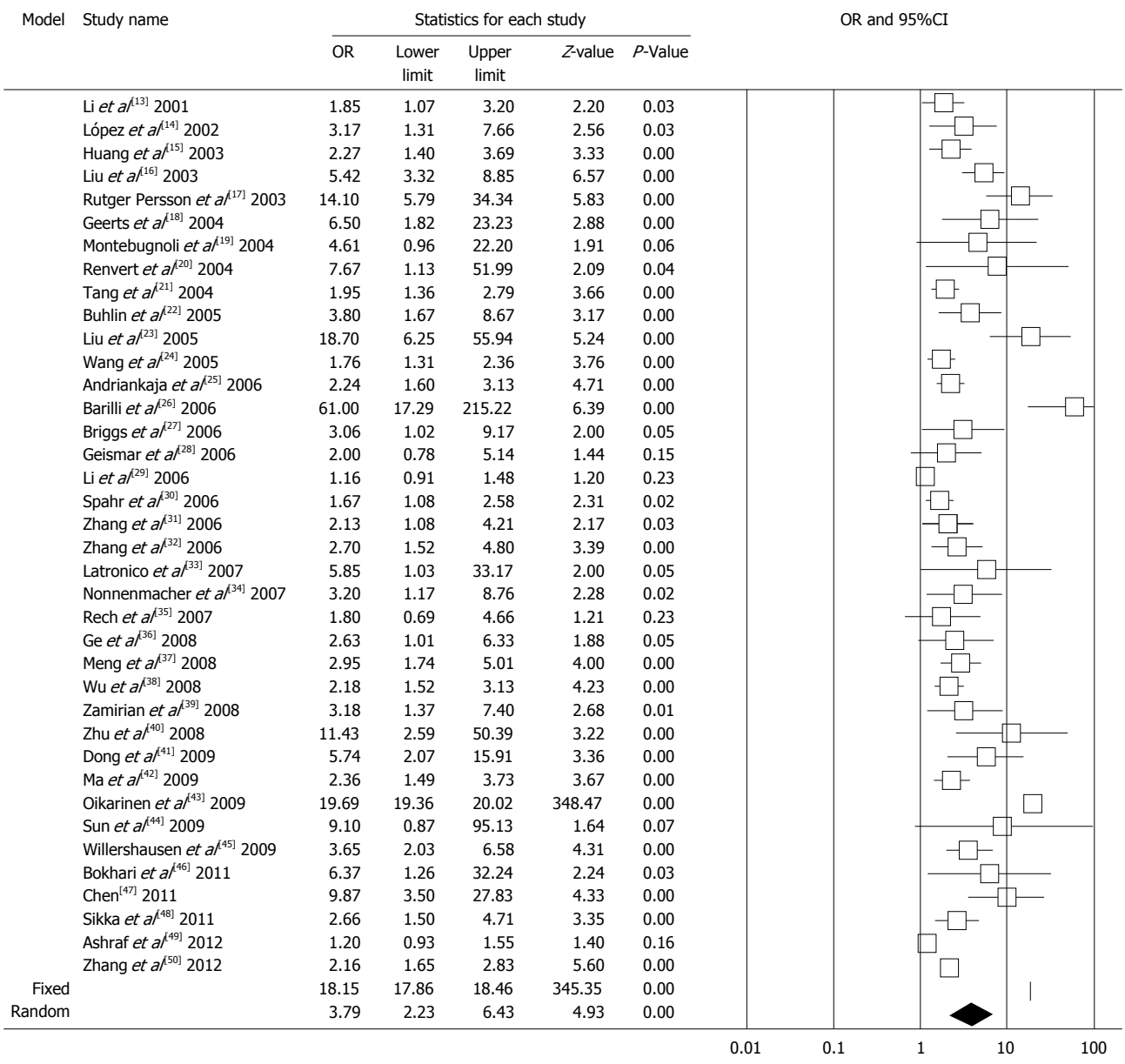

Figure 2 Forest plot of periodontal disease and risk of coronary heart disease, using pooled random-effects model. The pooled odds ratio is represented by a diamond of standard height, with the width indicating the 95%CI.

