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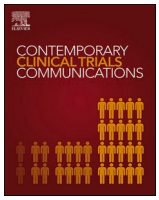

Effectiveness of an innovative treatment protocol for misophonia in children and adolescents: Design of a randomized controlled trial

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ABSTRACT

Background: Misophonia is a recently identified disorder in which individuals experience intense, uncontrollable and disproportional irritation, anger or disgust when confronted with specific sounds or stimuli associated with these sounds. Prevalence rates in children and adolescents are currently still to be investigated. The reported average age of onset is around 13 years, in clinical practice children from 8 years old are referred.
Misophonia is associated with avoidance and anticipation anxiety, possibly leading to serious educational and social consequences for children and families. Worldwide, no evidence-based treatment exists specifically for children and adolescents with misophonia.
This article presents the design of a randomized controlled trial testing the effectiveness of cognitive behavioral therapy (CBT) combined with psychomotor therapy (PMT) for misophonia in children and adolescents (aged 8–18).
Methods: In total, 82 patients will be randomly assigned to a treatment condition or waiting list condition of 3 months (WCG). Treatment consists of 7 weekly group therapy sessions (1.5 h CBT plus 1.5 h PMT) and a follow-up after 3 weeks. Pre and post treatment assessments will be conducted during a baseline assessment, after 3 and 6 months. The primary outcome will be assessed by the Amsterdam Misophonia Scale – Youth (AMISOS-Y) and secondary outcomes (e.g. quality of life) and putative predictors (e.g. parenting burden) will be studied.
Conclusion: This trial is the first study worldwide testing the effectiveness of a combined CBT plus PMT protocol for misophonia in children and adolescents. If proven effective, this protocol provides an innovation to improve care for youth with misophonia.

1. Background

Misophonia is a recently identified disorder in which patients experience extreme irritation, anger or disgust when confronted with certain stimuli. These stimuli include oral and nasal sounds (e.g. eating or breathing), other sounds produced by people (e.g. typing or pen clicking), sounds produced by objects (e.g. clock ticking), sounds produced by animals (e.g. birds) and visual triggers (e.g. jiggling legs) [1,2]. Triggering stimuli are context dependent and might develop because of the attached interpretation or meaning within the social context [3]. For instance, loud chewing of adult family members might elicit a strong misophonic response, while the same sound coming from a baby might not because this sound could be expected from a baby.

Preoccupation with triggering stimuli ('hyper focus') is a core characteristic commonly observed in misophonia. Individuals with misophonia do not only notice triggering stimuli earlier than other people, it is also extremely difficult for them to shift their attention away [2]. The triggering stimuli invoke immediate impulsive aversive emotional and physiological reactions, which is often accompanied by the feeling of losing control. To avoid these negative feelings, patients often pay more

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attention to potential triggers, which leads to an increased hyper focus [4]. Misophonia is associated with anticipation anxiety and avoidance of situations in which the triggering stimuli might occur [2].

Misophonia was first described in the audiology literature in 2001 [5]. In 2013, the research group at the Amsterdam UMC proposed the first diagnostic criteria for misophonia as a psychiatric condition [6]. Since then, more research emerged worldwide within various disciplines, using different definitions and methods to categorize and diagnose misophonia. Recently, a consensus definition of misophonia has been reached with the input of 15 experts, describing misophonia as a "*disorder of decreased tolerance to specific sounds or stimuli associated with such sounds*" [1, p.10].

Previous research has focused mainly on adults with misophonia. Currently, very little is known about misophonia in children and adolescents. The average age of onset is estimated around 13 years of age, as suggested by earlier retrospective research in adults [2]. Systematic epidemiological studies into misophonia in children have not yet been performed. Self-report studies among students suggest a prevalence of clinically relevant misophonia symptoms ranging from 6% (in Chinese students, aged 18–23 years; [7]) to almost 20% (in American students, aged 18–54 years [8]). However, based on longstanding expert clinical experience, we think these numbers may be overrated, since these study populations are not a representation of the general population. Moreover, the measurement of misophonia symptoms was based on self-report questionnaires, without the use of a diagnostic interview. It should be noted that none of these studies used the consensus definition of misophonia.

One tool to assess misophonia in youth is the Sussex Misophonia Scale for Adolescents (SMS-Adolescent) [9], a mono-informant self-report questionnaire, also containing questions reflecting potential other disorders (e.g. hyperacusis). The SMS-Adolescent is currently preliminary validated for adolescents aged 10–14 years old (N = 15) [9]. There remains an urgent need for validation of accurate screening and diagnostic tools for misophonia in children and adolescents [10].

