

## The Effectiveness of Psychosocial Interventions for Psychological Outcomes in Paediatric Oncology: A Systematic Review

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This manuscript contains two figures and two tables. Sixty references were used in the production of this systematic review.

The main text is 3,803 words. The abstract is 216 words long and the running title has 26 characters including spaces.

## Abstract

### Context

This review summarises the current randomised controlled trials literature on psychological and physical outcomes of psychosocial interventions in paediatric oncology.

### Objectives

To evaluate the effectiveness and impact of psychosocial interventions in children with cancer.

### Methods

A search of the literature resulted in a total of 12 randomised clinical trials which have evaluated psychosocial interventions in children under 18 years with current and previous diagnoses of cancer. The mean age of patients ranged between 7 to 18 years. Outcome measures included psychological (e.g. symptoms of anxiety, depression, quality of life, self-esteem) and physical (e.g. symptomatology, treatment adherence, pain). Interventions identified included cognitive-behavioural therapy (CBT;  $n=4$ ), joint CBT and physical exercise therapy ( $n=1$ ), family therapy ( $n=2$ ), therapeutic music video ( $n=2$ ), self-coping strategies ( $n=1$ ), a wish fulfilment intervention ( $n=1$ ), and joint family therapy and CBT ( $n=1$ ).

### Results

Nine studies reported statistically significant improvements on psychological outcomes. These findings suggest that psychosocial interventions are effective at reducing anxiety and depressive symptoms as well as improving quality of life. Additionally, six studies found psychosocial interventions to have positive impact on physical symptoms and wellbeing, including a reduction in procedural pain and symptom distress.

### Conclusion

These findings suggest that mental health needs in paediatric oncology patients can and should be addressed, which will lead to better mental and physical health outcomes.

### Key Words

*Paediatric oncology, systematic review, psychosocial interventions, randomized controlled trials, mental health*

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## Introduction

In the UK around 4000 children and young people are diagnosed with cancer yearly.(1) Also, due to recent advances in medical care and treatment, more children are now surviving cancer.(2) These survival rates, in addition to advances in diagnoses, result in an increased number of children living with the physical and psychological consequences of the disease and treatment. The psychological impact is diverse, ranging from worries about the future to concerns over 'looking ill' and viewing oneself as different from one's peers.(3) At least one-quarter of patients develop significant mental health disorders such as major depressive disorder, anxiety disorders and/or posttraumatic stress disorders (PTSD) (4,5) with half of all patients experiencing significant symptoms of depression,(6) although rates of disorders vary by study.(7)

The psychological impact of cancer has broader implications for quality of life (QoL), school attendance and the development of relationships and communication skills.(8,9) It can also negatively affect symptom management and treatment adherence.(10) In recognition of these consequences, the European Society for Paediatric Oncology developed the "Standards of Care for Children with Cancer", (11) which outlines recommendations of care which include specific psychological and psychosocial support. The recommendations state that every child with cancer should be offered psychological support through all stages of the illness. Moreover, there should be long-term monitoring of QoL, and efforts to reintegrate the child into society and education. The UK's National Institute of Clinical Excellence (12) also highlighted the social, educational and emotional needs for children with cancer in their "Improving Outcomes for Children with Cancer" guidance. The guidance states that the psychological needs of children and their families are individualised and change throughout the different stages of the patient pathway. Services should thus offer psychometric assessment to patients throughout treatment and into adult life to ensure optimal psychological health.

Given the high occurrence of psychological difficulties in paediatric cancer patients, it is important to know whether the interventions offered are effective. The last review of research in childhood cancer was over a decade ago, was narrative rather than systematic and suggested that the most effective interventions are those that are tailored to specific outcomes for the child; for example, understanding procedural pain and late effects of cancer.(13) A meta-analysis conducted around the same time reported that psychological interventions in paediatric oncology have significant effect sizes for improving adjustment and decreasing distress in parents, but show limited efficacy for child patients.(14) The authors argued that

the relatively small effect may be explained by weakened effectiveness of the treatment due to a mixture of modalities within interventions. Moreover, neither review examined specific outcomes such as depression and QoL.