Subgroup and sensitivity analyses

Table 3 shows the results of subgroup analyses by adjustment for covariates, source of control, methodological quality, end point, assessment of PD, assessment of CHD, and ethnicity. All these analyses indicated that PD is a risk factor for CHD. Sensitivity analysis was performed by sequentially removing each study, the significance of pooled ORs was not influenced by the omission of any single study (the values of ORs were between 3.05 and 3, 91, and the relevant 95%CIs between 2.06 and 6.62), suggesting that the results of this meta-analysis were stable (Figure 3).

Publication bias

Figure 4 shows that the funnel plot was asymmetrical, indicating publication bias existed; this was also confirmed by Egger linear regression test ($P < 0.001$). As the evidence of bias could be due to inadequate statistical power, we used the non-parametric method of "trim and fill" and estimated 3 possible missing studies based on random-effects model (black spots in Figure 4). The estimated OR including the "missing" studies did not substantially differ from our estimate with adjustment for missing studies (OR 4.15, 95%CI: 2.62-6.54, $P < 0.001$).

DISCUSSION

In 1989, Mattila *et al*[58] reported that dental health was significantly associated with acute MI, and this association remained valid after adjustment for age, social class, smoking, serum lipid concentrations, and the presence of diabetes. Since then, many observational studies have emerged to investigate the relationship between

Study name	Statistics with study removed				
	Point	Lower limit	Upper limit	*Z*-value	*P*-value
Li *et al*[13] 2001	3.86	2.26	6.61	4.93	0.00
López *et al*[14] 2002	3.80	2.22	6.51	4.87	0.00
Huang *et al*[15] 2003	3.84	2.24	6.58	4.90	0.00
Liu *et al*[16] 2003	3.75	2.18	6.45	4.77	0.00
Rutger Persson *et al*[17] 2003	3.65	2.13	6.26	4.71	0.00
Geerts *et al*[18] 2004	3.74	2.18	6.39	4.81	0.00
Montebugnoli *et al*[19] 2004	3.77	2.20	6.44	4.85	0.00
Renvert *et al*[20] 2004	3.73	2.18	4.37	4.82	0.00
Tang *et al*[21] 2004	3.86	2.26	6.60	4.93	0.00
Buhlin *et al*[22] 2005	3.79	2.21	6.40	4.85	0.00
Liu *et al*[23] 2005	3.63	2.12	6.22	4.70	0.00
Wang *et al*[24] 2005	3.87	2.27	6.61	4.96	0.00
Andriankaja *et al*[25] 2006	3.85	2.24	6.59	4.90	0.00
Barilli *et al*[26] 2006	3.53	2.06	6.04	4.60	0.00
Briggs *et al*[27] 2006	3.61	2.23	6.52	4.88	0.00
Geismar *et al*[28] 2006	3.85	2.25	6.59	4.92	0.00
Li *et al*[29] 2006	3.91	2.33	6.56	5.16	0.00
Spahr *et al*[30] 2006	3.88	2.27	6.62	4.96	0.00
Zhang *et al*[31] 2006	3.85	2.25	6.59	4.91	0.00
Zhang *et al*[32] 2006	3.82	2.23	6.55	4.88	0.00
Latronico *et al*[33] 2007	3.75	2.19	6.41	4.83	0.00
Nonnenmacher *et al*[34] 2007	3.80	2.22	6.51	4.87	0.00
Rech *et al*[35] 2007	3.86	2.26	6.61	4.94	0.00
Ge *et al*[36] 2008	3.83	2.24	6.55	4.90	0.00
Meng *et al*[37] 2008	3.81	2.22	6.54	4.86	0.00
Wu *et al*[38] 2008	3.85	2.25	6.59	4.90	0.00
Zamirian *et al*[39] 2008	3.80	2.22	6.52	4.87	0.00
Zhu *et al*[40] 2008	3.69	2.16	6.31	4.76	0.00
Dong *et al*[41] 2009	3.74	2.19	6.41	4.81	0.00
Ma *et al*[42] 2009	3.84	2.24	6.58	4.89	0.00
Oikarinen *et al*[43] 2009	3.05	2.48	3.75	10.52	0.00
Sun *et al*[44] 2009	3.72	2.18	6.36	4.82	0.00
Willershausen *et al*[45] 2009	3.79	2.21	6.50	4.84	0.00
Bokhari *et al*[46] 2011	3.74	2.19	6.40	4.82	0.00
Chen[47] 2011	3.69	2.15	6.32	4.76	0.00
Sikka *et al*[48] 2011	3.82	2.23	6.55	4.88	0.00
Ashraf *et al*[49] 2012	3.91	2.32	6.58	5.12	0.00
Zhang *et al*[50] 2012	3.85	2.24	6.60	4.90	0.00
	3.79	2.23	6.43	4.93	0.00

