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Review: Economic evidence of preventive interventions for anxiety disorders in children and adolescents – a systematic review

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Background: Anxiety disorders are common in children and youth. Also, in prevention, be it universal, selective or indicated, economic evaluation supports decision-making in the allocation of scarce resources. This review identified and summarised the existing evidence of economic evaluations for the prevention of anxiety disorders in children and adolescents. **Methods:** A systematic search was conducted on the EBSCO, Scopus, Web of Science, ProQuest, Cochrane and PubMed databases. We included studies that focused on children and adolescents under 18 years of age, aimed to prevent anxiety disorders and presented an incremental analysis of costs and effectiveness. A registered checklist was used that assessed the quality of the included articles. **Results:** The search yielded 1697 articles. Five articles were included in this review. Three were RCT-based, and two were model-based studies. Out of five included interventions, one was a universal school-based intervention, two selective interventions and two indicated interventions. Universal school-based prevention of anxiety was not cost-effective compared with usual teaching. Selective parent training and indicative child- and parent-focused CBT prevention were likely cost-effective compared with usual care or doing nothing. **Conclusion:** Parent education and cognitive behaviour therapy interventions can be cautiously interpreted as being a cost-effective way of preventing anxiety in children and adolescents. However, the evidence is weakly related to cost-effectiveness as there are only a few studies, with relatively small sample sizes and short follow-ups.

Key Practitioner Message

- Anxiety disorders in children and adolescents can have long-term health effects. Furthermore, they have significant economic repercussions on families, healthcare providers, societies and nations. Prevention would be the preferred option, but very little is known about the cost-effectiveness of the different prevention strategies.
- Decision makers need information about the economic evaluation of anxiety prevention to allocate scarce resources.
- The evidence suggests that selective and indicated prevention such as parent education and cognitive behaviour therapy interventions are likely cost-effective. Universal prevention in anxiety is not cost-effective use of limited resources. However, current empirical evidence on the cost-effectiveness of anxiety prevention programmes among children and adolescents is weak due to the paucity of studies, small sample sizes and short follow-up periods.

Keywords: Economic evaluation; cost-effectiveness; anxiety disorders; prevention; systematic review

Introduction

Anxiety disorders are the most common form of mental health disorders in children and adolescents as the global prevalence of any anxiety disorder is 6.5% (CI 95% 4.7–9.1) (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Anxiety and depression in childhood increase the risk of anxiety, depression and suicide attempts in later life (Pine, Cohen, Curley, Brook, & Ma, 1998). Anxiety disorders are also associated with impairments in academic, social and personal functioning and stress in family members (Baxter, Vos, Scott, Ferrari, & Whiteford, 2014; Donovan & Spence, 2000; Kendall, Safford, Flannery-Schroeder, & Webb, 2004). Mental health disorders in childhood and adolescence are associated with a wide clinical and economic impact (Knapp & Wong, 2020). Prevention aims to reduce problems at an early stage in order to diminish human suffering and economic costs.

Previous studies have shown that different types of prevention have associated with the effectiveness of prevention (Fisak, Richard, & Mann, 2011; Teubert & Pinquart, 2011; Werner-Seidler, Perry, Calear, Newby, & Christensen, 2017). The classification of disease

prevention is typically based on an understanding of the mechanisms between the cause of the disease and the occurrence of the disease in primary, secondary and tertiary prevention. Another classification system is based on a risk-benefit perspective. The risk to an individual of getting a disease must be weighed against the cost, risk and discomfort of the preventive intervention. According to this classification, prevention is divided into universal, selective and indicated forms of prevention (Gordon, 1983; Mrazek & Haggerty, 1994). This review uses the latter classification of prevention.

Universal prevention is targeted at the general public or an entire population group that has not been identified based on individual risk and does not involve any screening. Universal prevention can reach children who have limited access to treatment, and it reduces the stigma associated with participation. On the other hand, universal prevention can be costly and yield small effect sizes, as it is administered to large populations regardless of risk status (Donovan & Spence, 2000). Selective prevention is targeted at individuals or a subgroup of the population whose risk of developing mental disorders is significantly higher than average, and it involves screening, entailing risk factors associated with mental health disorders. The risk may be identified on the basis of biological, psychological or social risk factors that are known to be associated with the onset of a mental disorder. Indicative intervention is targeted at high-risk individuals who are screened and identified as having detectable signs and symptoms foreshadowing mental disorder, or biological markers indicating a predisposition for mental disorder, but who do not meet diagnostic levels at the time (Cho & Shin, 2013; Gordon, 1983; Mrazek & Haggerty, 1994). Nevertheless, there is a thin line between a risk factor and a symptom, and it is unclear in some cases how a factor (e.g. shyness) is classified.

Economic evaluation is necessary to enable decision makers to identify the best options for the efficient use of resources in terms of treatment, care services or prevention (Knapp & Wong, 2020). It is about comparing the costs and effectiveness of at least two alternative interventions (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005), and it can be conducted in clinical trials or in decision modelling. The trials and modelling studies have different roles; they are not competing alternatives. Economic analysis based on clinical trials aims to yield cost-effectiveness information from trial measurements, and decision models use parameters from published studies to simulate cost-effectiveness in the long term (Drummond et al., 2005).