The above concerns have been addressed in part by recent reviews, which have evaluated psychosocial interventions for adolescents and young adults with cancer.(15-17) Two reviews found that psychosocial interventions for young adults show a potential benefit.(15,17) In contrast, a meta-analysis of seven studies found small to non-significant effects.(16) These reviews specifically focused on adolescents and young adults rather than children based on the assumption that the effects of cancer are dependent on developmental stage.(15) This assumption is drawn from the fact that adolescents with cancer are under added stressors from the developmental transition from childhood to adulthood with increased vulnerability to emotional stress. Moreover, these reviews included a range of quantitative and mixed methods designs, with no requirement of control groups. These factors make it difficult to make clear conclusions about the effectiveness of such interventions for children aged under 18 years.

Given the limitations of the previous literature, a systematic review of randomised controlled trials (RCTs) of psychological and psychosocial interventions for childhood cancer patients and survivors under the age of 18 years old is warranted. The present study therefore aimed to conduct a systematic review to identify and compare psychosocial interventions on psychological outcomes for childhood cancer. Specifically, it addressed the following research questions:

- How effective are psychological and psychosocial interventions for children with cancer on specific psychological outcomes?
- Do psychosocial interventions have an effect on childhood cancer patient's physical health?

### **Method**

A systematic review was carried out in accordance with the Cochrane guidelines for Systematic Reviews on Interventions.(18)

### **Inclusion criteria**

**Study type.** Only randomised controlled trials (RCTs) were included in this review since they are the gold standard for evidence-based clinical research.(19)

**Participants.** The study samples consisted of children up to 18 years old. Cancer services in the UK are commonly provided in two tiers: children (0 to 13 years old) and teenage and young adults (TYA; 13 to 24 years old).(20) It was therefore considered acceptable for identified studies to include participants above 18 years old. However, unlike previous reviews, studies were only included if the mean age of participants was below 18. Participants must have had a current or previous diagnosis of cancer of any type. “Survivors of cancer” were also included to increase our study pool.(13) This decision was made based on previous intervention reviews in this area where only a few studies were identified when limiting the cancer diagnosis.(13) Interventions that included parents and siblings were also included provided that the primary therapeutic target was the child.

**Interventions.** Only studies using psychological or psychosocial interventions for children with cancer were included in this review. For the purpose of this study, we define a psychological intervention as an intervention that is intended to alleviate psychological distress and improve functioning.(14,15) Psychosocial interventions were those involving social, behavioural, cognitive and/or psychoeducational approaches. Both interventions carried out individually or in groups were included.

**Comparators.** Studies included in this review were required to have an active (e.g., alternative intervention) or passive (e.g., waiting list, treatment as usual) control condition.

**Outcomes.** The primary outcome for this review is the psychological effects, therefore studies were included if they reported any psychological outcomes, such as depression, anxiety and post-traumatic stress symptomology, defined by the DMS-IV (21) and DSM-5.(22) Studies reporting participant quality of life, self-esteem, perceived social support, or perceived emotional resistance were also included. Where available, secondary outcomes such as improvement in health symptomology and pain, educational benefits and adherence to medication were also included. All response modalities, e.g., self-report, parent-report and clinician reports, were included.

### **Exclusion criteria**

Interventions were excluded if the mean age of participants was greater than 18 years old. Trials solely investigating sibling and parent outcomes were excluded. Additionally, interventions aimed at reducing procedural pain were excluded, as were studies with pharmacological based interventions. There is already a wide body of research surrounding

the use of drugs for children with cancer and including pharmacological studies would remove from the focus on psychological treatments, as these are two very separate areas of clinical research. Therefore studies including drug treatment, for example a study comparing a psychological intervention to a pharmacological drug on anxiety outcomes, were excluded. Only studies printed in English were included.

