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Review Article

Effect of Animal-Assisted Activities on Symptoms and Emotions of Children with Neoplastic Disease: A Systematic Review with Meta-Analysis

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Background: Animal-assisted activities (AAAs) have long been present in pediatric oncology as a nonpharmacological intervention aimed at helping children cope with symptoms and negative emotions during hospitalization and antineoplastic treatment. Among the systematic reviews in the literature, there is a lack of one with meta-analysis that includes only RCTs centered on the effect of the intervention on symptoms and emotions in children with neoplastic disease.
Objective: To synthesize the effect of AAAs on symptoms and emotions of children with neoplastic disease.
Methods: Studies were searched from biomedical databases Cochrane Library, MEDLINE, EMBASE, CINAHL, PsycINFO, Web of Science, Scopus, AMED, sciELO, LILACS, CNKI, J-GLOBAL, J-STAGE, main trial registries and major sources of grey literature. Searching for useful documents took place from the inception of each resource until April 18, 2024. The risk of bias of included studies was assessed with RoB 2, and the overall effect size of the intervention was calculated by creating random-effects meta-analyses graphically represented by forest plots. The summary of findings was illustrated with a table in accordance with the GRADE method.
Results: Three parallel-group randomized controlled trials with low risk of bias were included (N = 151, mean age: 8.5-11.2 years). AAAs are promising for anxiety reduction (N = 134; SMD = -0.07 [95% CI: -0.40, 0.27], p > 0.05) and quality of life improvement (N = 84; SMD = -0.11 [95% CI: -0.53, 0.31], p > 0.05) in children and for anxiety reduction (N = 154; SMD = -0.50 [95% CI: -1.52, 0.52], p > 0.05) in parents/caregivers. The certainty/quality of evidence is low to very low.
Conclusions: The effect of animal-assisted activities to reduce anxiety and improve the quality of life of children with neoplastic disease and to reduce parent/caregiver anxiety is small to moderate; however, the quality/certainty of evidence is very low to low. Therefore, further studies on the topic that overcome the current limitations need to be conducted in order to collect more robust data in favor of implementing the intervention in pediatric oncology.

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Introduction

Although cancer remains a leading cause of death in the pediatric population [1], its prognosis has improved over the past decades [2]. The counterpart of this positive outcome is the use of intensive, and prolonged treatment protocols involving multiple hospitalizations and/or outpatient care over a period of time generally exceeding one year [3][4]. During this time, the child is exposed to invasive procedures that cause him or her physical and emotional suffering [5]. Pain is the most prevalent symptom, followed by fatigue, anxiety, fear, and depression [6][7][8][9][10]. Added to this is the sense of distress, which assails the child in seeing his or her body image gradually change [6]. The effects are manifested in terms of psychological disorders, social withdrawal and maladaptive behaviors, with a negative effect on the treatment process, the overall clinical condition [6][11][12][13], self-image and the ways of interacting with family members and peers [6][7]. In summary, the synergistic action of hospitalization and antineoplastic treatment can cause important and lasting negative effects on a child's mental health and quality of life.

The use of alternative therapies to complement traditional medical care, alleviate symptoms, manage and control negative emotions, promote positive ones, and improve the child's perceived quality of life during hospitalization and antineoplastic treatment must be a primary goal of nursing care in pediatric oncology [14][15]. These therapies include pet

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therapy, which has long been present in a wide variety of settings, including the oncology setting, benefiting large segments of the population, including the pediatric population [16].

The first documented study of the scientific use of animals for therapeutic purposes dates back to 1859 by Florence Nightingale, who discovered that the presence of small pets was an important support to the healing process of the acutely ill and an excellent companion for the chronically ill [17]. In 1964, child psychologist Boris Levinson was the first to coin the term "pet therapy"; he observed that his own dog spontaneously interacted with a child with autism, activating responses and reactions in him that had not been achieved with traditional treatment [18]. In 1977, veterinarian Leo K. Bustad and psychiatrist Michael J. McCulloch formed the Delta Foundation in Portland, Oregon, USA, which later became the Delta Society in 1981, with the goal of improving people's health and well-being through interactions with animals. In the late 1980s and early 1990s, among the initiatives promoted by the Delta Society was the Pet Partners® program, the first comprehensive and standardized training course on animal-assisted activities and therapy for volunteers and health care workers. In 2012, the Delta Society formally changed its name to Pet Partners, currently one of the largest organizations in the field of hospital-based pet therapy in the United States. In Italy, pet therapy has been recognized as an official treatment since 2003 [19]. Thanks to the partnership between the Istituto Superiore di Sanità, Centro di Referenza Nazionale per gli Interventi Assistiti da Animali (National Reference Center for Animal-Assisted Interventions) and the Ministry of Health, the National Guidelines for Animal-Assisted Interventions were issued in 2015 in order to protect people's health and the welfare of the animals used, define operational standards for the correct and uniform application of the interventions, provide guidance on the tasks and responsibilities of the professional figures and operators involved (e.g., nurses, veterinarians, physicians, psychologists, educators), and identify training methods [20].