Previous effectiveness and cost-effectiveness studies have considered the treatment of anxiety in children and adolescents. Studies of anxiety treatment have shown cognitive behavioural therapy (CBT) to be more effective than no therapy (James, James, Cowdrey, Soler, & Choke, 2015; Schwartz, Barican, Yung, Zheng, & Waddell, 2019). The cost-effectiveness of treatments for anxiety disorders has been reviewed by Ophuis et al. (2017), and only three of the included interventions targeted children (Bodden et al., 2008; Gospodarevskaya & Segal, 2012; Mihalopoulos, Magnus, et al., 2015). Study by Bodden et al. (2008) found an individual CBT cost-effective compared with a family CBT. In other studies, CBT treatment options were likely to be cost-effective compared with current practice (Mihalopoulos, Magnus, et al., 2015) and with no treatment (Gospodarevskaya & Segal, 2012).

Regarding the effectiveness of prevention, the evidence varies and appears to depend on the type of prevention and context. However, many preventive interventions can prevent anxiety in children and adolescents, despite the programme type (Christensen, Pallister, Smale, Hickie, & Calear, 2010; Fisak et al., 2011; Neil & Christensen, 2009; Werner-Seidler et al., 2017). In their systematic review, Waldron, Stallard, Grist, and Hamilton-Giachritsis (2018) focused on the long-term effects of school-based universal anxiety prevention programmes. Five out of eight studies in this review evaluated the FRIENDS programme and found a reduction in anxiety symptoms in the prevention group compared with the control group, but they found no evidence beyond 12 months. In three other studies, intervention based on cognitive behavioural principles had no long-term effects.

Indicated prevention of anxiety in at-risk children and adolescents show good results. In a meta-analysis of indicated prevention, 10 out of 15 studies were effective compared with the waitlist control group (Lawrence, Rooke, & Creswell, 2017). It has also shown that indicative and selective prevention programmes produced larger effect sizes for anxiety than universal programmes (Teubert & Pinquart, 2011).

Evidence of the cost-effectiveness of overall child and adolescent mental health including anxiety treatment is scarce and evidence concerning prevention is lacking (Hamilton et al., 2017; Knapp & Wong, 2020; Schmidt et al., 2019). To support decision makers, this review identifies and summarises the existing evidence of economic evaluations of programmes preventing children's anxiety disorders. To the best of our knowledge, this will be the first systematic review of this kind.

Methods

The methods and reporting of this systematic review are in accordance with the PRISMA statement (Moher, Liberati, Tetzlaff, & Altman, 2009) and the registered protocol (PROSPERO, CRD42018116716). The minor changes in the quality assessment between the protocol and the article are described in the quality assessment section.

Inclusion/exclusion criteria

The inclusion criteria were as follows:

1 Studies focusing on children and adolescents under 18 years of age.

2 Target population has a possibility of developing an anxiety disorder such as specific phobia, separation anxiety, generalised anxiety disorder, social phobia, panic disorder, and agoraphobia. Obsessive-compulsive disorder, reaction to severe stress and adjustment disorders were also included.

3 Interventions aimed at preventing the above-mentioned disorders.

4 The intervention has a comparison group if economic evaluation based on the cost-utility or cost-effectiveness analysis.

5 The outcome for economic evaluation has been reported (i.e. incremental cost-effectiveness ratio (ICER), cost-benefit ratio, benefit-cost ratio and net present value).

6 To be included in the review, the study needs to have quality scores of at least 50% (PROSPERO, CRD42018116716).

There were no exclusion criteria, for example on the basis of publication language.

Literature search

A pre-search, conducted in May 2018, showed that economic evaluation studies on the prevention of children's anxiety are rare. Thus, the search terms were broad in order to minimise the risk of excluding potentially relevant studies. The original systematic search was conducted between 15 and 25 January 2019 across several databases: EBSCO, Scopus, Web of Science, ProQuest, Cochrane and PubMed. An additional manual search was conducted on 2 April 2019 in the Health Economic Evaluations Database (HEED), cost-effectiveness analysis (CEA) registry and the Pediatric Economic Database Evaluation (PEDE) project, which did not yield any new studies. Appendix S1 describes the search strategy. As recommended, an update of the search was conducted on 14 February 2020 (Bramer & Bain, 2017; Lefebvre et al., 2019).

Study selection

After removing duplicates, two reviewers (VKK and MR) independently reviewed the first 100 studies in alphabetical order and discussed the inclusion/exclusion decisions based on titles and abstracts to ensure consistency. After the first 100 studies, the reviewers independently assessed the remaining studies. If no consensus was reached, a third reviewer (AKV) participated in the decision-making. Reasons for exclusion are provided in Figure 1. The consistency of the decisions of the two reviewers was assessed using the Kappa statistic (McHugh, 2012).

Data extraction

Data from the studies were extracted by one reviewer (VKK) and assessed for accuracy by the other (MR). The extracted data were collected with the help of the Consensus on Health Economic Criteria checklist. The extracted data comprised basic information about the studies, effectiveness and cost data, economic evaluation results and interpretation of the results. If the information in the article was not accurate enough, then other publications from the study were used, or the authors were contacted. We present the original monetary values and also the 2018 monetary values of the results. The conversion used the first price indices of each country (Bank of England, InflationTool, Reserve Bank of Australia), and then, the 2018 value was converted into euros (OANDA Currency Converter).