### Search Strategy

A literature search was conducted in April 2015 and updated in August 2016 using PubMed, PsycINFO, and the Comprehensive Index to Nursing and Allied Health Literature (CINAHL). Figure 1 shows the combination of search terms used; there were no restrictions on publication dates. The medical subject heading (MeSH) terms and key words used in the search included the terms: “cancer AND intervention AND randomized control trial” and (“cancer”[MeSH Terms] OR (“leukaemia”[All Fields] OR “oncology”[All Fields]) OR “lymphoma”[All Fields] OR “brain tumour”[All Fields] OR “Hodgkin disease”[All Fields] OR “medical oncology”[All Fields] OR “neoplasms”[All Fields]) AND (“intervention”[All Fields] OR “psychotherapy”[All Fields] OR “group therapy”[All Fields] OR “psychosocial”[All Fields] OR “support group”[All Fields] OR “psychological”[All Fields] OR “self-help techniques”[All Fields] OR “skills training”[All Fields]). A snowball method was also used and the reference lists of all relevant studies and reviews were inspected for additional intervention RCTs.

**Study selection.** Studies were selected using the inclusion and exclusion criteria, carried out independently by three authors (AC, AM, MS). First, titles of papers identified using the search terms were screened; papers which were clearly irrelevant to this review were excluded. Thereafter, abstracts of the remaining papers were considered and those not meeting the inclusion/exclusion criteria were excluded. Of the remaining papers, the full texts were accessed and further analysed before ending up with the final selection.

-- Insert Fig. 1 about here --

## Data Collection and Analysis

**Data extraction.** Data extracted from the studies included: participant demographics (e.g. age, gender and type of cancer), methodology (e.g., type and length of intervention and follow-up), and results (e.g., psychological and health outcomes, adherence rates).

**Methodological quality assessment.** Study quality was independently assessed by two authors (AC, AM) using the Cochrane Collaboration's tool for assessing risk of bias.(23) This tool was chosen for its suitability in assessing RCTs. Studies were rated as 'low', 'unclear' or 'high' risk of bias using predefined criteria on a range of areas: blinding, attrition, participant allocation, reporting, performance and other sources of biases.

## Results

The initial search identified 1660 independent papers of which 12 studies met the inclusion/exclusion criteria (see Figure 2 for study selection process). Table 1 shows the data extracted from the studies, including methodology and participant demographics.

A total of 1393 participants took part in the studies. All studies included childhood cancer patients with a mean age of less than 18 years with mean ages ranging between 7 and 18 years. Nine studies included participants currently diagnosed with cancer; three studies reported interventions with cancer survivors.

Participants in the studies received different forms of interventions. The interventions used fall under seven subheadings: cognitive-behavioural therapy (CBT) based ( $n = 4$ ), therapeutic music video therapy ( $n = 2$ ), self-coping strategies ( $n = 1$ ), family therapy ( $n = 2$ ), joint family therapy and CBT ( $n = 1$ ), joint CBT and physical exercise therapy ( $n=1$ ), and a wish-fulfilling intervention ( $n=1$ ). Control groups included standard treatment as usual ( $n = 4$ ), waitlist ( $n = 3$ ) and an alternative, low-dose intervention ( $n = 5$ ) such as speaking to a researcher about a mundane topic for the same amount of time as intervention.

-- Insert Fig. 2 about here --

## Risk of Bias

The Cochrane Risk of Bias tool concluded that all studies had some risk of bias. The risk of bias detected was generally low across most parts of the studies, but all studies had a high

risk of bias or an unclear conclusion for at least one criterion. Where a conclusion to the risk of bias could not be made a classification of “unclear” was given. No studies achieved low risk of bias across all domains.

All but one study (24) achieved a low risk of reporting bias. This study claimed to be reporting QoL data but did not present this in the results section of the paper. Attrition bias was low for all studies but one study (4) reported higher dropout rates in the intervention compared to control group. An “other form of bias” was found in the same study;(4) participants received a monetary incentive which may have reduced attrition. Performance bias was high for the majority of studies, as expected, since it may be difficult and sometimes impossible to blind a participant who is receiving a psychological intervention or not.

It is noted that this tool does not account for sample size. Where some studies may appear to have a low risk of bias, a very small sample may have been used which could have led to an underestimation of risk. In addition, the tool may be rigid when applied to intervention studies e.g. the blinding criteria may be too high. High or low risks of bias therefore need to be interpreted with caution.

-- Insert Table 1 about here --

## **Interventions**

Table 1 summarises the main findings of the reviewed studies.