The term "pet therapy" is widespread but inaccurate; more appropriately, one should speak generally of "animal-assisted intervention" (AAI), but specifically of "animal-assisted activity" (AAA) or "animal-assisted therapy" (AAT) [8][21][22]. Both of these interventions involve interaction between a pet and a human being, take place mostly in outpatient clinics, hospitals, or residential facilities, and are designed to complement and supplement traditional therapeutic modalities [6][23]. They are sometimes used interchangeably in the literature but possess distinctive characteristics [15].

AAT can be an essential part of individualized treatment aimed at people with physical, social, emotional, or cognitive difficulties, or suffering from conditions such as autism or depression; it requires stated goals for each session and is aimed at a specific clinical outcome [6][15][24][25][26]. The animal is carefully selected and undergoes a formal training period; the handler (who often coincides with the trainer) must undergo specific training based on the treatment to be delivered [25][27][28][29]. Progress must be documented, and sessions are multiple and scheduled to last a set period of time depending on the person's needs and resources [6][15][25].

AAA aims to manage symptomatology and negative emotions, offer comfort, and improve people's quality of life with brief (usually 15-30 minutes) informal pet visits accompanied by a handler (the owner or trainer); the manner of interaction with the animal is at the discretion of the person in agreement with the handler, and there are no specific therapeutic goals. No formal training of the animal or special training of the handler is usually required, and the same animal is not always paired with the same person [6][15][25]. Progress is not documented, and there are few sessions (sometimes only one) [6][15][25]. The theoretical frameworks underlying the effects observed after AAA in oncology include the biophilia hypothesis, social support theory, general human-animal bonding theory, cognitive stress activation theory, the object-self hypothesis, and the science of unitary humans (Holder 2020b). Specifically, the biophilia hypothesis holds that humans have a natural attraction to other living things [30][31][32][33] and this triggers the initial impulse to interact with the animal. This hypothesis would be able to justify the benefit observed even during a single session of short duration, a typical feature of AAAs [34].

According to Johnson et al. [35], specific populations that may benefit most from AAAs include individuals with malignancy, especially children. For them, the positive effects occur at several levels: (a) they reduce anxiety and pain, promote positive emotions, and improve mood [6][13][21][36][37][38][39]; (b) they increase interaction skills by acting as a "social lubricant" [8][15][21][38][40]; (c) they help normalize the experience of hospitalization [38][41], allow for the acquisition of self-esteem and confidence, and nurture a sense of responsibility, enabling the child to orient to the future by overcoming the sick condition [6]; (d) they improve cooperation in treatment and encourage active participation [12][42]; (e) they reduce blood pressure and heart rate [43]; (f) they increase plasma concentrations of endorphins, which help relieve pain, reduce stress, and generate a feeling of well-being; and (g) they decrease plasma concentrations of cortisol, which negatively affects the degree of stress.

There are three systematic reviews in the literature that have addressed the effectiveness of AAIs on children. A systematic review with meta-analysis [44] investigated the efficacy of AAIs on some clinical outcomes in children and adults; however, participants also had pathologic conditions that were not neoplastic in nature, and there was no subgroup analysis by age group. A systematic review [45] summarized the available evidence on the effectiveness of AAIs in pediatric oncology; however, the authors included both observational and experimental studies and did not perform a quantitative synthesis. Finally, a recent systematic review with meta-analysis [46] summarized the effectiveness of AAT on pain management in hospitalized children; however, again, participants had been hospitalized for pathological conditions including non-neoplastic conditions, and the authors included both randomized and nonrandomized controlled experimental studies. Thus, a systematic review with meta-analysis of

randomized controlled clinical trials summarizing the effect of AAAs on children with neoplastic pathology is lacking. It is considered important to undertake this study because the results could fill a significant gap in the knowledge of the effectiveness of this intervention in pediatric oncology and prove useful in obtaining new information to help optimize and personalize its application.

Objective

The study aims to summarize the effect of AAAs on the symptoms and emotions of children with neoplastic disease.

Methods

To achieve the objective, a systematic review with meta-analysis was conducted in accordance with PRISMA guidelines [47]. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42024540556).