Quality assessment

The quality of the articles was appraised by two independent reviewers (VKK and MR). According to the protocol (PROSPERO, CRD42018116716), we planned to assess the quality of the included studies by using the 19 questions from the Consensus on Health Economic Criteria (CHEC) checklist with three additional questions. We subsequently decided to use the more

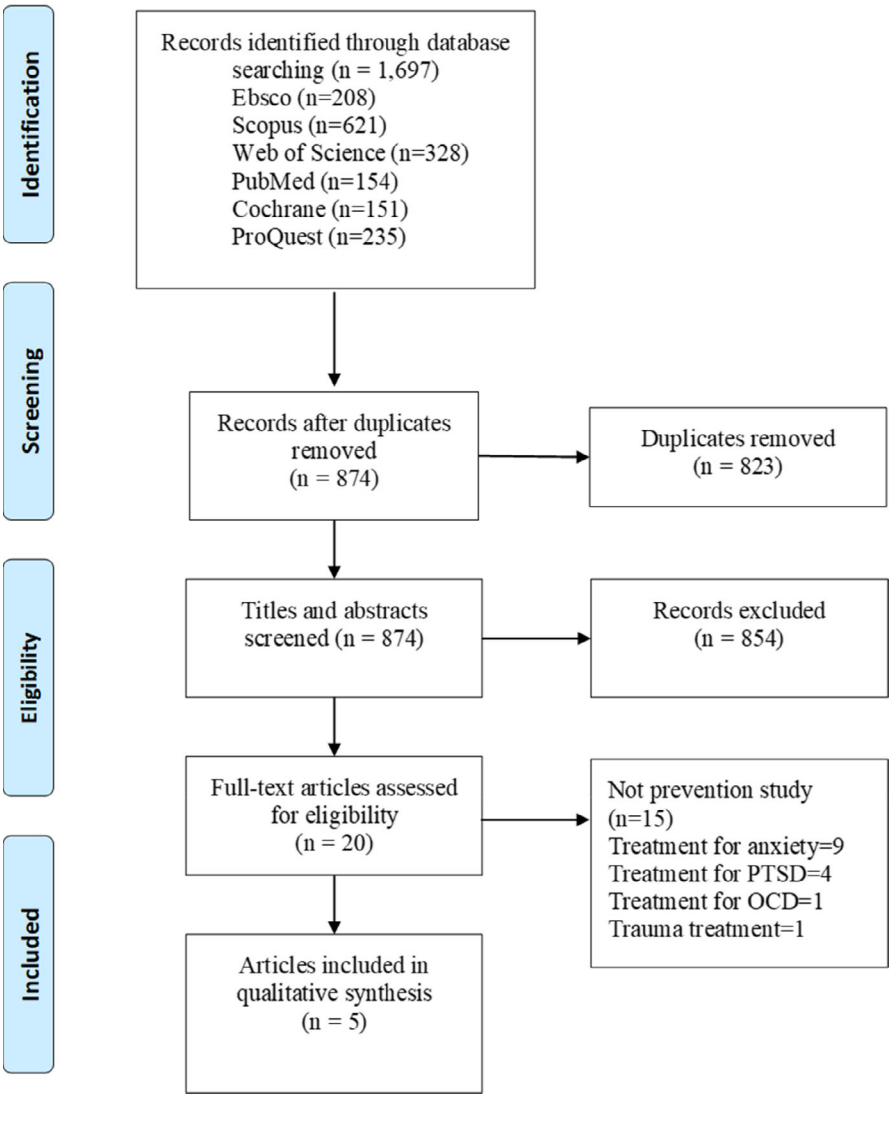

Figure 1. Flow diagram

detailed grading by Ophuis et al. (2017). Their description of the scoring instructions for quality assessment is transparent with explicit instructions, and they also provide a suboptimal = 0.5 score instead of using only yes = 1 or no = 0. The scoring and explicit instructions can be found in Table S1. Finally, one question was added: Was dealing with missing values reported (question number 6)? Dealing with individual's missing values is a frequent problem in CEA in a randomised controlled trial. If missing data are not handled using appropriate methods, it can lead to misleading economic evaluation results (Faria, Gomes, Epstein, & White, 2014). Additionally, we supplemented question 14 (Ophuis et al., 2017) by adding the condition 'When the ICER calculation is not conducted using the standard method, the score is never 1'. The standard way of calculating both incremental costs and effectiveness is important for making correct interpretations.

The threshold for the inclusion level was at least 50% of the scores of the methodological quality that needed to be achieved for inclusion in the final review. According to the instructions by Ophuis et al. (2017), the assessment was based solely on this included article with no information obtained from other publications of the study or through contacting the authors.

Results

Study selection

The original and updated searches yielded a total of 1697 articles (Figure 1). After duplicate removal, 874 articles remained. 854 articles had been excluded based on the title and abstract. The remaining 20 articles were read in more detail, and 15 were excluded because they were not preventive programmes. Only five articles (Chatterton et al., 2020; Mihalopoulos, Vos, et al., 2015; Simon, Dirksen, & Bögels, 2013; Simon, Dirksen, Bögels, & Bodden, 2012; Stallard et al., 2015), describing four unique studies, met the entry criteria. Cohen's kappa between the reviewers was 0.83, which refers to an almost perfect agreement.