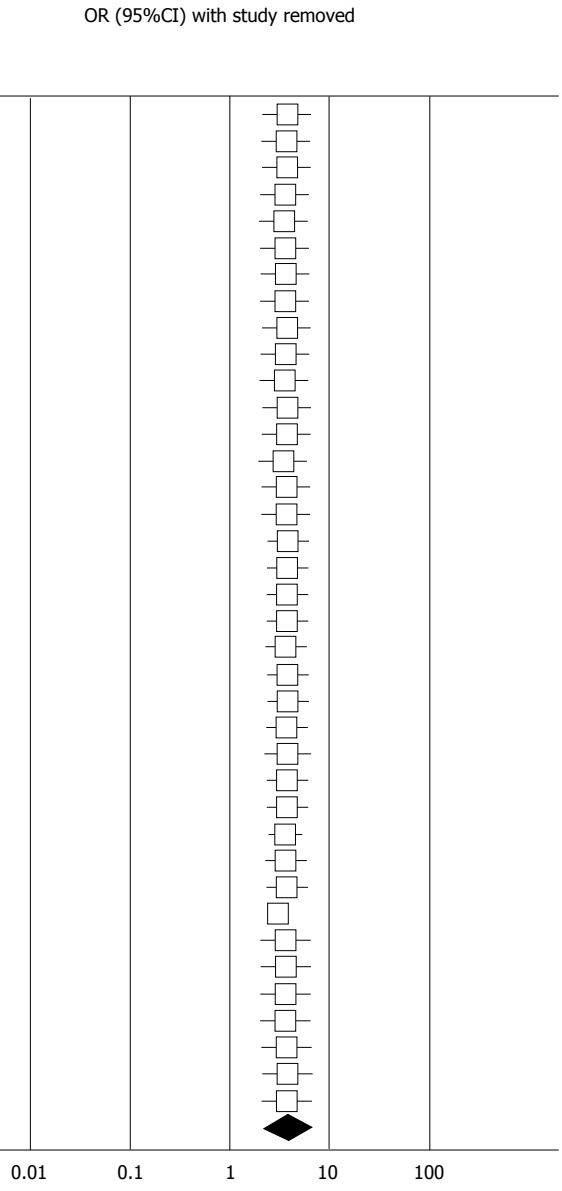

Figure 3 Forest plot of sensitivity analysis by removing each study in each turn. The pooled odds ratio is represented by a diamond of standard height, with the width indicating the 95%CI.

oral health and CHD, and PD was of special concern. However, the result remains controversial. In the present study, we performed a meta-analysis about the association between PD and CHD risk based on 38 case-control studies, and identified that subjects with PD had higher odds and higher risk of developing CHD than subjects without PD. Subgroup analyses based on adjustment for covariates, source of control, methodological quality, end point, assessment of PD, assessment of CHD, and ethnicity yielded significant and consistent results.

Compared with the previous meta-analysis by Blaizot *et al*[9] in 2009, whose result based on pooled 8 cross-sectional and 14 case-control studies identified 2.35 times higher risk of developing CHD in patients with PD (OR 2.35, 95%CI: 1.87-2.96, $P < 0.001$), our meta-analysis identified the higher risk (OR 3.79, 95%CI: 2.23-6.43, $P < 0.001$) based on 38 case-control studies. Obviously, our meta-analysis separated case-control studies from cross-sectional studies, therefore, the result was subjected to fewer confounding and biases of study design.