Eligibility Criteria

The research question was formulated in accordance with the PICOS framework [48] (Table 1); the inclusion criteria were as follows: (1) participants: subjects with established neoplastic disease, aged 0-18 years, to be treated with oncology care during inpatient, outpatient, or day hospital; (2) intervention: animal-assisted activities; (3) control: standard of care; (4) outcomes: (a) primary - child's pain or anxiety, measured by any instrument at the end of the first visit or at the end of the study period; (b) secondary - child's fear, distress, fatigue, depression, stress, mood, discomfort, quality of life, measured by any instrument at the end of the first visit or at the end of the study period; (c) parent/caregivers' anxiety, measured by any instrument at the end of the first visit or at the end of the study period; (5) study design: parallel-group randomized controlled trials.

Studies were excluded: (1) with mixed populations (adults and children) in which the effect of the intervention on children could not be assessed; (2) in which the intervention was delivered to a group of children and not to the individual subject; (3) that compared the intervention in question with other interventions; (4) in which at least one of the outcomes, primary or secondary, of interest was not present; (5) conducted in the community.

P	Patient	Children with neoplastic disease
I	Intervention	Animal-assisted activities
C	Comparison	Standard of care
O	Outcome	Symptoms, emotions
S	Study design	Parallel-group randomized controlled trials
Research Question - In children with neoplastic disease, are animal-assisted activities more effective on symptoms and emotions than standard of care?		

Table 1. PICOS framework.

Information sources and search strategy

To answer the research question, the biomedical databases Cochrane Library, MEDLINE via PubMed, EMBASE via Elsevier, CINAHL via EBSCOhost, PsycINFO via Ovid, Web of Science via Clarivate, Scopus via ELSEVIER, AMED via EBSCOhost, sciELO, LILACS, CNKI, J-GLOBAL, J-STAGE were queried. In addition, web resources BASE, TRIP Medical Database, IBSS via ProQuest, Social Science Premium Collection via Proquest, Dissertations & Theses Global via Proquest, Google Scholar, and clinical trial registries ICTRP, ClinicalTrials.gov, EU Clinical Trials Register, ISRCTN were consulted. "Animal-assisted therapy," "neoplasm," and related synonyms were used as keywords to search the documents. The keywords were connected to each other with Boolean AND/OR operators; the search string was adapted to the characteristics peculiar to the queried information sources. The search strategy implemented on MEDLINE is shown in Table 2 as an example. References of eligible studies and available reviews were searched to retrieve other relevant studies. The search was restricted to records pertaining to the pediatric population and containing keywords or synonyms in the title and/or abstract. No language or publication date limits were imposed. Searching for useful documents took place from the inception of each resource until April 18, 2024.

Animal Assisted Therapy	AND	Neoplasm	AND	Preschool Child
OR		OR		OR
Animal Assisted Therapies		Neoplasms		Preschool Children
OR		OR		OR
Animal-Assisted Therapy		Tumor		Pre-school Child
OR		OR		OR
Animal-Assisted Therapies		Tumors		Pre-school Children
OR		OR		OR
Animal Facilitated Therapy		Tumour		Preschooler
OR		OR		OR
Animal Facilitated Therapies		Tumours		Pre-schoolers
OR		OR		OR
Pet Therapy		Neoplasia		Child
OR		OR		OR
Pet Therapies		Neoplasias		Children
OR		OR		OR
Pet Facilitated Therapy		Cancer		Adolescent
OR		OR		OR
Pet Facilitated Therapies		Cancers		Adolescents
OR		OR		OR
Pet-Assisted Therapy		Malignant Neoplasm		Adolescence
OR		OR		OR
Pet-Assisted Therapies		Malignant Neoplasms		Teen
OR		OR		OR
Pet Therapy Animal		Malignancy		Teens
OR		OR		OR
Pet Therapy Animals		Malignancies		Teenager
OR		OR		OR
Emotional Support Animal		Neoplastic Disease		Teenagers
OR		OR		OR
Emotional Support Animals		Neoplastic Diseases		Youth
OR		OR		OR
Comfort Animal		Neoplastic Entity		Youths
OR		OR		
Comfort Animals		Neoplastic Mass		
OR		OR		
Emotional Support Dog		Tumoral Mass		
OR		OR		
Emotional Support Dogs		Tumoural Mass		
OR		OR		
Therapy Dog		Tumorous Mass		

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OR		OR		
Therapy Dogs		Tumourous Mass		
OR				
Pet Therapy Dog				
OR				
Pet Therapy Dogs				

Table 2. Search strategy.