Description of the included studies and interventions

The five included articles (Chatterton et al., 2020; Mihalopoulos, Vos, et al., 2015; Simon et al., 2012, 2013; Stallard et al., 2015) studied four different interventions. Two articles concerned studies conducted in Australia (Chatterton et al., 2020; Mihalopoulos, Vos, et al., 2015), two were based on the same RCT study in the Netherlands (Simon et al., 2012, 2013) and one study was conducted in the UK (Stallard et al., 2015). Two articles reported different studies but were based on the same prevention programme, currently called *Cool Little Kids* (Chatterton et al., 2020; Mihalopoulos, Vos, et al., 2015). The interventions were compared with the do-nothing group in an article by Mihalopoulos, Vos, et al. (2015) and to the usual care group in an article by Chatterton et al., 2020. The type of prevention was universal in one study (Stallard et al., 2015), selective in two studies (Chatterton et al., 2020; Mihalopoulos, Vos, et al., 2015) and indicated in two publications from the same study (Simon et al., 2012, 2013). Three studies comprised a cost-effectiveness analysis in randomised controlled trials (RCT) (Chatterton et al., 2020; Simon et al., 2012; Stallard et al., 2015), and two were economic modelling studies (Mihalopoulos, Vos, et al., 2015; Simon et al., 2013). The intervention cost per participant varied from 64€ to 557€. Universal prevention was the least expensive (Stallard et al., 2015), and the most expensive was child-focused CBT intervention (Simon et al., 2012, 2013). Table 1 presents the study characteristics.

The universal CBT-based preventive intervention (FRIENDS) aimed to develop skills to counter the cognitive, emotional and behavioural aspects of anxiety (Stallard et al., 2015). From the 14 school-led interventions, five were led by class teachers, four by PSHE (personal, social and health education) coordinators, three by learning support assistants and two by head teachers. Two external health facilitators assisted them in delivering the intervention. Health-led FRIENDS was delivered by two health facilitators. The facilitators were either school nurses or psychology assistants, external to the school, with the class teacher providing support.

The studies by Mihalopoulos, Vos, et al. (2015) and Chatterton et al. (2020) were based on the same selective prevention intervention called *Cool little Kids* developed by Rapee, Kennedy, Ingram, Edwards, and Sweeney (2005). Rapee et al. (2005) described it as a selective/indicated intervention for the prevention and early intervention of anxiety disorders. However, we classify it as selective because a certain level of shyness, and inhibition was assessed and estimated to be a risk for the development of anxiety disorders. The content of the parenting sessions comprised themes such as motivating parents, principles of parent-management techniques, the importance of overprotection in maintaining anxiety, principles and application of exposure hierarchies, etc. The sessions were led by a clinical psychologist with experience in treating anxious children.

In the RCT study (Simon et al., 2012), the prevention intervention consisted of child-targeted intervention (CI) and parent-targeted intervention (PI). Two therapists, with a background in psychology, provided cognitive behavioural therapy (CBT). Both interventions (CI and PI) were guided by age-appropriate workbooks and were based on existing CBT techniques. In the PI sessions, parents trained to be a lay therapist for their children. In the CI sessions, children could also act as lay therapists for each other. Additionally, the results of the RCT were used by the same authors (Simon et al., 2013) in a modelling study. The model also included screening information and intervention was also offered to median-anxious children who were regarded as representing all children who were not high anxious. Four strategies were modelled: CI, PI, NI and a strategy in which the type of intervention offered (CI/PI) depended on parental anxiety. Families with parental anxiety were offered PI, and families with no parental anxiety were offered CI (Simon et al., 2013). A description of the interventions is shown in Table 1.

Economic evaluation results

Four articles comprised cost-effectiveness analyses and included anxiety-specific outcome measures as primary outcomes: One article used the validated RCAD (Revised Child Anxiety and Depression Scale) as a health outcome measure (Stallard et al., 2015), and three other articles used the validated ADIS measure (Anxiety Disorder Schedule) (Chatterton et al., 2020; Simon et al., 2012, 2013). Two articles included cost-utility analyses, one used DALY (Disability-Adjusted Life Year) (Mihalopoulos, Vos, et al., 2015) as a primary outcome, and Stallard et al. (2015) used QALY as a secondary outcome. Most of the studies found a small or modest favourable