Second, except for geographic area, end point, and assessment of PD, we added subgroup analysis according to adjustment for covariates, source of control, methodological quality, and assessment of CHD. We found that the populations of America (OR 4.75, 95%CI: 1.50-15.02) had higher risk than Europeans (OR 3.81, 95%CI: 2.46-5.91), and Europeans had higher risk than Asians (OR 3.46, 95%CI: 1.73-6.94). This was different from previous meta-analysis, whose result showed American populations seem to present weaker association between PD and CHD than European ones. If it is due to the individual and social economic factors, why the oral health awareness and healthcare level of European and American populations are higher than Asians, but the trend of

Table 3 Results of overall and subgroups analyses of pooled odds ratios and 95%CIs

Total and subgroup	No. of trials	Heterogeneity		Model	Meta-analysis		
		I^2 (%)	*P*		OR	95%CI	*P*
Total	38	98.59	< 0.001	Random	3.79	2.23-6.43	< 0.001
Adjustment for covariates							
Yes	21	66.02	< 0.001	Random	2.72	2.13-3.46	< 0.001
No	17	98.68	< 0.001	Random	4.62	2.10-10.18	< 0.001
Source of control							
HB	22	98.5	< 0.001	Random	4.04	2.00-8.12	< 0.001
PB	16	80.38	< 0.001	Random	3.08	2.23-4.26	< 0.001
Methodological quality (NOS)							
< 6	11	83.28	< 0.001	Random	3.38	1.75-6.52	< 0.001
⩾ 6	27	98.73	< 0.001	Random	4.16	2.71-6.40	< 0.001
End point							
CHD	31	98.75	< 0.001	Random	3.63	2.00-6.59	< 0.001
MI	7	70.15	< 0.001	Random	4.12	2.35-7.22	< 0.001
Assessment of PD							
ABL	8	97.93	< 0.001	Random	5.57	1.90-16.33	< 0.001
CAL	10	0	0.5	Fixed	2.54	2.13-3.04	< 0.001
CPI	5	90.24	< 0.001	Random	2.76	1.45-5.23	< 0.001
PI	5	91.95	< 0.001	Random	3.12	1.38-7.05	< 0.001
PPD	8	0	0.76	Fixed	3.55	2.39-5.27	< 0.001
Questionnaire	2	0	0.86	Fixed	2.19	1.73-2.77	< 0.001
Assessment of CHD							
CAG	22	73.04	< 0.001	Random	2.85	2.23-3.64	< 0.001
Cardiologists	10	99	< 0.001	Random	5.09	1.71-15.14	< 0.001
ECG	6	60.72	0.03	Random	3.55	2.06-6.12	< 0.001
Ethnicity							
America	4	88.24	< 0.001	Random	4.75	1.50-15.02	0.01
Asia	23	99.01	< 0.001	Random	3.46	1.73-6.94	< 0.001
Europe	11	56.82	0.01	Random	3.81	2.46-5.91	< 0.001

PD: Periodontal disease; CHD: Coronary heart disease; NOS: Newcastle-Ottawa Scale; OR: Odds ratio; CAG: Coronary arteriography; ECG: Electrocardiograph; MI: Myocardial infarction; CAL: Clinical attachment loss; PPD: Periodontal pocket depth; ABL: Alveolar bone loss; CPI: Community periodontal index; PI: Periodontal index.

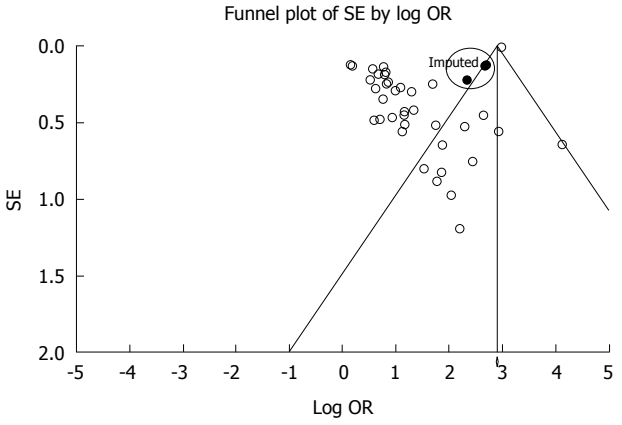

Figure 4 Filled funnel plot with pseudo-95%CIs of the 38 studies. Log of odds ratio (OR) represents the natural logarithm of the OR of individual studies; Standard error by Log OR represents the standard error in the natural logarithm of the OR of individual studies. A circle in the figure represents a study, while a black spot represents an unpublished study which may exist to negate the results of the meta-analysis.

risk is just opposite. Whether other factors, such as racial predisposition of CHD or dietary difference (*e.g.*, Asians like drinking green tea) caused this result still needs to be identified by further researches.