Study selection and data extraction

After the production of a shared search strategy, the authors independently queried the information sources by eliminating duplicates and selecting records based on relevance of title and/or abstract or, in doubtful cases, after full-text analysis. The record screening process was managed with a Microsoft Excel version 2016 spreadsheet. Any disagreements were resolved by comparison and discussion. From each included study, using a standardized and shared template, the authors independently extracted the following information: first author and year of publication; country; hospital or research facility and setting; sample characteristics; inclusion and exclusion criteria; intervention and control characteristics; outcome and its measurement tools; and any notes.

Risk of bias

The authors independently assessed the risk of bias of included studies with RoB 2 [49]. Any disagreement was resolved by comparison and discussion. RoB 2 is a tool for assessing the risk of bias of RCTs. It is structured in the following domains, in which biases may have been introduced: (a) bias deriving from the randomization process; (b) bias due to a change in the pre-established intervention; (c) bias due to missing data; (d) bias in the measurement of outcomes; (e) bias in the selection of the results reported in the study. For each domain, after having answered one or more signalling questions, through an algorithm it is possible to formulate a judgment of low risk of bias, "some concerns" or high risk of bias.

Data analysis and synthesis

The authors independently extracted the data and resolved any differences of opinion through comparison and discussion. The variables of interest for each outcome were sample size, mean, and standard deviation. In the presence of median, range, or interquartile range, conversion equations were used [50][51][52]. The overall effect size of the intervention was calculated with the standardized mean difference (SMD) and Cohen's d [53]. Effect size was considered small, moderate, or large for thresholds of d of 0.2, 0.5, 0.8, respectively [53]. In the presence of at least two studies per outcome, a meta-analysis was performed by applying a random-effects model and generating the corresponding forest plot. A 95% confidence interval was considered as the deviation from the point estimate for each individual study and from the overall estimated value for the aggregated studies. The presence of statistical heterogeneity ($p < 0.05$) was highlighted with Cochran's Q-test [54] and quantified with Higgins' I^2 index [55]. Values of $I^2 \leq 30\%$, $30\% < I^2 \leq 60\%$, $60\% < I^2 \leq 90\%$, or $I^2 > 90\%$ were assigned a low, moderate, high, or very high degree of statistical heterogeneity, respectively [56]. Statistical processing was performed with ProMeta© version 3.0 software.

Publication bias

Publication bias was assessed by inspecting the funnel plot [57] and applying the trim and fill method [58] in the presence of at least ten studies. Objective assessment of publication bias was performed with Egger's test [59] and Begg and Mazumdar's test [60].

Sensitivity analysis

In the presence of studies at high risk of bias, sensitivity analysis was performed by regenerating the meta-analysis after their exclusion.

Additional analysis

Subgroup analyses were planned to assess the effect of animal-assisted activities according to participants' gender and age.

Summary of findings

The authors independently performed the overall assessment of certainty/quality of evidence using the GRADE method [61] applied to the meta-analysis results. Disagreements that emerged were resolved by comparison and discussion.

Results

Selection of studies

Searching for useful records took place on April 18, 2024. The PRISMA flowchart [47] in Figure 1 illustrates the record selection process. A total of 178 records were identified. Net of duplicates and irrelevant records after reading titles and abstracts, 30 studies, for as many records, were analyzed in full text and evaluated for eligibility. Twenty-seven were excluded because they did not meet the inclusion criteria, while three were included in the systematic review and quantitative synthesis [62]

[63][64]. No other studies of interest were found after consulting the references of eligible studies and relevant reviews.

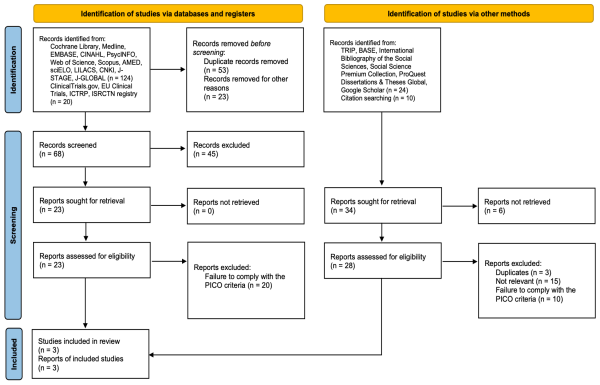

Figure 1. PRISMA Flow Diagram.