Recently, research was conducted into the clinical characteristics of misophonia in children and adolescents [9–11]. Within a sample of 102 adolescents with misophonia (8-17 years-old), 79% of patients met the criteria for at least one other psychiatric diagnosis, with mood disorders, anxiety disorders, obsessive-compulsive disorder and ADHD being the most prevalent [10]. Another study with a relatively small, population based sample of 15 adolescents with misophonia (10-14 years-old) reported higher rates of autistic characteristics [11]. However, the relationship between autism and misophonia appeared less specific in the larger sample of Guzick and colleagues [10]. Perhaps there are underlying transdiagnostic factors, such as sensory and emotional hyperreactivity, that play an important role in the pathogenesis of misophonia [10]. Indeed, it was found that adolescents with misophonia experience greater (parent reported) sensory hypersensitivity across different domains (e.g. in tactile or visual senses) and greater emotional dysregulation in response to negative emotions [11], however more research is warranted to discover the exact mechanisms involved in misophonia in youth [10].

Misophonia can lead to serious social and educational impairments in children and adolescents [10]. It is commonly reported that children can no longer eat, sleep or be in a car together with their family, negatively affecting family relations. Social life outside of home and school work are also often negatively affected by misophonia [10]. At school, misophonia may lead to concentration problems, social isolation or school dropout. Misophonia severity is associated with poorer quality of life in adolescents [9,10].

To the best of our knowledge, no evidence-based treatment specifically for children and adolescents with misophonia exists worldwide. To date, only one small-scale randomized controlled trial (RCT) has been proposed by Lewin and colleagues (N = 44) [12] for youth with misophonia aged 8–16 years, comparing transdiagnostic family-based treatment for emotional disorders to misophonia education and emotional/physiological relaxation exercises. Their treatment protocol, named The Unified Protocols for Transdiagnostic Treatment of Emotional Disorders in Children and Adolescents (UP-C/A) is based on the assumption that targeting the putative common underlying emotional and behavioral processes misophonia shares with other conditions (such as poor emotion regulation) might provide a reduction of misophonia symptoms [12].

While the study protocol of Lewin [12] and our current study protocol share common characteristics (e.g. family involvement), there are notable differences. For instance, the current study protocol is designed to specifically target misophonia in a group setting, while the protocol used by Lewin is developed for individual families to target underlying general mechanisms commonly observed across different disorders.

Moreover, while the core ingredient of the protocol of Lewin consists of cognitive behavioral therapy (CBT), our protocol combines CBT and psychomotor therapy (PMT), which has shown promising results in adults with misophonia [13]. Within our protocol, CBT is used to counteract core symptoms in misophonia, by targeting dysfunctional associations, cognitions and behaviors. Various single case studies have indicated positive results of CBT on reducing misophonia [14–16]. Psychomotor therapy is a treatment method that employs body perception and movement to foster psychosocial development of children and to reduce psychological symptoms and their impact on daily life [17]. In the Netherlands and Belgium, PMT is used to aid in the treatment of various mental health disorders, such as depression and eating disorders [18]. Evidence suggests PMT might serve as a viable add-on to CBT group therapy [19]. Within our protocol, PMT contains exercises such as attention training and relaxation training, which reduce the hyper focus and heightened state of alertness commonly observed in misophonia patients [2].

In an adult sample of patients with misophonia (N = 54, drop-out rate 15%), our CBT + PMT group treatment protocol resulted in a statistically significant reduction of misophonia symptoms at 3 months follow-up with very large effect size (−9.7 AMISOS-R; 95% CI [−12.0 -7.4]; $p < .001$, $d = 1.97$), effects were maintained at 1-year follow-up [13]. We chose for an adaptation of this protocol for children and adolescents, aged 8–18 years old. In this paper, the trial design of a randomized controlled trial into the effectiveness of this innovative group protocol for children and adolescents will be described. Our hypothesis is that our group treatment protocol is effective in reducing misophonia in the treatment group (N = 41), as compared to a waiting list control group (N = 41).

Furthermore, during our study we aim to validate two innovative multi-informant self-report misophonia questionnaires for screening and diagnosis: the Misophonia Screening List – Child and Youth and the Amsterdam Misophonia Scale - Youth (AMISOS-Y). The latter is an adaptation from the widely used adult self-report questionnaires A-MISO-S [6,10] and the revised version AMISOS-R [13,20,21], specifically attuned to Dutch children. Lastly, by including a wide range of secondary outcomes (emotional and behavioral problems of the child, school functioning, attention problems, sensory processing, (care-related) quality of life, cost of illness) and predictors (demographic variables, parenting burden, parental behavioral and emotional problems, family accommodation) we aim to investigate potential underlying mechanisms in the etiology and maintenance of misophonia in children and adolescents. Finally, we aim to improve our findings by incorporating ratings of misophonia severity of the child over time by the psychologist-researcher, as well as ratings of social validity after treatment by children and parents.

