BMJ Open

The child's perspective on discomfort during medical research procedures: a descriptive study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016077
Article Type:	Research
Date Submitted by the Author:	25-Jan-2017
Complete List of Authors:	Staphorst, Mira; Erasmus University Medical Center, Psychiatry, section Medical Psychology and Psychotherapy; Emma Kinderziekenhuis AMC, Paediatrics Benninga, Marc; University of Amsterdam, Department of Pediatric Gastroenterology and Nutrition Bisschoff, Margriet; Erasmus University Medical Center Bon, Irma; VU medisch centrum Busschbach, Jan; Erasmus MC, Department of Psychiatry, Section of Medical Psychology & Psychotherapy Diederen, Kay; Emma Kinderziekenhuis AMC, Paediatrics van Goudoever, Johannes; VU University Medical Center (VUmc), Pediatrics; Academic Medical Center, Pediatrics Haarman, Eric; VU medisch centrum Hunfeld, Joke; Erasmus University Medical Center, Psychiatry, section Medical Psychology and Psychotherapy Jaddoe, Vincent; Erasmus Medical Centre de Jong, Karin; Academisch Centrum Tandheelkunde Amsterdam de Jongste, Johan; Erasmus MC / Sophia Childrens Hospital, Paediatrics Kindermann, Angelika; Emma Kinderziekenhuis AMC, Paediatrics Königs, Marsh; Vrije Universiteit Amsterdam Oosterlaan, Jaap; Vrije Universiteit Amsterdam Passchier, Jan; VU University, Department of Clinical Psychology/EMGO+ Pijnenburg, Marielle; Erasmus MC / Sophia Childrens Hospital, Paediatrics Renemna, Liesbeth; Academic Medical Center de Ridder, Lissy; Erasmus MC / Sophia Childrens Hospital, Paediatrics Tamminga, Hyke; Academic Medical Center Tiemeier, Henning; Erasmus Medical Center, Child and Adolescent Psychiatry/Psychology Timman, Reinier; Erasmus MC, Department of Psychiatry, Section of Medical Psychology & Psychotherapy van de Vathorst, Suzanne; Erasmus Medical Centre
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Ethics, Evidence based practice
Keywords:	ETHICS (see Medical Ethics), MEDICAL ETHICS, PAEDIATRICS

The child's perspective on discomfort during medical research procedures: a descriptive study

Mira S. Staphorst[1,2] on behalf of the BURDEN-group

The BURDEN-group:

Marc A. Benninga[2], Margriet Bisschoff[3], Irma Bon[4], Jan J.V. Busschbach[1], Kay Diederen[2], Johannes B. van Goudoever[2,4], Eric G. Haarman[4], Joke A.M. Hunfeld[1], Vincent V.W. Jaddoe[3], Karin J.M. de Jong[5], Johan C. de Jongste[3], Angelika Kindermann[2], Marsh Königs[6], Jaap Oosterlaan[6], Jan Passchier[7], Mariëlle W. Pijnenburg[3], Liesbeth Reneman[2], Lissy de Ridder[3], Hyke G. Tamminga[2], Henning W. Tiemeier[3], Reinier Timman[1], Suzanne van de Vathorst[8]

Affiliations

[1] Department of Psychiatry, section Medical Psychology and Psychotherapy, Erasmus University Medical Centre, Rotterdam, the Netherlands

[2] Department of Paediatrics, Emma Children's Hospital, Academic Medical Canter (AMC), Amsterdam, the Netherlands

[3] Departments of Paediatrics and Child Psychiatry, Sophia Children's Hospital, Erasmus University Medical Centre, Rotterdam, the Netherlands

[4] Department of Paediatrics, VU University Medical Centre (VUmc), Amsterdam, the Netherlands

[5] Department of Pedodontology, Academic Centre Dentistry Amsterdam (ACTA), Amsterdam, the Netherlands

[6] Section of Clinical Neuropsychology, VU University, Amsterdam, the Netherlands

[7] Department of Clinical Psychology/EMGO+, VU University, Amsterdam, the Netherlands

[8] Department of Ethics and Philosophy, Erasmus University Medical Centre, Rotterdam, the Netherlands

Corresponding author

Mira S. Staphorst, MSc.