Table 1. Description of included studies and interventions

	Chatterton et al. (2020)	Mihalopoulos, Vos, et al. (2015)	Simon et al. (2012)	Simon et al. (2013)	Stallard et al. (2015)
Country	Australia	Australia	The Netherlands	The Netherlands	UK
Year of intervention	NA (Screening 2011–2012)	2003–2004	2004–2008	2004–2008	2011–2012
Prevention type	Selective	Selective	Indicated	Indicated	Universal
Intervention (sample size)	*Cool Little Kids*, psychology-led parenting course, 6 × 1.5-hr group sessions over 10 weeks (n = 265) (Rapee et al., 2005)	Psychology-led parenting course, 6 × 1.5-hr group sessions over 10 weeks (n = 63). (Rapee et al., 2005)	Parent-focused CBT (PI), 3 group sessions and 5 telephone sessions for parents (n = 49). Child-focused CBT (CI), 8 × 90-min group sessions for children (n = 47). Estimated duration of intervention: 2–3 months	Parent-focused CBT (PI), 3 group sessions and 5 telephone sessions for parents (n = 49). Child-focused CBT (CI), 8 × 90-min group sessions for children (n = 47). Estimated duration of intervention 2–3 months.	FRIENDS, an evidence-based CBT, health-led (n = 122) or school-led (n = 96). 60-min sessions over 9 consecutive weeks.
Comparative alternative (sample size)	Usual Care (n = 280)	Do nothing (n = 53) (Rapee et al., 2005)	NI (n = 43)	NI for high-anxious (n = 43) NI for median anxious (n = 63)	Usual school PSHE lessons (n = 90)
Follow-up	1 year	3 years	2 years	2 years	6 months
Recruitment	Preschools (n = 307) in Melbourne, Victoria. A screening questionnaire was distributed to all parents of children enrolled in preschool (n = 17,661). 6346 questionnaires were returned.	Preschools within a 10-km radius of Macquarie University in Sydney, Australia. 5609 screening packages were distributed to parents. 1647 were returned. Additionally, 73 participants were recruited via telephone.	Children and parents were recruited via primary school. Out of the 136 schools that were approached, 50 participated in the study.	Children and parents were recruited via primary schools. Out of the 136 schools that were approached, 50 participated in the study.	A list of primary schools in Bath, North East Somerset, Swindon and Wiltshire within a 50-mile radius of the University of Bath was compiled from local authority information (n = 268). 45 schools volunteered.
Study population	Preschool children aged 4 years who scored as inhibited (STSC) n = 703.	Preschool children aged 3–4 years who scored as inhibited (STSC) n = 281.	Primary school children aged 8–12 years who scored as high-anxious (SCARED-71 questionnaire) n = 412.	Primary school children aged 8–12 years who scored as high or median anxious (SCARED-71 questionnaire) n = 584.	Primary school children aged 9–10 years attending school and participating in PSHE n = 1448.
Drop-out rate	Interview 10.5% Questionnaire 10.1%	17%	77%	77%	13%
Cost of intervention per participant	$AU349 (225€) Cost of Screening $AU 200 (129€)	NA	CI 484€ (565€) PI 389€ (454€)	CI 514€ (557€) PI 413€ (448€) Cost of screening 8€ (9€)	Health-led £52 (65€) School-led £56 (71€)

(), monetary values in 2018 euros; CBT, cognitive behavioural therapy; CI, child-focused intervention; NA, not applicable, only the total cost of the intervention was mentioned; NI, no intervention; PI, parent-focused intervention; PSHE, personal, social and health education; SCARED-71, The Screen for Child Anxiety Related Disorders; STSC, Short Temperament Scale for Children.

Table 2. Description of economic evaluations

	Chatterton et al. (2020)	Mihalopoulos, Vos, et al. (2015)	Simon et al. (2012)	Simon et al. (2013)	Stallard et al. (2015)
Study design	RCT	Modelling	RCT	Modelling	RCT
Type of economic evaluation	CCA, CEA[a]	CEA, CUA	CEA	CEA	CEA, CUA
Primary effectiveness outcome	ADIS-diagnosed anxiety	DALY	ADIS improved	ADIS improved	RCAD
Cost perspective	Healthcare sector and societal	Healthcare sector	Societal	Societal	The joint perspective of the health sector (NHS) and the education/social services sector
Included costs	Screening costs, intervention costs, child's use of healthcare services, medication and hospitalisation over the preceding 12 months for managing the child's behaviour, use of healthcare services by the parents, travel costs for the parents, parental lost productivity, childcare costs.	Teacher costs (salary) and psychologist costs, inhibition scale plus postal charges, parents' time-use costs and travel costs.	Direct healthcare costs (e.g. visits to a psychologist), direct non-healthcare costs (e.g. professional out-of-pocket costs or over-the-counter medication). Only child-related costs.	Direct healthcare costs (e.g. visits to a psychologist), direct non-healthcare costs (e.g. professional out-of-pocket costs or over-the-counter medication), screening costs. Only child-related costs.	Intervention costs (staff time, training, supervision, facilitation, travel costs, printing and recruiting schools), GP visits, nurse consultations, medication, hospital services, mental health services, psychologist, school nurse, counsellor.
Percentage of quality points (Evers, Goossens, de Vet, van Tulder, & Ament, 2005; Ophuis et al., 2017)	78%	78%	76%	76%	84%

ADIS, Anxiety Disorder Schedule; CCA, cost-consequences analysis; CEA, cost-effectiveness analysis; CSRI, Client Services Receipt Inventory; CUA, cost-utility analysis; DALY, Disability-adjusted life year; RCAD, Revised Child Anxiety and Depression Scale; RCT, randomised controlled trial.

[a]Authors defined the analysis as CCA, but CEA was conducted.

difference in the effectiveness measure between the intervention group and the comparator, but only Simon et al. (2012) reported a statistically significant difference ($p < .05$), that is a higher proportion of ADIS-improved children in the intervention group compared with the no-intervention group. More detailed information can be found in Tables 2 and 3.

The costs were identified according to the chosen perspective in four articles (Chatterton et al., 2020; Simon et al., 2012, 2013; Stallard et al., 2015). However, in the article by Mihalopoulos, Vos, et al. (2015), detailed information about costs per participant was not available. Costs between articles are difficult to compare due to the different perspectives used. Cost data were mainly collected via self-reported questionnaires and interviews from participating families in all articles. Micro-costing was partially used in the articles by Chatterton et al. (2020) and Stallard et al. (2015). The project records offered information such as records of staff working hours, health facilitators' salaries and other expenditure. More detailed information about the types of costs is included in Table 2. Costs per participant varied between 1267€ and 3774€ from a societal perspective and between 84€ and 1371€ from a narrower perspective (health sector) (Table 3).