2. Design and methods

Design: this study is a single-center, single-blinded randomized controlled trial (RCT). It compares group cognitive behavioral therapy and psychomotor therapy for misophonia to a waiting list control group.

Inclusion: children are eligible for inclusion if they are between the

age of 8–18 years, suffering from misophonia symptoms and for these misophonia symptoms referred to one out of two divisions of our center (Psychiatry Department of the Amsterdam UMC, or the Academic Center for Child and Adolescent Psychiatry, Levvel, Amsterdam) for diagnosis and treatment of misophonia between August 2021 and January 2023. Written informed consent will be obtained from children (12+) and both parents. Considering the ongoing validation study of our assessment tools, no specific misophonia cut-off scores will be used for inclusion. Children will only be included in this study if they and/or their parents express serious suffering and severe impairment of daily life during an extensive intake with trained psychiatrists/psychologists.

Exclusion: ineligible are children who:

- have another primary diagnosis than misophonia (e.g. ADHD), since we want to test the effectiveness of our protocol on misophonia as primary diagnosis
- have psychiatric comorbid symptoms that hinder group functioning (e.g. severe autism)
- have psychiatric comorbid symptoms requiring adjustment of the misophonia treatment protocol according to therapists (e.g. severe autism)
- have received cognitive behavioral therapy for misophonia in the past year
- display self-injurious behavior (i.e. auto-mutilation) at present or in the past year, since this behavior might negatively affect other group members and would require deviation of treatment protocol
- have an estimated IQ below 85
- are unable to read or write Dutch, since treatment and questionnaires are in Dutch
- have serious family problems (e.g. divorcing parents). The experience of misophonia might be context dependent [3] and is often reported to be mainly directed towards a close family member [2], impacting family relations. Therefore, the family will play an active role within the group therapy, for instance by receiving psychoeducation and separate parent sessions, and joining in exercises. However, some families might experience serious problems extending beyond the problems caused by misophonia, for instance an acrimonious divorce. This might hinder protocol adherence and is therefore an exclusion criterion.

2.1. Patient recruitment and procedure

Children referred to our academic center for diagnostics and treatment of misophonia and their parents will be contacted and briefly informed about this research project by telephone. During this telephone call, a first short screening will take place regarding suitability of the child for this project by the psychologist-researcher (LR). Afterwards, an intake will be planned with psychiatrists or psychologists from our center.

During the intake, the in- and exclusion criteria will be assessed further, as well as the presence of comorbid disorders. The presence of misophonia will be assessed by a structured diagnostic interview, using the diagnostic criteria as proposed by Jager and colleagues [2]. In addition, to support a possible diagnosis, two misophonia questionnaires will be administered, the Misophonia Screening List – Child and Youth and the Amsterdam Misophonia Scale – Youth (AMISOS-Y), to both the child and the parents.

After the diagnostic intake procedure, parents of eligible children will be orally informed about the RCT by the psychologist-researcher. Parents and children will also receive written information. Written informed consent will be obtained from both parents/guardians for all children. From the age of 12, informed consent will also be obtained from the child. Only children (≥12 years), who have given informed consent, and whose parents have signed informed consent will participate in this study.

Fig. 1 shows an overview of procedures and randomization.

2.2. Randomization

After informed consent has been provided, the Structured Clinical Interview for DSM-5 disorders in children and adolescents (SCID-5 Junior) [22] will be conducted with children and parents. This interview measures the psychiatric comorbidity of the child and will serve as both a predictor and a final check of the exclusion criteria. Afterwards, children will be randomly assigned to group treatment for misophonia (N = 41) or the waiting list control group (WCG: N = 41). Children assigned to the WCG will have to wait 3 months before receiving treatment. Both groups will be treated with the same group treatment protocol (CBT/PMT) for misophonia.

Randomization will occur within the computerized data collection system Castor. Permuted block randomization will be used, with block sizes of 2 and 4, in a 1:1 ratio stratified by age and gender. Randomization will be performed by an independent researcher. The psychologist-researcher who performs the assessments will be blinded for participant's allocated intervention. Children and parents, as well as the treatment staff, will be explicitly instructed to refrain from sharing the randomization condition with the psychologist-researcher.