Department of Psychiatry, section Medical Psychology and Psychotherapy

Erasmus University Medical Centre

PO box 2040

3000 CA Rotterdam

the Netherlands

Phone: +31 10 7038336

Email: mstaphorst@gmail.com

Keywords: child; discomfort; ethics; research participation; self report

Word count: 3027 words

ABSTRACT

Objective: the evaluation of discomfort in paediatric research is scarcely evidence-based. In this study, we make a start in describing children's self-reported discomfort during common medical research procedures, compare this with discomfort during dental check-ups, and explore whether age, anxiety-proneness, gender, medical condition, and previous experiences are related to discomfort. We also describe children's suggestions for reducing discomfort.

Design: cross-sectional descriptive study.

Setting: paediatric research at three academic hospitals.

Patients: 357 children with and without illnesses (8-18 years, mean=10.6 years) were enrolled: 307 from paediatric research studies and 50 from dental care.

Main outcome measures: we measured various generic forms of discomfort (nervousness, annoyance, pain, fright, boredom, tiredness) due to six common research procedures: buccal swabs, MRI-scans, pulmonary function tests, skin prick tests, ultrasound imaging and venipunctures.

Results: most children reported limited discomfort during the research procedures (means: 1.0-2.6 on a scale from 1-5). Compared with dental check-ups, buccal swab tests, skin prick tests and ultrasound imaging were less discomforting, while MRI-scans, venipunctures and pulmonary function tests caused a similar degree of discomfort. 60.3% of the children suggested providing distraction by showing movies to reduce discomfort. Only anxiety-proneness was positively related to discomfort.

Conclusions: the findings of this study support the acceptability of participation of children in the studied research procedures, which stimulates evidence-based research practice. Furthermore,

the present study can be considered as a first step in providing benchmarks for discomfort of procedures in paediatric research.

Strengths and limitations of this study

- This is the first large-scale study on children's discomfort of research procedures.
- The findings of this study support the acceptability of participation of children in the studied research procedures, which stimulates evidence-based research practice.
- This study can help to establish benchmarks for discomfort of research procedures in pediatric research.
- We included a limited number of children for measuring discomfort, of which most were healthy 11-year-olds. For generalizability, future research should include larger numbers and more heterogeneous groups of children.
- Although this study gives insight into the degree of discomfort, it needs to be established whether these degrees correspond with minimal, a minor increase over minimal discomfort, or more than minimal discomfort.
- A limitation of this study is the cross-sectional design for comparing discomfort during research procedures and dental check-ups. A design with paired measurements from the same child might have given a better estimation.

INTRODUCTION

There is a need to improve treatments and licensed medication for children by conducting paediatric research. For instance, it is estimated that 25 to 65% of all prescribed paediatric drugs are used off-label,[1] which exposes children to an increased risk of medication under- or overdose. Paediatric research, however, is complicated by the obligation to protect children against the risks and discomfort of research procedures. It is the responsibility of Institutional Review Boards (IRBs) to estimate the risks and discomfort of research procedures, and evaluate whether these are acceptable for the children. Primarily in case of discomfort, IRBs base this evaluation on their intuition and experiences, which may not necessarily give a representative view of children's experiences.[2-5] Consequently, this can lead to the rejection of studies when discomfort is expected to be excessive, and vice versa.

Unfortunately, there is a lack on data on children's discomfort. In this study we therefore make a start in describing children's self-reported discomfort during research procedures. These data are an important first step in providing an empirical basis for the evaluation by IRBs and eventually providing benchmarks for the level of discomfort that might be expected for children with a given procedure.