Detailed cost-effectiveness results are shown in Table 3. In the universal school-based programme, the only statistically significant difference between the groups at six months was the cost difference between health-led FRIENDS and usual school provision. The FRIENDS programme was dominated (i.e. more costly and less effective than the comparator), so it was not cost-effective (Stallard et al., 2015).

Screening inhibited temperament of preschool children and offering parenting course offered very good value for money at 8000$AU (5422€) per averted DALY compared with doing nothing. A threshold value of 50,000$AU per DALY was used for the value-for-money

Table 3. Cost-effectiveness results

	Chatterton et al. (2020)	Mihalopoulos, Vos, et al. (2015)	Simon et al. (2012)	Simon et al. (2013)	Stallard et al. (2015)
Effectiveness	ADIS-diagnosed anxiety: 44.2% Intervention 50.2% Control	460 DALY in three years	ADIS improved: 51% in CI 45% in PI 28% in NI	Expected ADIS improved: 19% in CI 18% in PI 19% in CI/PI 18% in NI	RCADS: Health-led 25.61 School-led 23.98 TAU: 27.70
Costs	Total health sector costs/child: Intervention: 1371 $AU (923€) Control: 935$AU (629€) Total societal costs/child: Intervention: 1882$AU (1267€) Control: 2384$AU (1605€)	Total costs 3.8 M $AU (2.57 M€)	Mean costs/participant: CI: 3234€ (3774€) PI: 2972€ (3468€) NI: 2987€ (3485€)	Expected costs/participant: CI: 1311€ (1422€) PI: 1304€ (1414€) CI/PI: 1297€ (1406€) NI: 1296€ (1405€)	Health-led: 64 €/child (84€), School-led: 64 €/child (86€), TAU: 11 €/child (14€)
ICER	Intervention was dominant from a societal perspective. Health sector perspective77$AU/anxiety case avoided (52€)	8000 $AU/ DALY with cost offsets (5422€) 12,000 $AU/DALY without cost offsets (8133€)	CI vs. PI: 4364 €/ADIS-improved child (5092€) PI versus NI: PI dominant PI would be the most cost-effective at a threshold of <3000€/ADIS-improved child, CI most cost-effective at higher thresholds	CI/PI vs. NI 107€/ADIS-improved child (125€)	TAU was dominant
Authors' conclusion	Screening and parental intervention from a societal perspective is likely to be cost-effective. From a health sector perspective, intervention appears to be favourable.	Screening and parental intervention in the prevention of anxiety in children and adolescents represent very good value for money.	Child- or parent-focused preventive interventions are cost-effective compared with the doing nothing option. The parent-focused intervention was the optimal approach when parents were anxious and also at lower monetary thresholds set by society.	The implementation of screening and offering child- or parent-focused prevention based on parental anxiety, compared with doing nothing, requires a societal investment of 107€ (125€) for each additional ADIS-improved child. However, the difference between the effects and costs were small, so the results should be treated with caution.	It is unlikely that the FRIENDS intervention is cost-effective compared with the usual way of teaching.

ADIS, Anxiety Disorder Schedule; CI, child-focused intervention; CI/PI, offering child- or parent-focused intervention based on parental anxiety; cost offsets, costs saved by diseases or disorders that are avoided; DALY, Disability-adjusted life year; NI no intervention; PI, parent-focused intervention; QALY, Quality-adjusted life year; RCAD, Revised Child Anxiety and Depression Scale.

criterion (Mihalopoulos, Vos, et al., 2015). Chatterton et al. (2020) evaluated the same parenting course *Cool Little Kids* but did not include the cost of screening in their ICER calculation. They took screening costs into account in their sensitivity analyses. From a societal perspective, they concluded that the parenting course was likely to be cost-effective because it was associated with lower incremental societal costs and fewer anxiety diagnoses. From a healthcare perspective, the incremental cost was 77$AU (52€) for each additional anxiety case avoided compared with usual care.

Both parental- and child-focused CBT interventions would be cost-effective compared with 'no intervention', but the choice between PI and CI remained uncertain (Simon et al., 2012). The sensitivity analysis revealed that PI would be the most cost-effective intervention when the parents were high-anxious, and CI would be the most cost-effective intervention if only the child was high-anxious. The ICER of CI vs. PI per ADIS-improved child was 4364€ (5092€). In the modelling version, the comparison of four strategies showed that screening and offering child- or parent-focused prevention based on parental anxiety, compared with doing nothing, required a societal investment of 107€ (125€) for each additional ADIS-improved child (Simon et al., 2013).

Quality of articles

Table S1 describes the quality scores for the included articles. The range of scores varies between 76% (Simon et al., 2012, 2013) and 84% (Stallard et al., 2015). All studies received full scores from five questions: research question, economic study design, identification of outcomes and conclusions. The chosen time horizon was mentioned in all the included studies, and it was also applied to both effectiveness and costs.

The study population was well described by Chatterton et al. (2020) and Stallard et al. (2015). In the other articles, we needed to search earlier publications in order to identify the populations from which the participants were recruited. In two RCT studies (Simon et al., 2012; Stallard et al., 2015), the competing alternatives were clearly described, but in the RCT study by Chatterton et al. (2020) and in both the modelling studies (Mihalopoulos, Vos, et al., 2015; Simon et al., 2013), we needed to search for the description from previous studies. The model-based structural assumptions were easy to find in the modelling article by Simon et al. (2013), but in the article by Mihalopoulos, Vos, et al. (2015), they were only superficially described.