**Cognitive behavioural therapy.** Four studies investigated cognitive and behavioural based interventions for paediatric cancer patients. These studies can be divided into participants with a current or previous cancer diagnosis.

***Survivors of cancer.*** Butler et al. (25) assessed the effects of a Cognitive Remediation Programme on cognitive functioning and academic achievement in cancer survivors aged 6-17 who had attentional problems. Secondary measures included patient-reported self-esteem, as measured with the Culture-Free Self-Esteem Inventory (35), **a self-reported measure of self-image that assesses overall independent reliance and perception of academic adjustment. It addresses self-image over the course of the developmental span.** Parent/teacher ratings of attention were also reported as secondary measures. Results indicate that self-esteem did not significantly differ pre- and post-treatment in both groups. Significant improvements for the experimental group were reported for academic achievement, and parent reports suggested improved attention.



Huang et al. (26) incorporated social cognitive theory (58) within a tailored weight-management intervention for clinically overweight cancer survivors (aged 8-18). Participants in the experimental group reported significant reductions in negative mood compared to controls and older participants showed significant improvements in weight management and physical activity.

**Current diagnosis.** Kato and colleagues (27) used a video-game intervention to improve cancer treatment adherence in 13-29 year old cancer patients (with 87% of participants being under the age of 18 years at the time of the intervention and follow-up). Results suggested significant improvement in self efficacy, treatment adherence and cancer-related knowledge in the experimental group. Although there was an improvement in QoL, this did not reach significance.

Varni and colleagues (28) used social skills training in addition to usual school reintegration for children with a current diagnosis of cancer aged 5 to 13 years old. The participants were given specific homework tasks after each session similar to CBT and when they met again for follow-ups material from the intervention was again shared and feedback taken. Booster sessions were used to utilise the skills learned. Significant improvements in state anxiety (at 6 month follow-up) and behaviour (at 6 month and 9 month follow-up) were reported by participants in the experimental group compared to treatment as usual controls. Lower means of depressive symptoms were found for the experimental group but this result was not statistically significant.

**CBT in conjunction with physical exercise training.** One study (29) evaluated the effects of a combined physical exercise and psychosocial intervention on QoL, behavioural problems, and self-perception on a small sample ( $n = 68$ ) of cancer patients (age 8-18) in the Netherlands using both self-report and parental report measures. In contrast to initial hypotheses, the authors found no significant differences between the intervention group and the treatment as usual control group when analysing self-report measures. Analyses of parental reports, on the other hand, showed significant improvements in the perceived level of procedural anxiety. This discrepant finding may reflect the difference between the observed (external) level of physical exercise, and the actual (internal) feeling of pain, as measured with the patient-reported Pain and Hurt subscale of the QoL questionnaire (37). For example, children participating in the intervention may be more willing to do exercise and perform normal activities, despite still feeling the same level of pain. Parents, however, may interpret this increase in exercise and activity as their child experiencing less pain, thus

reporting greater improvement for their children on the Pain and Hurt scale, compared with parents in the control group.

**Family therapy.** Two studies considered the effects of a family therapy approach to improving psychological outcomes for children with cancer. The Family-Centred Advance Care Planning for Teens with Cancer intervention was investigated in a 3 month follow-up RCT for adolescents aged 14 to 20 years old with a current cancer diagnosis facing end of life treatment.(30) Depression scores were significantly lower in the experimental group compared to controls after the intervention, whereas anxiety scores dropped significantly in both groups. There were no significant differences in quality of life scores; however both groups showed improved ratings. For physical symptom outcomes, measured by integrated Pediatric Quality of Life Cancer-Specific Module (37), there were no differences reported pre and post intervention.

The second of the family-therapy centred interventions (24) compared two nursing intervention models of the socialisation abilities of pre-school children on adaptation and QoL in young children, aged 3 to 7 years old, with a current cancer diagnosis. A significant difference for social adaptation capability between groups was identified. Furthermore, all results from the sub categories of the assessment including self-help, socialization and self-direction, were significantly higher for the experimental group compared to the controls. Although the study's objectives specified an investigation on the reported quality of life of participants, it failed to report such results.