We measured discomfort during research *procedures* instead of during a research study *as a whole* to make the results generalizable to children who undergo these procedures in future research and because IRBs often evaluate the research procedures of a study separately.[6-8] By addressing research procedures, this study provides a crucial complement to previous studies that have measured children's overall reactions to participation in research studies, such as the understanding of your rights of being a research participant.[9-12] We compared the outcomes to discomfort of children during dental check-ups, which enabled us to compare discomfort

experienced in research with a medical procedure most children encounter ('reference level'). Furthermore, we explored whether age, anxiety-proneness, gender, medical condition and previous experiences with the procedure were related to children's discomfort. In addition, children were asked for suggestions to reduce discomfort.

MATERIALS AND METHODS

Participants

We used a convenience sample in which we aimed to include 50 children for each research procedure, or as much we could enrol within the timeframe of our study.[13] Children were eligible to participate if they met the following criteria: a) aged between 8-18 years, b) fluent in Dutch, c) no current psychological treatment for pain or anxiety disorders, d) no psychosocial problems as diagnosed in the Diagnostic and Statistical Manual of Mental Disorders at the time of enrolment, and e) accompanied by a parent or caretaker. This information was determined by consultation of parent(s) or the child's medical record.

The children were recruited from research studies being conducted at three academic hospitals in the Netherlands. In addition, children without a known illness who had had a check-up visit to the dentist were included. The same inclusion criteria were applied to this group. Children were enrolled between March 2014 and June 2015.

Procedure

First, the researchers conducting the research studies approached children and their parents if they were willing to participate in our study. Interested children and parents were provided with more information about the study by the first author or a research assistant. After agreement,

written consent from parents and written child assent (>12 years) were obtained. Children younger than twelve gave oral assent to participate. Directly after the research procedure, the children completed two questionnaires on an iPad mini tablet to measure discomfort and anxiety-proneness. Parents provided demographic information. All children received a gift card (€7.50) after completing the questionnaires.

Instruments

Discomfort

We developed the Children's Discomfort during Research Procedures Questionnaire (CDRPQ) because no appropriate instrument existed for the aim of the current study.[14] Instruments that measure children's self-reported experiences in medical situations often focus on the measurement of pain, distress or anxiety. Discomfort - which is mentioned as an important assessment criterion for research participation in most ethics guidelines and regulations - also involves other aspects than pain, distress and anxiety, as was shown in an interview study we conducted about the face-validity of discomfort from the child's perspective.[15] Measuring various forms of discomfort therefore provides a more thorough measure of the child's discomfort than only focusing on anxiety or pain. We aimed for an instrument that measures forms of discomfort that are applicable to all kinds of research procedures. Therefore the CDRPQ can be considered as a generic questionnaire.

The CDRPQ contains: 1) six questions about generic types of discomfort (nervousness, annoyance, pain, fright, boredom, and tiredness), which are measured using Likert scales ranging from 1='not discomforting' to 5='extremely discomforting', and 2) one open question about suggestions for reducing discomfort (Appendix A. Note: the CDRPQ was developed in Dutch

and then translated to English for this manuscript). Validity and test-retest reliability were acceptable.[14]

Anxiety-proneness

The influence of anxiety-proneness on discomfort was measured using the Dutch translation of the trait scale of the State-Trait Anxiety Inventory for Children (STAI-C),[16] or the anxiety scale of the Child Behaviour Checklist (CBCL),[16] depending on which questionnaire was already being used by the participating studies. Previous research shows that there are little differences in measuring anxiety by the trait scale of the STAI-C and the anxiety scale of the CBCL when parent-reported,[17] and that these scales are highly correlated (r=0.77).[18] The trait scale of the STAI-C is self-reported and addresses the frequency and intensity of anxiety symptoms in general. It consists of 20 items (e.g. *"I worry about school"*).[19] The STAI-C trait scale has shown good internal consistency (Cronbach's α>0.80) and acceptable test–retest reliability (r>0.65).[20] The anxiety scale of the CBCL is parent-reported and includes six questions on anxiety problems (e.g. "fear of animals, situations or places"). The CBCL has shown good validity and reliability.[16]

Demographics

Parents provided information on demographics.