The effectiveness outcome measure was clearly identified in all other articles, except the article by Mihalopoulos, Vos, et al. (2015), in which we needed to search for the information from an earlier publication (Rapee et al., 2005). Chatterton et al. (2020) did not report baseline outcome measures but baseline sample characteristics are reported in another publication (Bayer et al., 2020). The cost measurement in all included studies was based on self-reported measures. The discounting for costs was conducted when follow-up was longer than one year. However, it was only in the article by Mihalopoulos, Vos, et al. (2015) that the discounting was conducted for both costs and effectiveness. In the articles by Simon et al. (2012, 2013), the discounting was conducted solely for costs. The incremental analysis of costs and effectiveness was presented in all articles.

Of these five articles, in three of them, authors declared their competing interest (Chatterton et al., 2020; Mihalopoulos, Vos, et al., 2015; Stallard et al., 2015). In the article by Simon et al. (2013), the authors declared that they had no competing interest, but they did not report this in their earlier article (Simon et al., 2012). Ethical and distributional issues were discussed in two studies (Mihalopoulos, Vos, et al., 2015; Stallard et al., 2015). Generalisability was not explicitly reported in any of the articles.

We also searched for the published protocols of the included studies. Two articles (Chatterton et al., 2020; Stallard et al., 2015) referred to a study protocol (Bayer et al., 2011; Stallard et al., 2012, 2014) and one (Mihalopoulos, Vos, et al., 2015) referred to a general ACE prevention protocol (Carter, Vos, Barendregt, & Mihalopoulos, 2005). For the study by Simon et al. (2012, 2013), no protocol was mentioned.

Discussion

This review summarised the health economic evidence of anxiety prevention interventions for children and adolescents. The results indicate that the evidence is weak for the cost-effectiveness of anxiety prevention in children and adolescents, and differences between the types of prevention. This is the first review to consider the cost-effectiveness of anxiety prevention in children. The number of economic evaluations was small, and there were limitations and differences between the articles, which complicated the review summary.

We found only one universal prevention study, and it appears that universal CBT-based anxiety prevention (FRIENDS intervention) is unlikely to be cost-effective. They found no significant difference in effectiveness between the intervention and control group at 6 months (Stallard et al., 2015). In their systematic review, Waldron et al. (2018) found that the FRIENDS intervention had achieved long-term effects, but more data are needed. A recently published review by Schmidt et al. (2019) stated that evidence of the cost-effectiveness of school-based anxiety prevention interventions is lacking and also highlighted that there is a need for long-term cost-effectiveness studies.

The *Cool Little Kids* selective prevention (parent training intervention) was evaluated in two articles. Mihalopoulos, Vos, et al. (2015) regarded parent training as 'good value for money' based on their modelling study, whereas in their RCT study, Chatterton et al. (2020) found no statistically significant difference in effectiveness compared with care as usual. Another indicated prevention also showed signs of cost-effectiveness. Child-focused and parent-focused CBT intervention groups differed statistically significantly from the control group, with more anxiety-free children. Between the intervention groups, there were no statistical differences. The parent-focused programme was a cost-effective choice if a parent was also anxious. The child-focused intervention was the better option when only the child was anxious, compared with the no-intervention option (Simon et al., 2012). On the other hand, according to the results of the modelling study with screening information by Simon et al. (2013), if society's willingness-to-pay threshold is very low (below 107€), then the no-intervention option is cost-effective. Nevertheless, the difference between the effects and costs of all comparative strategies was small. Thus, the results should be interpreted with caution. Other reviews (Lawrence et al., 2017; Schwartz et al., 2019) also noted that targeted, including indicated and selective, prevention was effective. Bodden et al. (2008) found that individual CBT treatment is more cost-effective than family CBT treatment, although the choice between individual and family CBT in the context of prevention remains uncertain.

Based on this review, the evidence about the cost-effectiveness of anxiety prevention in children and adolescents is weak. It has been stated that indicated and selective prevention is more effective than universal prevention (Fisak et al., 2011; Teubert & Pinquart, 2011; Topper, Emmelkamp, & Ehring, 2010). Based on this review, it appears that these are more likely to be cost-effective than universal prevention. This raises the question of to whom and in what way should prevention actions be offered. It appears that the effect of universal prevention is not sufficient to cover the participation of individuals who have no need for prevention. On the other hand, screening increases costs, and these studies do not address the question of whether the cost of screening is worth the improved effectiveness. As this

review showed, a limited number of prevention studies have been conducted in the field of anxiety in children and adolescents. Many studies were excluded because they turned out to be treatment studies. The reason for the small number of prevention studies could be attributable to the small effect sizes of prevention interventions discouraging further research (Fisak et al., 2011; Waldron et al., 2018).

Evidence from health economics studies is important for ensuring that all stakeholders who deal with children and adolescent mental health issues make better resource allocation decisions. Previous economic evaluation reviews have focused on the treatment of anxiety disorders. Their results are similar to this review: The CBT method can be interpreted, with caution, to be a cost-effective way of reducing anxiety in children and adolescents. However, the different national service systems and the conceptualisation of anxiety complicates the generalisability of the research evidence. Anxiety may also be culturally related and national studies on anxiety prevalence are needed to define what is regarded as normal. In some countries, children tend to be more inhibited than in other countries. Thus, the same screening criteria might not work in all environments.