Characteristics of the studies

The studies cover a 6-year time frame from 2018 [64] to 2024 [63] (Table 3) and were conducted in the United States. One of these studies is multicenter [64]. All studies received funding; the last author of one study [62] reported a possible conflict of interest. There were a total of 151 children recruited and 187 parents/caregivers. The age range was 3-17 years, the mean age 8.5-11.2 years (63.2-69.2% Caucasian), and the percentage of males 47.4-57.7%. The prevalent diagnoses were acute lymphoblastic leukemia (51.9%) [64], leukemia or lymphoma (61.5%) [62], and advanced solid tumor (52.6%) [63]. The percentage of participants who owned a pet was 57.9-84.6%. The most frequent exclusion criteria were the presence of cognitive impairment in the child and/or parent/caregiver and fear or allergy to animals. Animal-assisted activities all included the presence of a trained dog and its handler. The breed of dogs was specified in only one study [64], and these were predominantly Labradors and Golden retrievers. The intervention was weekly for all studies, was individual, and could take place in the outpatient clinic, in the inpatient room, or in dedicated spaces within the hospital. The duration of the intervention was 10-20 minutes; activities were at the discretion of the child and/or handler but generally involved the child petting, cuddling, or playing with the dog. Studies have compared animal-assisted activities with standard of care; of the latter, no study has provided a description. The outcomes assessed after the intervention were as follows: (a) child anxiety [62][63][64], measured by PedsQL VAS - anxiety item [65] or STAI-CH [66]; (b) child quality of life [62][64], measured by PedQL VAS [65] or PedsQL [67]; (c) caregiver/parent anxiety [62][63][64], measured by STAI Short Form [68] or STAI [69]. In addition, one study [62] measured the levels of clinically important pathogens on each child's hands, and one study [64] measured the child's heart rate and blood pressure. The outcomes were assessed at baseline, after the first view [62], at the first and fourth views [63] or at the end of the intervention [64], in this case as arithmetic averages of the values measured in the previous sessions. The duration of the studies was 1-4 months. In two studies [62][63] the COVID-19 pandemic conditioned the recruitment of participants.

Study (year)	*Country*	*Setting*	*Sample*	*Inclusion criteria*	*Exclusion criteria*	*Intervention*	*Control*	*Outcome*	*Notes*
Chubak (2023)	United States	Seattle Children's Hospital (Seattle, WA)	N = 26 (IG = 12, CG = 14), mean age 11.2 years, range 5–12 years, males 57.7%, Caucasian race 69.2%, diagnosed with leukemia or lymphoma 61.5%, pet owner 84.6% Caregivers or parents: N = 19	English-speaking subjects aged 5 to 17 years regardless of the type of neoplasm and gender, race, or ethnicity	Allergy to or fear of dogs, subjects undergoing bone marrow transplantation or isolation precautions, with skin on hands not intact, without an English-speaking parent or legal guardian	Weekly inpatient room visits One visit per child lasting 20 minutes Hand hygiene before and after visit Activities at the discretion of the child and handler	Standard of care	Quality of life of the child Anxiety of caregivers/parents Detection of clinically relevant pathogens on children's hands after the first AAA	Data collection performed before randomization, before and after the first AAA, approximately 9 days after the first AAA, at discharge, 2–3 days after discharge (follow-up 1), 9 weeks after discharge (follow-up 2) Outcome assessed after the first AAA; subsequent assessments not illustrated due to poor adherence to follow-ups. At the first AAA, three children did not complete the questionnaire
Mahoney (2024)	United States	Vanderbilt Children's Hospital (Nashville, TN)	N = 19 (IG = 9, CG = 10), mean age 9 years, range 3–17 years, males 47.4%, Caucasian race 63.2%, diagnosed with solid tumor 52.6%, pet owner 57.9% Caregivers or parents: N = 21	English-speaking subjects aged 3–17 years, diagnosed with advanced cancer (relapsed or refractory)	Children or parents with cognitive impairment or fear of or allergy to dogs	Weekly outpatient visits (92.5%), occasional inpatient room One visit per child lasting 15 minutes Activities at the child's and/or handler	Standard of care	Child anxiety Anxiety of caregivers/parents	Data collection performed before randomization and weekly after each AAA (4 visits). Outcomes assessed after the first and last AAAs
McCullough (2018)	Unites States	Vanderbilt Children's Hospital (Nashville, TN); Randall Children's Hospital at Legacy Emanuel (Portland, OR); UC Davis	N = 106 (IG = 60, CG = 46), mean age 8.5 years, range 3–17 years, males 53.8%, Caucasian race 67.9%, diagnosed with acute lymphoblastic leukemia	Subjects aged 3 to 17 years, diagnosed with a type of cancer that would have required at least monthly outpatient	Children or parents with significant cognitive impairment, allergy or fear of dogs	Weekly visits in private and semi-private areas of the hospital, occasionally in the inpatient room	Standard of care	Anxiety of the child Anxiety of caregivers/parents Child's quality of life Blood pressure and heart rate of the child	Data collection conducted before randomization and weekly after each visit Outcomes assessed before randomization and at the end of the intervention

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Study (year)	*Country*	*Setting*	*Sample*	*Inclusion criteria*	*Exclusion criteria*	*Intervention*	*Control*	*Outcome*	*Notes*
		Children's Hospital (Sacramento, CA); St. Joseph's Children's Hospital (Tampa, FL); UMass Memorial Medical Center - Children's Medical Center (Worcester, MA)	51.9%, pet owner 67% Caregivers or parents: N = 147	treatment (e.g., leukemia, lymphoma, solid tumor, brain tumor), English or Spanish as the primary language of the child and his or her parents		One visit per child lasting 10-20 minutes Activities at the discretion of the child and handler			Seven children discontinued the study due to changes in treatment plan and/or noncompletion of questionnaires

Table 3. Main features of included studies.