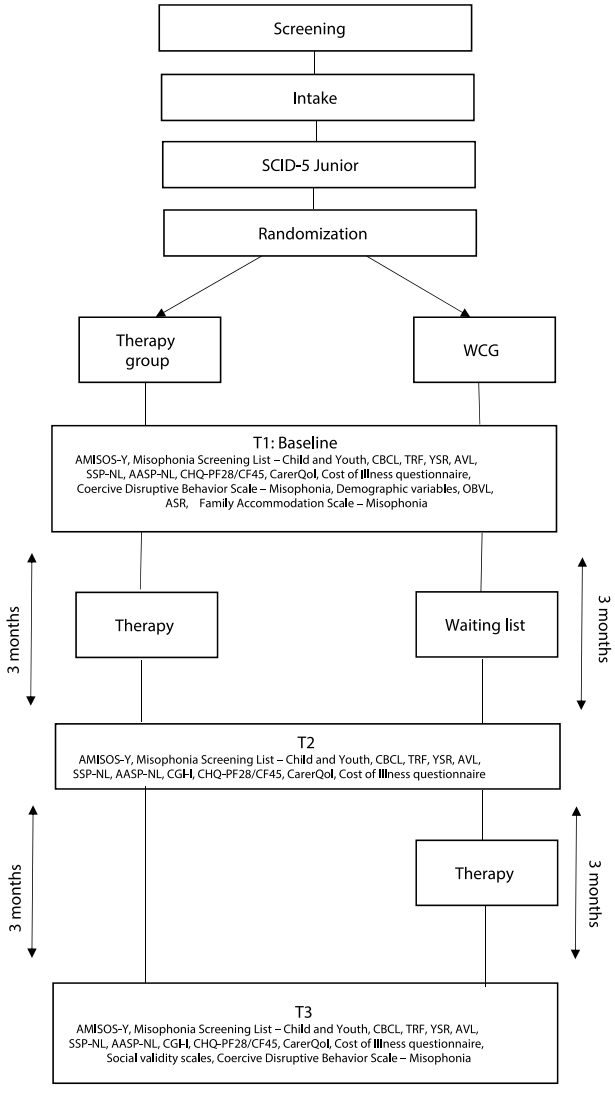

Fig. 1. Overview patient procedures and randomization RCT.

2.3. Intervention

A standardized, cognitive behavioral therapeutic protocol combined with psychomotor therapy (in group format) was previously developed at the Amsterdam UMC to treat misophonia in adults. This protocol showed both short-term and long-term positive effects in adults [4,13]. Based on this adult protocol, two recent versions have been adapted and fine-tuned to fit the needs of children/adolescents in two different age groups: children (ages 8–13) and adolescents (ages 13–18). The adaptations for children/adolescents include changes in language and form of education and exercises (e.g. use of simple words, alternating theory with simple children's games such as 'Simon Says') and the addition of active involvement of parents. Parents are required to join the therapy during session 1, 5 and 6 and during the follow-up. Parents receive psychoeducation and separate parent sessions, and are actively involved in the exercises and take-home assignments. Additionally, in the child groups (ages 8–13), parents are invited to join the last 15 minutes of each session to receive an update of the session. In the adolescent groups (13–18), parents receive an e-mail after each session with an update of the session.

The therapy will be administered in groups of 6–8 children or adolescents, with 7 weekly sessions of 1.5 h of CBT and 1.5 h of PMT, and a follow-up of 1.5 h after 3–4 weeks. Additionally, the children/adolescents will receive assignments to complete at home with their parent(s). Table 1 shows the core components of the CBT and PMT program. Table 2 lists an overview of the most important themes for each session.

2.4. Treatment integrity

To ensure treatment integrity, all therapists will be trained in the CBT/PMT protocol by two licensed CBT/PMT therapists or psychologists with expertise in the treatment of misophonia before providing the current treatment protocol. During all group treatments, ongoing two-weekly therapist peer supervision will be provided by the expert CBT/PMT therapists to avoid protocol drifting.

To study treatment integrity, group therapy sessions will be audio-recorded after having received written consent of children and parents. If children or parents do not provide written consent, treatment sessions will be rated live (during the group sessions) by an independent member of the research team. In total, a random 15% of all sessions will be rated by two trained, independent master students of psychology.

Table 1
Core components of the cognitive behavioral and psychomotor group treatment protocol for misophonia in children and adolescents.

Program	Core component	Content
CBT		
	Stimulus manipulation	Children are trained to hear trigger sounds in a different way (e.g. triggering sounds of eating potato chips as the neutral sounds of footsteps in snow).
	Counterconditioning	Children learn to connect neutral associations to triggering sounds.
	Re-evaluating norms	Families learn to re-evaluate strict eating rules and to introduce more fun at the dinner table.
	Stress management	Children learn to balance demanding and relaxing activities in daily life.
PMT		
	Attention training	Children practice with a range of exercises to help divert their attention away from the triggering stimulus, reducing hyper focus.
	Relaxation training ("arousal reduction")	Children learn to detect tension and stress within their body and to implement various relaxation exercises.