Medical procedures

Research procedures

We measured children's experiences during six research procedures: buccal swabs, MRI-scans,

pulmonary function tests, skin prick tests, ultrasound imaging and venipunctures (Table 1). The research procedures were selected based on the following criteria: no general anaesthesia necessary, perceived by a consulted group of paediatric healthcare professionals as possibly causing discomfort, and performed in the participating hospitals during the timeframe of our study. Almost all children underwent the research procedures for non-therapeutic research purposes; the pulmonary function tests and some venepunctures were performed as part of therapeutic research studies.

Dentist

We measured the experiences of a group of children without a known illness during regular check-up visits to a general academic dental centre (Table 1). Fifth-year dentistry students perform supervised dental check-ups on children at this academic dental centre.

Data analysis

The data were analysed using SPSS version 21. For each procedure, we calculated the means of the different forms of discomfort, the percentage who reported the research procedure as 'very' or 'extremely' discomforting, and an average discomfort score based on the six forms of discomfort. As most data were skewed, we used non-parametric statistics. A Kruskal-Wallis Test and Mann-Whitney U tests were used to explore differences between the procedures in the average discomfort score. We used Spearman correlations to explore the relation between the average discomfort score, and age and anxiety-proneness. Mann-Whitney U tests were used to explore differences in the average discomfort score between children with and without an illness, boys and girls, and children with and without previous experiences. We did a multivariate

analysis to measure the variance in discomfort explained by the above-mentioned factors. The first author coded the question 'What would you suggest to make *[procedure X]* less annoying?' into categories. A supervising researcher checked these categories (JH), and disagreements were discussed until consensus was reached.

Ethical approval

The IRB of the VU Medical Centre in Amsterdam (The Netherlands) indicated that there was no risk or discomfort associated with this study (i.e. completing the questionnaires), and stated that it is exempt from requiring approval under Dutch Law (2014/010).

RESULTS

Participants

434 children were potentially suitable for participation in our study, of which 38 children (8.8%) did not meet the inclusion criteria (24 in research and 14 from the dental clinic): two children did not speak Dutch fluently, five children were not accompanied by a parent and 31 children were too young or too old. Of the 396 children who were invited to participate, 357 children agreed to participate (90.2%). The most frequently mentioned reason for declining was lack of time of the parents (56%), followed by 'no interest' (26%). 307 children were enrolled from clinical research, and 50 from an academic dental clinic. The majority of the children did not have a known illness (85.2%). Mean age was 10.6 years. Further characteristics of the children are presented in Table 2.

Discomfort during research procedures (CDRPQ)

Table 3 shows the discomfort children experienced: the mean of each form of discomfort, and the percentage of children who reported 'very' (score 4) or 'extreme' (score 5) discomfort. For almost all procedures, the mean scores on the different forms of discomfort were low. Exceptions were: children undergoing the buccal swab test generally indicated that they were 'slightly' bored; most children felt the MRI-scan was 'slightly' tiring and 19% felt it was 'very' or 'extremely' tiring.

There were significant differences in discomfort between the procedures ($p<0.001$). Compared to check-up visits to the dentist, discomfort of buccal swab tests, skin prick tests and ultrasound imaging were less discomforting ($p=0.002$-0.007), while MRI-scans, venipunctures and pulmonary function tests caused a similar degree of discomfort ($p=0.05$-0.26).

Suggestions to reduce discomfort

A large group of the children in clinical research (62.6%) suggested that distraction during the research procedures, preferably in the form of a movie, would reduce discomfort (Table 4).

Potential influencing factors

There was a significant correlation between anxiety-proneness, measured with the STAI-C ($p=0.004$), and discomfort. Anxiety-proneness, measured with the CBCL ($p=0.09$), and discomfort showed a trend for a correlation between these factors. There was no significant correlation between age and discomfort ($p=0.32$). There were no significant differences in discomfort between healthy children and children with a chronic condition ($p=0.78$), boys and girls ($p=0.89$), and children who had a previous experience or children who underwent the research procedure for the first time ($p=0.31$). Regarding the multivariate analysis, anxiety-

proneness appeared to be significantly related to discomfort (β=0.315, p=0.005). The total model, however, was not significant (p=0.088); it only explained 11.6% of the variance of discomfort.