CG = Control Group; IG = Intervention Group.

Risk of bias

In a study [64], the risk of bias is low; in the other two, the risk of bias is of some concern, since there is no information on assignment sequence concealment (Figure 2 and Figure 3).

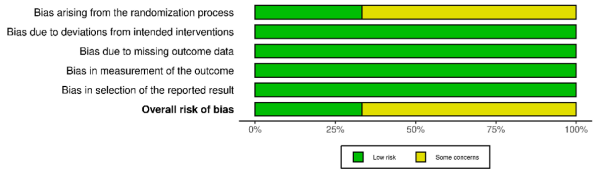

Figure 2. Risk of bias (summary plot).

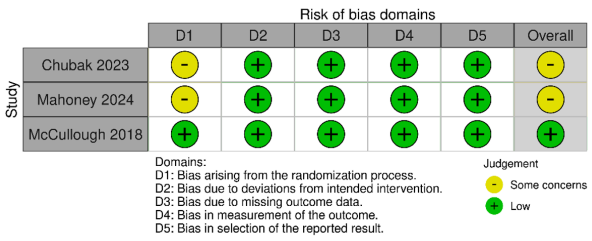

Figure 3. Risk of bias (traffic light).

Primary outcomes

Child pain

No studies have evaluated this outcome.

Child's anxiety

The child's anxiety was assessed by all studies. The values considered were those measured after the first visit [62][63] or the mean value calculated at the end of the study [64]. The analysis of the effect of AAAs on child anxiety compared with standard of care included 134 participants. The SMD (95% CI) was -0.07 ([-0.40,0.27], I2 = 0.00) in favor of the intervention in a statistically nonsignificant manner (Table 4). To help understand the clinical relevance of result obtained, the number of children to be subjected to intervention to reduce anxiety to one was estimated; this was done by converting Standard Mean Deviation (SMD) to Number-Needed-to-Treat (NNT). The calculated effect size (SMD = -0.07) corresponds to an NNT = 25,331: roughly speaking, more than 25 children need to be treated to observe anxiety reduction in one child.

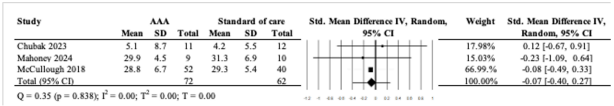

Table 4. Child's anxiety: AAAs vs standard of care.

Secondary outcomes

No studies assessed child's fear, distress, fatigue, depression, stress, mood, or discomfort.

Child's quality of life

The child's quality of life was assessed in two studies [62][64]. The values considered were those measured after the first visit [62] or the average value calculated at the end of the study [64]. The analysis of the effect of AAA on the child's

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quality of life compared to standard of care included 84 participants. The SMD (95% CI) is equal to -0.11 ([-0.53,0.31], I2 = 98.59%) in favor of the intervention in a statistically insignificant way (Table 5).

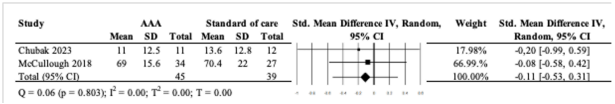

Table 5. Child's quality of life: AAAs vs standard of care.

Parental/caregivers anxiety

Parental/caregiver anxiety was assessed in all studies. The values considered were those measured after the first visit [62] [63] or the average value calculated at the end of the study [64]. The analysis of the effect of AAA on parents/caregivers' anxiety compared to standard of care included 154 participants. The SMD (95% CI) is equal to -0.50 ([-1.52,0.52], I2 = 83.48) in favor of the intervention in a statistically insignificant way (Table 6).

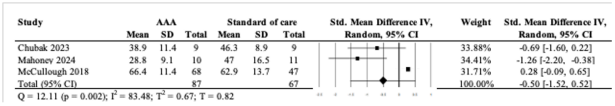

Table 6. Parental/caregivers anxiety: AAAs vs standard of care.

Additional analysis

Gender

No study has measured the effect of the intervention according to the gender of participants.

Age

No study has measured the effect of the intervention according to the age group of participants.