CBT = Cognitive behavioral therapy.
PMT = Psychomotor therapy.

Table 2
Main themes of the cognitive behavioral and psychomotor group treatment protocol for misophonia in children and adolescents.

Session	Participants	Theme
1	C + P	CBT – Psychoeducation on the model of misophonia
	C + P	PMT – Attention training (e.g. body scan) and relaxation training (e.g. progressive relaxation)
2	C	CBT – Discuss misophonia model for each child, stress management (e.g. listing personal demanding and relaxing activities)
	C	PMT – Attention training (e.g. evaluating own attention) and relaxation training (e.g. recognizing body symptoms of stress)
3	C	CBT – Stimulus manipulation (e.g. identifying sounds similar to trigger sounds)
	C	PMT - Attention training (e.g. evaluating and switching own attention) and relaxation training (e.g. progressive relaxation)
4	C	CBT – Classical conditioning (e.g. explanation Pavlov) and counterconditioning (e.g. making commercial in which misophonia sound fades into neutral sound)
	C	PMT – Attention training (e.g. switching own attention) and relaxation training (e.g. breathing exercises)
5	C	CBT – Practicing counterconditioning (e.g. replaying personal commercial), discussing eating norms
	P	Separate parent session – discuss progress
	C	PMT - Attention training (e.g. practicing with eating sounds in controlled situation) and relaxation training (e.g. recognizing body symptoms)
6	C + P	CBT – Preparing action plan for applying learned techniques at home and retaining booked profit
	C + P	PMT – Practicing eating situations with parent, preparing action plan
7	C	CBT – (Evaluating) action plan, additional psycho-education misokinesia
	C	PMT – Practicing attention training (e.g. in real life situations in hospital) and relaxation training (e.g. recognizing body symptoms)
8	C + P	CBT - Follow-up after ± 1 month, evaluation and future plans
		No PMT

C = children/adolescents only.
C + P = children/adolescents and parents.
P = parents only.

Moreover, four sessions of this 15% of sessions rated will also be rated by the PI's/supervisors of this study.

2.5. Assessments

Assessments will be administered online and by telephone/video calls to children, parents and teachers at three time points. At baseline assessment (T1), a clinical interview will be conducted with parents and children along with the questionnaires. T2 is 3 months after the baseline assessment (thus, either directly after treatment or directly after waiting list). After the T2 measurement, treatment for the WCG starts. T3 is 6 months after baseline, either 3 months after treatment or directly after treatment.

An overview of the instruments is provided in Table 3. The majority of the instruments used are part of our regular clinical care and are psychometrically sound and validated [22–51]. Research to date has not yet determined the psychometric properties of our two misophonia

Table 3
Overview instruments per assessment moment.

Instrument	Variable	Assessment moment		
		T1	T2	T3
Primary outcome				
Amsterdam Misophonia Scale – Youth (AMISOS-Y)	Misophonia severity	P/C	P/C	P/C
Secondary outcomes				
Misophonia Screening List – Child and Youth	Misophonia symptoms	P/C	P/C	P/C
Child Behavior Checklist (CBCL)	Emotional and behavioral problems child	P	P	P
Teacher Report Form (TRF)	Emotional and behavioral problems child, school functioning	T	T	T
Youth Self Report (YSR)	Emotional and behavioral problems child	C	C	C
ADHD questionnaire (ADHD-vragenlijst; AVL)	Attention problems	P	P	P
Short Sensory Profile – NL (SSP-NL)	Sensory processing	P	P	P
Adolescent/Adult Sensory Profile – NL (AASP-NL)	Sensory processing	C	C	C
Clinical Global Impression Scale – Improvement (CGI-I)	Severity of psychopathology		PR	PR
Child Health Questionnaire (CHQ) – PF28/CF45	Quality of Life	P/C	P/C	P/C
Carer Quality of Life (CarerQol)	Care-related quality of life	P	P	P
Cost of Illness questionnaire[a]	Cost of illness	P[c]	P[c]	P[c]
Social validity scales CBT/PMT[b]	Social validity treatment			P/C[e]
Coercive Disruptive Behavior Scale – Misophonia[a]	Coercive disruptive behavior child	P		P
Predictors				
Demographic variables	Demographics	P/C		
Structured Clinical Interview for DSM-5 disorders in children and adolescents (SCID-5 Junior)	Psychiatric comorbidity child	P/C[d]		
Parenting burden questionnaire (Opvoedingsbelastingvragenlijst; OBVL)	Parenting burden for parents	P		
Adult Self Report (ASR)	Parental behavioral and emotional problems	P		
Family Accommodation Scale – Misophonia[a]	Family accommodation to misophonia	P		