Strengths and limitations of the included studies

The quality of the included studies was good. This quality is particularly evident in the cost description, which was conducted in detail in most of the studies. However, the measuring and valuing of costs were suboptimal in all of the studies. Measuring effectiveness was conducted appropriately, and the conclusions followed the data coherently in all of the studies. However, the generalisability was weakly represented. Generalisability should be particularly considered when the sample sizes are small, and the interventions are dependent on the context. It is important for generalisability to confirm that the recruitment processes are clearly defined and reported in studies. This information is valuable for the implementation of intervention and for assessing population-level effectiveness.

The costs of healthcare service use were included in four articles (Chatterton et al., 2020; Simon et al., 2012, 2013; Stallard et al., 2015). However, data based only on self-reported data could cause bias. A systematic review by Leggett et al. (2016) showed that self-reported questionnaires on resource utilisation had good agreement with administrative data. However, visits to general practitioners, outpatient days and nurse visits had poorer commonality (Leggett et al., 2016). The use of administrative data would be valuable if it were available.

The primary outcome was symptom specific in most of the articles. Symptom-specific outcomes give a narrow picture about welfare and they lack economic threshold values which makes comparing and confirming cost-effectiveness difficult. Three of the articles used a validated measure ADIS as an effectiveness outcome. Although the measure is validated, researchers must confirm that the modified measure is also validated (i.e. ADIS improved). In economic evaluation studies, QALYs (Quality-adjusted life year) or DALYs (Disability-adjusted life year) are recommended effectiveness measures as they enable comparison across studies. In some countries, those measures have stated threshold values for unit of effectiveness. Future studies should consider inclusion of QALYs or DALYs as an effectiveness measure. However, issues in using QALYs in economic evaluation related to children and youth are identified (Rowen, Rivero-Arias, Devlin, & Ratcliffe, 2020).

There are also issues in the quality of studies related to small sample size and, short follow-ups, which weaken the usability of the study results in decision-making. The time horizon is an important factor in economic evaluation, particularly in the field of children's mental health (Knapp & Wong, 2020). The length of the follow-up had an effect on the results of cost-effectiveness in studies of depression. The cost-effectiveness results fluctuated between shorter and longer follow-up points, and this illustrates the enduring impact of childhood mental health problems in the long term. Long-term analyses are required in order to understand the economic impact of interventions with long-term consequences (Knapp & Wong, 2020).

The calculation of ICER requires both baseline and follow-up measurements so that a calculation of change within group and difference in changes between groups can be made. The ICER calculation can be based on follow-up measures only if there are no differences in baseline both outcome measures and costs as is the case if the randomisation is properly done and succeeds. The reporting of both baseline and follow-up data is important to assess the similarity of the groups. Chatterton et al. (2020) report that they did not have data on resources, that is costs at the baseline. The information on background characteristics at the baseline is reported (Bayer et al., 2020), and the likelihood of significant baseline differences in effectiveness outcome is low.

Decision-making concerns resource allocation and the choice regarding which interventions are adopted. Most articles in this review investigated the developed interventions compared with 'doing nothing' or 'care as usual'. Simon et al. (2012, 2013) studied two different interventions (child- or parent-focused CBT) and compared them with each other. It would be useful to compare a wider selection of interventions in order to identify the best option to adopt and help decision makers prioritise different interventions (Sampaio, Enebrink, Mihalopoulos, & Feldman, 2016).

Strengths and limitations of this review

A strength of this review was its broad search strategy combined with its strict inclusion criteria. In this broad search, we aimed to reduce the risk of relevant studies being excluded from the search. The consistency of the decisions by the two reviewers was assessed using the kappa statistic, and it resulted almost perfect agreement. Another strength is that the quality assessment of the included studies was conducted using the detailed description of the scoring instruction of the extended CHEC by Ophuis et al. (2017). The quality of the studies included in this review was good. Nevertheless, there is a chance of publication bias. Studies with negative or null-difference results might not be published (Dickersin, 1990). In this review, all monetary figures have also been presented in the same monetary values (2018 value converted to euros) in order to make the results more comparable.

We followed the recommended practice for conducting a systematic review: 'protocol registered before

commencement of the review, adequacy of the literature search, justification for excluding individual studies, and consideration of risk of bias when interpreting the results of the review' (Costa, Cary, Helling, Pereira, & Mateus, 2019). This systematic review follows the PRISMA statement (Moher et al., 2009), although we experienced some challenges. We could not conduct a quantitative synthesis of the results due to the methodological differences in the studies, that is different effectiveness outcomes and challenges in calculating the cost-effectiveness of the primary outcome. Also, differences in cultures and structures between countries made it difficult to pull results together.

Conclusion

Anxiety disorders can have long-term health effects and broad economic effects. Nevertheless, only a few economic evaluation studies have been conducted on anxiety prevention in children and adolescents. From the limited evidence available, the universal prevention of anxiety does not appear to be cost-effective. Other types of prevention, namely, selective and indicative prevention, might constitute a cost-effective use of resources. This review highlights the existing paucity of evidence in prevention research.

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Ethical information

No ethical approval was required for this review.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search strategy.
Table S1. Quality assessment of the included articles.

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