**Cognitive-behavioural family therapy intervention.** Kazak and colleagues (4) looked primarily at the treatment for Post-Traumatic Stress Symptoms (PTSS) in adolescents aged 11-19 years old who had survived cancer, and their immediate families.(4) Given the potential association of anxiety with PTSS, anxiety was examined as a secondary outcome. For PTSS outcomes, the experimental group reported a greater reduction in symptoms relative to the wait-list control condition. Adolescent participants reported a greater reduction in arousal compared to the controls. For reported anxiety measures, no differences between groups were detected.

**Self-help coping.** One study (31) evaluated an intervention integrating self-help coping strategies for dealing with the demands of a new cancer diagnosis in adolescents aged 12 to 21. The three-part educational-intervention incorporated self-care coping, behavioural coping strategies and rehearsal techniques to encourage coping with the demands of the diagnosis. No significant differences were found between groups on any measure. However, hopefulness significantly increased at post-intervention for the experimental group.

**Therapeutic music video.** Two studies used a Therapeutic Music Video intervention targeting protective factors for psychological difficulties. This intervention uses music to provide predictability through choices, autonomy support and relationship building in a therapeutic relationship for children and young people. An initial feasibility study reported improvements in QoL and improved mood following the intervention.(32) A subsequent full scale trial of the intervention in a large sample size of 11 to 24 year old patients with a current cancer diagnosis found significant increases in courageous coping and social integration compared to controls.(33) For illness-related distress, the experimental group's mean was lower than controls but not significantly so, as measured by the Symptom Distress Scale (61), a 10-item Likert scale intended to measure an individual's perceived degree of discomfort from specific symptoms.

**Make a wish intervention.** Shoshani and colleagues (34) evaluated the efficacy of a wish-fulfilling intervention service in 66 children aged 5-12 in Israel. Children were interviewed about a wish that they wanted to come true, which was subsequently fulfilled after 5-6 months. Measures of psychiatric symptoms, QoL, sense of hope, and positive and negative affect were collected at baseline and five weeks after fulfilment of the wish. Results showed significant decreases in anxiety and depression in the intervention group compared to a waitlist control group. In addition, the intervention group reported significantly increased sense of hope, physical health (subscale of QoL) and positive emotions.

-- Insert Table 2 about here --

## Discussion

This review aimed to evaluate psychological and psychosocial interventions for childhood cancer patients and survivors aged 18 years and under, focusing primarily on specific psychological outcomes, and secondarily on physical outcomes. A comprehensive search of existing literature confirms that research into psychological interventions for children with cancer is sparse and only twelve RCTs were found. Findings from the studies converge on reported improvements in both the experimental and control groups in terms of reduced anxiety and depressive symptoms, and improved QoL.

Of all the studies identified, two studies reported no improvements for the intervention group.(25,29) Butler and colleagues (25) aimed to evaluate the effectiveness of a Cognitive Remediation Programme for survivors of cancer. This study concluded that it would be naïve to expect significant improvements in a short time period and at future follow-ups they would expect to see improvements in neurocognitive abilities due to the rehearsal of skills learned from the CBT aspect of the intervention. However, other studies of a similar follow-up period analysed in this review did report significant improvements from their intervention.(28,31)

A further study (29) also reported no significant improvements for the intervention group for self-reported outcomes, although parental reports indicated improvements in perceived procedural anxiety. The lack of effects in this study may in part be explained by the relatively good psychosocial functioning reported in their sample (most participants scored within the normal range at baseline). In addition, the sample was specifically selected to include participants <12 months after treatment. Therefore, it is also possible that the natural recovery in the first year after treatment may have overshadowed any intervention effects. Future studies comparing children within clinical range of psychosocial functioning and studies including longer follow-up periods are needed to investigate this further. Moreover, future studies will benefit from including additional groups who receive only CBT or only exercise therapy to distinguish whether intervention effects are attributed to one type of intervention or the combination of both.