P: Parent(s).
C: Child.
T: Teacher.
PR: psychologist-researcher.
[a] Modified for this study.
[b] Constructed for this study.
[c] Through telephone.
[d] Through online interview.
[e] Filled in after having received therapy (at T2 or T3).

questionnaires, the Misophonia Screening List – Child and Youth and the Amsterdam Misophonia Scale – Youth (AMISOS-Y). Therefore, these questionnaires will be validated for the purpose of this study, and this may be considered as an additional aim of the study. A parent and child version exists (with parallel items) for both questionnaires.

2.6. Primary outcome

The severity of misophonia according to parents and child will be assessed by the Amsterdam Misophonia Scale Youth – (AMISOS-Y). The AMISOS-Y consists of 7 multiple-choice items about the nature of misophonia, and 10 items on a 4 point- Likert scale (different response categories per question). An example question is "How bad do the sounds make you feel?".

The validation of the two misophonia questionnaires, the AMISOS-Y and the Misophonia Screening List – Child and Youth, will be based on the baseline scores (T1) of the participants compared to a healthy control group (N = 240), recruited from elementary and secondary schools from urban and rural parts of the Netherlands.

2.7. Secondary outcomes

The nature of the misophonia symptoms according to parents and child will be assessed by the Misophonia Screening List – Child and Youth. This questionnaire consists of 14 items on a 4 point- Likert scale. An example item is "If I enter a situation in which family or friends are eating, I feel angry immediately".

Emotional and behavioral problems of the child will be assessed by the Child Behavior Checklist (CBCL; parent version) [23], the Teacher Report Form (TRF; teacher version; see also school functioning) [23], and the Youth Self Report for children older than 11 (YSR; child version) [23]. Specifically the subscales anxious/depressed, social problems, attention problems and aggressive behavior are of interest, since these scales might be especially related to misophonia. Reliability statistics are sufficient to good (based on a Dutch sample of children), validity statistics are sufficient [23,32].

School functioning will be assessed by the Teacher Report From (TRF) [23,32].

Attention problems will be assessed by the Dutch ADHD questionnaire (ADHD-vragenlijst; AVL) [24]. Both reliability and construct validity are rated as good by the Dutch Committee on Tests and Testing (COTAN) [33].

Sensory processing will be assessed by the Short Sensory Profile – NL (SSP-NL) [34] and the Adolescent/Adult Sensory Profile – NL (AASP-NL) [25]. The SSP-NL will be used for children under the age of 11 and is answered by parents. Reliability scores of seven out of eight sections are sufficient to good, however the validity of the SSP-NL remains debatable due to lack of information about convergent and divergent validity in a Dutch sample [35]. The AASP-NL will be used for children aged 11 or older and is answered by children. Evidence of test-retest reliability and internal validity is provided in the manual [25].

The severity of psychopathology will be assessed by the Clinical Global Impression Scale – Improvement (CGI-I) [36]. This scale is used to measure change in psychopathological problems over time according to the psychologist-researcher, and is filled in after a short interview with parents and child at the three time points. The CGI-I has been found to be a reliable and valid measure of clinical change [26].

Quality of life will be assessed by the Child Health Questionnaire (CHQ) – PF28 (parent version) [37], showing moderate to excellent test-retest reliability and adequate discriminant validity in a Dutch child sample [27] and the CHQ - CF45 (child version) [37], found to be reliable and valid [28]. Care-related quality of life will be assessed by the Carer Quality of Life (CarerQol) [29].The CarerQol has been found to be valid for informal caregivers, such as parents [38,39] and displays adequate test-retest reliability [40].

Cost of illness: we aim to measure the costs associated with misophonia to estimate the total financial burden of misophonia on society (i.e., conduct a cost of illness study [41]) by comparing baseline data of patients and a healthy control group on a retrospective cost questionnaire. In addition, using an existing Cost of Illness questionnaire [42,43], changes in costs after treatment (from T2 to T3) will be assessed [42,43].

Social validity is defined as the perceived impact of the treatment on treatment goals and outcomes [44]. Four standardized social validity forms were created for this research (CBT/PMT; child version/parent version) and will be handed over to children and parents at the end of the treatment.

Misophonia might result in coercive and disruptive behavior of the

child. This behavior will be assessed by the Coercive Disruptive Behavior Scale - Misophonia. This questionnaire is an adaptation from the Coercive and Disruptive Behavior Scale - Pediatric OCD (CD-POC) [46], which has shown good psychometric qualities [45,46].