DISCUSSION

This is the first large-scale study investigating children's self-reported discomfort during research procedures. It is in line with the trend of actively involving children in expressing their experiences in medical and research situations. Our study shows that children experienced limited discomfort during the studied research procedures.

Although the studied research procedures may not be the most invasive ones, it is important to have actual data on the discomfort children experience during these research procedures rather than making assumptions. Besides, research shows that there are significant differences in the evaluation of discomfort of some of these research procedures in similar children (i.e. healthy 11-year-olds) among IRB members,[21, 22] which supports the importance of self-reported data by children during the evaluation of study protocols.

Looking at the different forms of discomfort, it is remarkable that the scores of the children in our study on being bored and tired are higher than the scores on the other forms of discomfort. Although a boring or tiring research procedure may not be considered by IRBs as unacceptable in terms of discomfort, these are important forms of discomfort for children and can be a reason for them to refuse undergoing this procedure (in the future). For this reason, we believe it is important that these forms of discomfort are explicitly taken into account when evaluating discomfort by IRBs.

In several ethics codes and guidelines, minimizing discomfort is a requirement for paediatric research.[23, 24] According to the majority of the children in our study, distraction can help to achieve this. Distraction is proven to be (cost-)effective in reducing discomfort during medical procedures in children of all ages.[25-30] While children preferred to be distracted by movies, during some procedures it may be more feasible to distract children by providing music, toys, or decoration on walls and ceilings.

Strengths and limitations

The outcomes of this study can help to establish benchmarks for the discomfort of research procedures in children, and thereby assist IRBs, paediatric researchers, parents and children in their estimation of the acceptability of these procedures for research participation. Other strengths of the study are the multi-site enrolment for generalizability; the large number of children in some of the procedures; the comparison with a common 'everyday' medical procedure (i.e. a dental check-up); the use of a specifically developed questionnaire to measure different forms of discomfort (CDRPQ); and the suggestions for reducing discomfort.

As we were dependent on the participating studies, we were unable to include the intended number of children for some procedures, because fewer children took part in these studies than expected, or were included at a later stage than initially planned. This has reduced the power of the outcomes of some research procedures (e.g. pulmonary function tests). On the other hand, the power of the outcomes of other procedures was enlarged because more children were included than planned (e.g. MRI-scans).

We used different groups of children to compare discomfort in clinical research with dental check-ups. A design with paired measurements from the same child might have given a better estimation.

Furthermore, the degree of discomfort may be relative to the presence of other research procedures the children underwent in the studies. As there was little variation in their ratings of discomfort, we assume that the other research procedures did not have much influence on children's reports.

All children included in our study assented to undergo the research procedures, which is why our study might be hampered by a selection bias (note: this is applicable to all studies investigating children's experiences in paediatric research). It may be possible that highly anxious children declined to undergo the research procedures because of expected discomfort or anxiousness, or that they may not have been approached to participate for this reason (i.e. gatekeeping by the researcher/paediatrician).[31] The fact that we did not have to exclude children with anxiety-disorders (i.e. one of the exclusion criteria) nor that children did have high scores on the anxiety-proneness measures, supports this. The findings of this study therefore cannot just be generalized to children in clinical care.

Implications and recommendations for those involved in pediatric research

Ethics committees

We encourage ethics committees to use self-reported data of the children when evaluating discomfort for reasons mentioned above. To be able to use children's self-reported information on discomfort of *all* kinds of research procedures and across children from all kinds of backgrounds, it is needed that these data are collected and disseminated. Ethics committees can

play a key role in this by requiring these data as part of a study protocol and recommending pediatric researchers to register children's experiences.