Third, when stratified by adjustment for covariates, the risk of adjusted data was lower (OR 2.72, 95%CI: 2.13-3.46, $P < 0.001$) than unadjusted ones (OR 4.62, 95%CI: 2.10-10.18, $P < 0.001$), and the relevant 95%CI was also narrower. This showed that adjusted data could obtain more precise point estimate than unadjusted data, and also confirmed that PD was an independent risk factor of CHD. When stratified by assessment of CHD, we observed that a definite diagnosis by cardiologists showed higher risk (OR 5.09, 95%CI: 1.71-15.14) than by CAG (OR 2.85, 95%CI: 2.23-3.64) or ECG (OR 2.06, 95%CI: 2.06-6.12). This may be because that objective diagnostic approach is more accurate than subjective one, therefore, similar researches in future combining objective and subjective diagnostic approaches would be more beneficial to confirm CHD. The high methodological quality studies obtained narrower CI (OR 4.16, 95%CI: 2.71-6.40) than low quality ones (OR 3.38, 95%CI: 1.75-6.52), and this was in accordance with PB (OR 3.08, 95%CI: 2.23-4.26) compared with HB (OR 4.04, 95%CI: 2.00-8.12). It could be concluded that high methodological quality and PB study can more effectively control confounding bias.

Some limitations also should be indicated. The major limitation of this meta-analysis was the clinical heterogeneity among the studies with regard to both outcome and exposure definitions. Although we performed subgroup analyses according to the possible sources of heteroge-

neity, clinical heterogeneity also could not be removed completely. However, the result of sensitivity analysis supported that overall result was not influenced by any included single study. Second, 17 studies did not adjust covariates, and the pooled results also showed that the risk reduction sequence was unadjusted, followed by total (combined with adjusted and unadjusted), and adjusted. This means that the overall result may exaggerate the risk. Third, this study only included articles published in Chinese and English, and articles in the other languages (representing the populations of other races) were underrepresented. The funnel plot, Egger linear regression test, and "trim and fill" method also indicated publication bias. Finally, according to the the American Association of Periodontology in 1999, PD should be confirmed by the measure of clinical attachment loss (CAL). However, other periodontal outcomes such as periodontal pocket depth, alveolar bone loss, community periodontal index, periodontal index, or by dentist according to questionnaire were conducted in 28 included studies. This variety of criteria leads to careful interpretation of the meta-analysis results.

In conclusion, this meta-analysis indicated that PD was associated with CHD risk independently and significantly, and we can conclude that an effective oral hygiene regimen would effectively prevent the progression of CHD, an effective PD intervention treatment can control CHD, and correct and effective brushing of teeth, use of dental floss, and regular periodontal scaling would be the simplest and most cost-effective actions. However, whether this is a causal association or PD is only a marker of CHD needs to be confirmed by well-designed studies with larger sample sizes and by taking the certain genetic or environmental confounding factors into account; and whether periodontal interventions are effective also needs to be validated by high quality studies with strict design, large sample size and the standardized implementation, and multi-center randomized controlled trials.

COMMENTS

Background

Growing evidence indicated that periodontal disease (PD) might be associated with coronary heart disease (CHD), however, results from these studies were inconsistent. Thus, whether PD is a risk factor of CHD remains to be clarified.

Research frontiers

CHD is one of the major causes of mortality, account for nearly 30% of deaths worldwide; PD is one of the major two oral diseases and affect up to 90% of the worldwide population. Therefore, it is very important to identify the association between PD and CHD, in order to provide evidence for prevention and treatment of the diseases.

Innovations and breakthroughs

This is a comprehensive meta-analysis, in which the authors performed subgroup analyses to identify the similarities and differences between the adjustment for covariates, source of control, methodological quality, end point, assessment of PD, assessment of CHD, and ethnicity. All these analyses indicated that PD is a risk factor for CHD.

Applications

According to this meta-analysis, an effective oral hygiene regimen would effectively prevent the progression of CHD, an effective PD intervention treatment can control CHD, and correct and effective brushing of teeth, use of dental floss, and regular periodontal scaling would be the simplest and most cost-effective actions. In addition, whether this is a causal association or PD is only a marker of CHD, and whether periodontal interventions are effective remain to be confirmed.

Peer review

The authors have made a good meta-analysis, complete and deep enough.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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