For the studies that specifically included anxiety and depressive symptoms as outcome measures, (4, 26, 28, 30, 32) CBT showed significant improvement in outcome. In CBT, there is an element of rehearsal of techniques and behavioural changes between sessions with therapists encouraging clients to complete “homework” tasks.(59) Participants who are encouraged to rehearse what they have learned in intervention sessions have a higher likelihood of making concrete emotional and behavioural changes; this may suggest why follow-up results are positive. These results corroborate findings of a systematic review on psychological interventions for mental health disorders in children with chronic disorders,(60) which concluded that CBT has a positive effect in the treatment of anxiety and depression in these clinical populations. Chronic illnesses follow a similar treatment trajectory to cancer: long treatment times, periods of absences from education and painful procedures. Therefore, this conclusion of intervention effects may be transferable. Although there are, of course, large differences between diagnoses of chronic illnesses and cancer, such as morbidity, side effects of treatment and possible mortality, it is beneficial for clinical practice that CBT methodology is effective across diagnoses.

It is notable that the one study incorporating family-therapy and cognitive behavioural methodology (4) produced high results overall. A significant reduction in symptoms of PTSD and a complete reduction of arousal for the experimental group were reported. Findings indicate participants enjoyed the intervention which may be due to the incorporation of family members into the therapy sessions.

Another study identified in this review utilised technology to deliver incorporated psychosocial support with physical activity and reported a significant reduction in negative mood compared in the intervention group to controls.(26) Support was delivered via text messages and phone-calls, which is an inventive way of improving access to the intervention. Participants in the experimental group received daily contact which improved compliance and therapeutic alliance between the child and experimenter. The intervention was tailored for age, sex and needs of participants which were deemed more helpful than a generic approach, in line with the suggested benefits of tailoring interventions previously reported in a review of interventions for childhood cancer survivors.(13)

Overall there was a paucity of RCTs for other treatment modalities for example solution focused approaches, narrative therapy or psychotherapy, despite these being used in clinical practice. Future research would benefit from exploring the effectiveness of these approaches and identifying which interventions work best for whom.

As a secondary exploration, this review aimed to analyse the effect psychosocial interventions can have on children's physical symptoms and well-being. When analysing these outcomes, eight studies reported physical outcomes for patients.(13, 27, 29, 30- 34) All of these studies, except one (30) reported positive physical outcomes, including reduction in procedural pain and symptom distress. It should be noted though that participants in that study (30) were facing end-of-life care and as such, suffered from severe physical symptoms which would not improve over time. Aside from two studies,(26, 29) none of the interventions were developed with the aim of improving physical health outcomes. These are promising results for real-life application of these interventions which demonstrate the close interplay between physical and mental health and the potential value of integrating services.

This area of research is exceptionally important for the thousands of children suffering with cancer and their families. This review indicates that a range of psychosocial interventions are effective and can impact positively on both mental and physical health. The specificity of any particular intervention has yet to be established. Overall, the findings indicate that the mental health needs of children and adolescents with cancer can and should

be addressed, and that integration of mental and physical health has positive impacts in both domains.