2.8. Predictors of treatment outcome

Demographic variables such as age, gender, social-economic status and nationality will be assessed by a short online questionnaire.

Psychiatric comorbidity of the child will be assessed by a semi structured clinical interview for children and parents, the Structured Clinical Interview for DSM-5 disorders in children and adolescents (SCID-5 Junior) [22]. If performed in the correct way by a trained interviewer, the SCID-5 Junior is a reliable and valid instrument to assess DSM-5 diagnoses in children and adolescents [22].

Parenting burden will be assessed by the Dutch Parenting burden questionnaire (Opvoedingsbelastingvragenlijst; OBVL) [30]. Reliability is rated as good, and construct validity as sufficient by the Dutch Committee on Tests and Testing (COTAN) [47].

Parental behavioral and emotional problems will be assessed by the Adult Self Report (ASR) [31]. The ASR appears to be a reliable and valid measure of adult psychopathology [48].

Misophonia is often associated with accommodation of the family to the misophonia complaints of the child (e.g. no family meals together, no trips by car). The family accommodation to the misophonia complaints of the child will be assessed by the Family Accommodation Scale – Misophonia, an adaptation from the Family Accommodation Scale – Anxiety (FASA) [49], which is a reliable and valid questionnaire for family accommodation in childhood anxiety [50].

3. Statistical analysis

3.1. Power, sample size calculation and dropout for the RCT

There are no previous studies into treatment of misophonia in children, but an RCT into misophonia treatment among adults showed a large positive treatment effect (in terms of Cohen's d, $d = 1.97$ [13]). Assuming a more conservative, yet still large effect ($F = 0.25$ in ANOVA, see statistical analysis below, which corresponds to $d = 0.80$) and desiring a minimum power of 0.80, a sample size of 82 (41 per group) is sufficient to demonstrate significant differences in the primary outcome (severity of misophonia, difference in group treatment versus WCG). This power analysis has been performed with the use of IBM SPSS. It is therefore our intention to include 82 children, a number which we consider realistically feasible.

Clinical experience suggests that dropout during treatment is rare. Considering the severity of misophonia and unfortunately the lack of treatment opportunities in the Netherlands, we find that children and parents are often considerably motivated to participate in the entire treatment. In view of these findings, and by taking our intended sample size and a conservative estimate of the effect size into account, we consider our study sufficiently powered. We will study differences between the population that drops out and the population that participates until the end of treatment (to study a possible selection bias).

3.2. Plan of statistical analysis for the RCT

For the primary study outcome a 3×2 within-group-between-group factorial AN(C)OVA

will be carried out on the repeatedly measured AMISOS-Y scores. T2 will be regarded the primary endpoint, T3 the secondary endpoint. If the results are significant, post-hoc analyses (e.g. Tukey) can be used to determine which differences contribute to this significant effect. It will then be assessed which of the two groups shows the larger change in AMISOS-Y score and in which direction. If there is a reduction on T2, and this reduction is larger for the experimental group than the WCG, we will conclude treatment is effective.

If assumptions underlying AN(C)OVA are violated, we will turn to a nonparametric equivalent. Gender, age, and socio-economic status will be included as covariates ($p < .05$). Differences in demographics and clinical background between children in the treatment group and in the WCG will be analyzed using t-tests, chi-squared tests and Fisher's exact tests, if needed.

For the secondary outcomes, the same analyses will be used.

For the predictors of treatment outcome, multivariate regression analyses will be performed with all potential predictors entered and the severity of misophonia at T2 as outcome. Moderating influences will be investigated by including interaction terms in the linear mixed models between the significant predictor variables and the treatment group. Separate analyses will be performed for child versus parent scores (i.e. per informant).

The statistical analyses will be based on an intention-to-treat principle.

3.3. Validation of the AMISOS-Y and Misophonia Screening List – Child and Youth

Statistical analyses for validation of the misophonia questionnaires will be performed using baseline data of the patient population, along with data of 240 healthy control children of primary and secondary schools. For the healthy control group, children will be recruited from both the Amsterdam region and peripheral regions, from both rural and urban cities, in order to enhance the representativeness of the healthy control children and the generalizability of the results. We strive for a proportional, comparable distribution of school levels. Age and gender ratios from the healthy control group will be adjusted to the ratio in the patient population.