Sensitivity analysis

Sensitivity analysis was not performed as none of the included studies is at high risk of bias.

Publication bias

The studies included are less than ten; therefore, the funnel plot was not created, and the trim and fill method was not applied for the graphic evaluation of risk of bias. However, the objective assessment suggests that risk of publication bias, although possible, seems unlikely; in fact, the Egger test and the Begg and Mazumdar test are not statistically significant (p = 0.942 and p = 0.602, respectively).

Summary of findings

With the GRADE method, findings relating to the effect of AAAs on children with neoplastic pathology were summarized. Despite the trend in favor of intervention, the certainty/quality of evidence on children's anxiety and quality of life is low, and on parents'/caregivers' anxiety is very low (Table 7).

Summary of findings. Animal-assisted activities (AAAs) for symptoms and emotions in children with neoplastic disease.					
AAAs compared to standard of care for symptoms and emotions in cancer children					
Patient or population: children with cancer Setting: hospital, clinic, day hospital Intervention: AAAs Comparison: standard of care					
Outcome	Anticipated absolute effects* (95% CI)		N° of participants (studies)	Certainty/quality of the evidence (GRADE)	Comments**
	Risk with standard care	Risk with AAAs			
Children anxiety	-	The mean level of anxiety with AAAs was 0.07 standard deviation lower (0.40 lower to 0.27 higher).	134 (3 RCTs)	⊕⊕⊖⊖ Low[a]	There is no evidence of an effect of AAAs.
Children quality of life	-	The mean level of anxiety with AAAs was 0.11 standard deviation lower (0.53 lower to 0.31 higher).	84 (2 RCTs)	⊕⊕⊖⊖ Low[a]	There is no evidence of an effect of AAAs.
Parental/caregivers anxiety	-	The mean level of anxiety with AAAs was 0.50 standard deviation lower (1.52 lower to 0.52 higher).	154 (3 RCTs)	⊕⊖⊖⊖ Very low[a,b]	There is no evidence of an effect of AAAs.
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **0.2 represents a small difference, 0.5 a moderate difference, and 0.8 a large difference. AAAs: Animal-Assisted Activities; CI: confidence interval; RCT: Randomized Controlled Trial; QoL.					
GRADE Working Group grades of evidence High certainty - We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty - We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty - Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect Very low certainty - We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect					

Table 7. Effect of AAAs on symptoms and emotions of children with neoplastic disease: summary of findings.

[a] *Downgraded twice for imprecision: analysis based on < 100 participants per group.*

[b] *Downgraded once for inconsistency due to substantial heterogeneity (60% < I^2 < 90%).*

Discussion

Main results

The study aimed to summarize the effect of animal-assisted activities (AAAs) on symptoms and emotions of children with neoplastic disease. The included studies evaluated the benefit of the intervention on children's anxiety and quality of life and on parental/caregivers' anxiety. The results, statistically non-significant, reveal that (a) the intervention has a small effect on children's anxiety (SMD = -0.07; N = 134) and improvement in their quality of life (SMD = -0.11; N = 84); b) the intervention also has a moderate effect on parental/caregivers' anxiety (SMD = -0.50; N = 154). The level of certainty/quality of evidence is low or very low, so confidence in the effect estimate is limited or very limited: it is likely that the real effect is substantially different.

Comparison with other reviews

The results obtained from our study are consistent with those of previous systematic reviews [44][45][46], which demonstrates the benefit of the intervention both on child anxiety [44][46] and on parental/caregivers' anxiety [45][46]. As regards the effect on children's quality of life, it is not possible to make a comparison because previous reviews did not evaluate this outcome.

Implications for practice

Although statistical heterogeneity is zero for both anxiety and child quality of life, there are several sources of heterogeneity. First, there are two limitations common to all the studies: (a) the

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average age of the participants is between 8.5 and 11.2 years (school-age children), but the age range is very wide (3-17 years), and this may have resulted in the intervention's effectiveness varying depending on the child's level of neurocognitive development; (b) the children are mostly Caucasian and living in the United States, so it is not a given that the intervention works on children of other races or living in other countries. The main type of neoplasm and degree of severity are different, and these aspects may have resulted in different sensitivity and susceptibility in children. Other sources of heterogeneity include the following: (a) the role -active, passive, or neutral- of the handler is not known; this makes it difficult to distinguish the net effect of the intervention, because any positive interactions between the handler and parents/caregivers, promoted by the social lubrication function of AAAs, may in itself have played a role in reducing the child's anxiety; (b) the standard of care has not been described; (c) for all the studies, visits took place weekly, but one study [62] limited the maximum number of visits per child to four, while the other two studies, lasting 12 weeks [63] and four months [64], did not state a maximum limit of visits; (d) the outcome measurement instruments have different inherent characteristics (e.g., length of compilation, method of administration, sensitivity and specificity). Finally, the intervention seems to work when the animal is a dog, but there is no evidence that the same benefit is obtained with other animals. The dog is the most commonly used animal for AAAs due to its ease of training, docility, obedience, and predictability of behavior [15][70][71]; furthermore, compared to other animals, it is more in tune with human moods and emotions [72].