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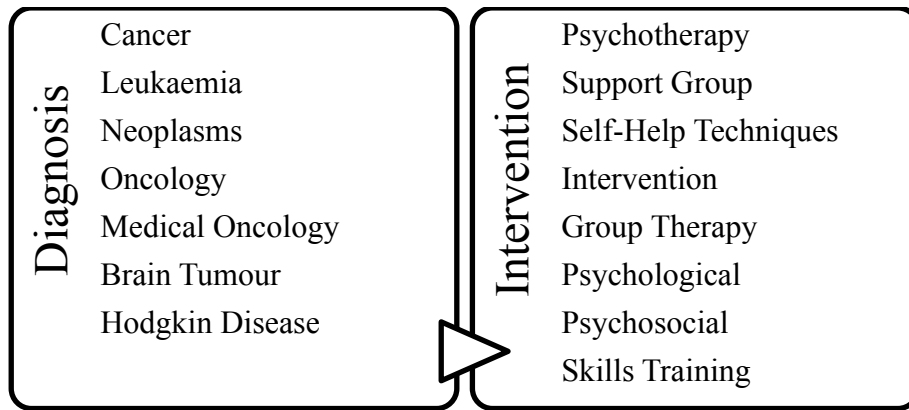
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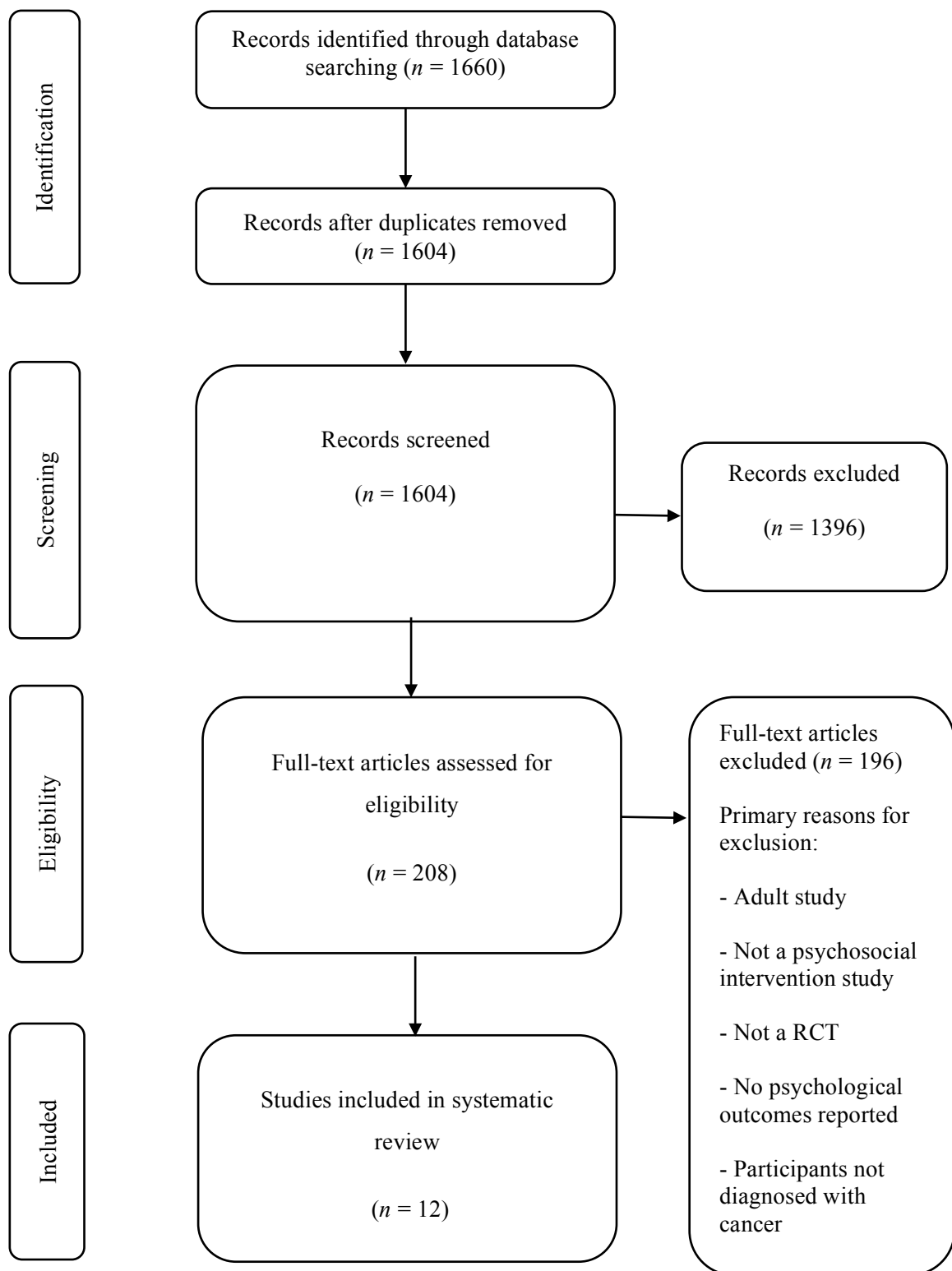
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**Figure 1.** Search terms used to identify psychosocial intervention RCTs for children and adolescents.



**Figure 2.** PRISMA (2009) flow diagram of literature search.