Both questionnaires (AMISOS-Y and Misophonia Screening List–Child and Youth) will be validated by:

1. (Exploratory) factor analyses.
2. Internal consistency determinations, based on the data of the patient group and control group. The reliability of the item/response scale (items' response scale) is determined.
3. The sensitivity and specificity discriminant validity. These factors will determine the distinguishing capacity of the misophonia questionnaires between children with and without misophonia complaints.
4. The divergent and concurrent validity, by determining the indicators of misophonia as measured by the misophonia questionnaires and scores on the following questionnaires:
   - The Dutch ADHD questionnaire (ADHD-vragenlijst; AVL) [24].
   - The subscales anxious/depressed, social problems, attention problems and aggressive behavior of the Child Behavior Checklist (CBCL; parent version) [23] and the Youth Self Report (YSR; child version) [23].
   - The Short Sensory Profile – NL (SSP-NL) [34] and the Adolescent/Adult Sensory Profile – NL (AASP-NL) [25].

3.4. Cost of illness (COI)

Health care costs (e.g., visit to the general practitioner or psychologist, medication, hospitalization) as well as non-health care costs (e.g., school absence, loss of daily activities, productivity losses of parents) will be calculated by multiplying the resources used (administered by the cost questionnaire) by the unit prices of the resources. Unit prices will be obtained from the Dutch Guidelines for Cost-research [51]. To estimate the annual costs of misophonia for society the mean total costs (derived from the cost questionnaire covering 3 months) are multiplied by four (mean annual costs), and are then multiplied by the number of children with misophonia during that year (prevalence-based COI). In addition, bootstrap analyses are used to calculate the incremental costs between the group of children with misophonia and the control

children.

4. Discussion

Misophonia is a recently recognized disorder that is assumed to originate in childhood. If left untreated, misophonia might lead to serious negative consequences for children and their families, such as impaired family relations, social isolation and school dropout according to patients. To our knowledge, no research has been performed worldwide into treatment of misophonia for children and adolescents. This study is the first large RCT to investigate the effectiveness of the CBT plus PMT group treatment protocol for misophonia in children and adolescents, to ensure that evidence-based treatment is available.

This study has several strengths. First, sound assessment instruments (both generic and misophonia specific) and an adequate sample size are used. We aim to validate two misophonia questionnaires, improving screening and diagnostics. Second, a standardized combined CBT/PMT treatment protocol is used in group format, with two-weekly therapist peer supervision, and treatment integrity being analyzed. Earlier, this protocol showed both short-term and long-term effects in an adult sample [13]. Lastly, this study aims to contribute to general knowledge about misophonia in children and adolescents, by including a wide range of secondary outcomes and predictors of treatment success, and by using multiple informants (child, parents, teacher, psychologist-researcher).

4.1. Limitations

There are some limitations in our study that need to be addressed. First, children might differ from adults in their intrinsic treatment motivation and therapeutic needs. Although the treatment protocol is adjusted to children in language and nature of exercises, the treatment duration remains unchanged, possibly forgoing children's needs for more reinforcement, practice moments and repetition.

Second, this study only includes one follow-up after 3 months. A follow-up after 6 months or a year might be more helpful in monitoring the long-term treatment outcomes.

Third, this study entails several exclusion criteria, which might limit the generalizability of the findings. We have decided to use these to create a homogenous group of children with misophonia, since this is the first RCT of a combined CBT/PMT protocol for children and adolescents with a primary diagnosis of misophonia.

Fourth, at the start of this study, no Dutch validated assessment tool for misophonia in children was available to be used as outcome measure. Therefore, we aim to validate two Dutch assessment tools for misophonia in this study.

Lastly, this study uses a passive waiting list control group receiving the same treatment after 3 months, instead of an active control group. This might hinder drawing conclusions about the effectiveness of specific treatment elements of the program.

4.2. Implications for clinical practice

Worldwide, there is limited knowledge about misophonia in children and adolescents. Information about characteristics of misophonia in Dutch children remains lacking, as well as validated Dutch questionnaires and evidence-based treatment to adequately screen, diagnose and treat misophonia in children. This research will lead to a global improvement of knowledge and care by improving the diagnostics and treatment of misophonia in children and adolescents. We expect that the results will be immediately relevant for clinical practice.

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Available data and materials

Not applicable. This paper presents the study protocol and does not contain any data or results.

Author's contribution

All authors critically reviewed the manuscript for intellectual content. All authors have read and approved the manuscript for publication.

Trial registration

Dutch Trial Registry: NL9724.

Ethical approval and consent to participate

The Medical Ethics Committee of the Academic Medical Center has approved this trial. This study will be conducted according to the Helsinki Declaration and its later amendments or comparable ethical standards. Informed written consents will be obtained from the parents or guardians of the participating children, and from the children (12+) themselves. This article does not contain any studies with animals performed by any of the authors.

Consent for publication

Not applicable. This paper presents the study protocol and does not contain any data or results.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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