One of the main concerns that often affects the application of AAAs in a healthcare setting is the infectious risk and the allergic risk. Although animals carry germs and can unintentionally serve as mechanical vectors of hospital-associated pathogens, contributing to their transmission between patients, there is insufficient evidence demonstrating increased infection rates during AAAs [73]. Furthermore, with the application of adequate hospital infection control protocols, the associated risks are minimized [74]. People most likely to contract diseases from animals include infants, children under five years of age, organ transplant patients, people with HIV/AIDS, or those being treated for cancer [73]. However, for these subjects, the risk of infection can be significantly mitigated with simple preventive measures, including washing hands with soap and water or an alcohol-based antiseptic solution before and after touching the animal, carefully selecting both the patient and the animal, and ensuring that the animal is subjected to rigorous veterinary care [41][71][73][75]. Confirming this, in one of the included studies [62], there was no significant transfer of germs from the animal to the child during visits. To reduce the risk of allergic reactions to the animal's hair, it is recommended to bathe within 24 hours of the session, perform grooming just before the session, and wear clothing that blocks loose hair [76].

Implications for research

Although the literature on the therapeutic implications of AAA in pediatric oncology is limited, the results of some studies would lean towards their benefit. However, research focused on the effectiveness of intervention continues to not be definitive for several reasons: a) in general, there is a lack of rigor in theoretical frameworks underlying therapeutic human-animal interactions. This problem perpetuates a lack of empirical evidence based on clear hypotheses, hinders understanding of the mechanisms that drive the observed benefit, and therefore makes it difficult to optimize the intervention; b) many studies are preliminary in nature (e.g., pilot studies) and/or have methodological weaknesses that produce statistically insignificant effects even in the presence of clear clinical significance. Furthermore, when good-quality controlled experimental designs are implemented, not all previously observed positive results are validated; c) since AAAs are an unstructured intervention, it is complex to evaluate their effectiveness; d) there is a lack of data to support the effectiveness of the long-term intervention (e.g., at least one year of follow-up).

According to what has been written, greater rigor is therefore needed in the conduct of clinical research on AAAs; for example, the studies should be multicenter to reach a sample size that guarantees good statistical power, they should have the support of a more solid theoretical framework capable of understanding the mechanism underlying the observed results, and they should be capable of modifying some aspects of the intervention to personalize it and make it more effective for the child to whom it is proposed. It remains problematic to evaluate the effectiveness of AAAs, but perhaps efforts could be made to borrow some aspects of TAAs in order to make the intervention more structured without distorting its original characteristics (e.g. declare the therapeutic objective to be achieved at each session and document the progress, plan the duration of each session and of the intervention based on the child's personal and clinical characteristics, subject both the animal and the handler to formal certified training). Finally, the results seem to suggest that the intervention benefits caregivers/parents' anxiety more than the child's, but further studies are needed to confirm this difference in effect size. However, it might be useful to conduct studies to evaluate the effect of AAAs aimed only at parents/caregivers: the results obtained would be valuable to verify their possible impact on the child's anxiety.

Limitations

The small number of participants did not allow subgroup analysis by age and gender; furthermore, the intervention was applied to subjects predominantly of Caucasian race and resident in the same country. These limitations taken together suggest the need to adopt great caution both on the reliability of results and on their external validity. Finally, there is a lack of randomized controlled clinical trials focused on the effect of AAAs on symptoms or emotions such as pain, fear, distress, stress, discomfort, fatigue, depression, mood.

Conclusions

Animal-assisted activities have a small to moderate effect on anxiety and quality of life of children with neoplastic disease and anxiety of parents/caregivers, but the certainty/quality of evidence is low to very low. At the current state of research, therefore, it is not possible to make a definitive judgment on the real effect of the intervention.

Statements and Declarations

Authors' contributions

Luca Giuseppe Re conceived and designed the study
All authors collected the clinical data
All authors interpreted the clinical data and assessed the risk of bias
Luca Giuseppe Re performed the statistical analysis
Silvia Porcarelli drafted the text of the manuscript
Camilla Ripari drafted the tables and figures
Sara Marotta critically reviewed the manuscript for important intellectual content
All authors read and approved the final manuscript

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Declarations

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