Pediatric researchers

We recommend that pediatric researchers routinely include a brief assessment of the impact of the research procedures of their studies by asking the participating children, e.g. the CDRPQ, which we developed for this purpose. To avoid overloading pediatric researchers with extra work and responsibilities during a study visit, it would be ideal if children can report their experiences directly on a website/app. As such, paediatrics researchers can limit their tasks to emphasizing the opportunity and importance of reporting these experiences to children (and their parents) and to refer them to the website/app concerned. Of course, this website/app need to be developed first.

During the informed consent procedure, we encourage researchers providing parents and children with information on expected discomfort of research procedures based on empirical data, in order to facilitate their decision-making for participation.

It is important that discomfort in pediatric research is reduced as much as possible. This can be achieved by standard asking children for their suggestions to reduce discomfort, and - if feasible - to apply these in their studies. As we showed in this study, many children suggested providing (more) distraction, for instance by showing short movies.

Children and parents

For children (and parents) who are approached for research participation, it can be helpful when they have access to information on discomfort of research procedures of children in previous

research. It provides them with additional information on what to expect from undergoing research procedures from the perspective of their peers. This information can facilitate decision-making for (parts of) research participation, as they will be better informed. For instance, if the majority of children do not experience a specific research procedure as discomforting, it may be a reason for others to agree with undergoing this procedure too.

The availability of children's self-reported data on discomfort is dependent on the willingness of children to report on their experiences during research participation. As we learned from this study, most children are willing to report these experiences as long as it does not require much extra time.

Future research

For generalizability, future research should include larger numbers and more heterogeneous groups of children, in particular during pulmonary function tests. Future research is also needed to describe children's discomfort during other (more invasive) research procedures. We therefore recommend paediatric researchers to include measures in their studies (e.g. CDRPQ) to investigate discomfort related to the research procedures involved, and also disseminate these results (note: recently in the Netherlands an addition to the law on research participation was accepted which requires to define and monitor discomfort in paediatric research (parliamentary meeting of October 25th, 2016). [https://www.eerstekamer.nl/wetsvoorstel/33508_verrichten_van_medisch]).

For IRBs and paediatric researchers who evaluate the level of discomfort of (non-therapeutic) research procedures, it is important to know which research procedures involve minimal, a minor increase over minimal discomfort, or more than minimal discomfort.

Unfortunately, there are no clear guidelines for this. Future research - in which IRBs, paediatric researchers, children and their parents are consulted - is therefore needed to determine cut-off levels for this.

CONCLUSION

Our findings support the acceptability of participation of children in the studied procedures for research purposes because children experienced limited discomfort. The results are an important first step in providing benchmarks for discomfort of research procedures in paediatric research, and contribute to the evidence-based evaluation of discomfort in research.

REFERENCES

1. Kimland E, Odlind V. Off-label drug use in pediatric patients. *Clin Pharmacol Ther* 2012;91:796-801
2. Chambers CT, Giesbrecht K, Craig KD, et al. A comparison of faces scales for the measurement of pediatric pain: children's and parents' ratings. *Pain* 1999;83:25-35 doi: S030439599900086X [pii]published Online First: Epub Date]|.
3. McCarthy AM, Kleiber C, Hanrahan K, et al. Factors explaining children's responses to intravenous needle insertions. *Nurs Res* 2010;59:407-16 doi: 10.1097/NNR.0b013e3181f80ed5published Online First: Epub Date]|.
4. Rid A, Emanuel EJ, Wendler D. Evaluating the risks of clinical research. *JAMA* 2010;304:1472-9 doi: 10.1001/jama.2010.1414published Online First: Epub Date]|.
5. Romsing J, Moller-Sonnergaard J, Hertel S, et al. Postoperative pain in children: comparison between ratings of children and nurses. *J Pain Symptom Manage* 1996;11:42-6 doi: 0885392495001360 [pii]published Online First: Epub Date]|.
6. Weijer C. The ethical analysis of risk in intensive care unit research. *Crit Care* 2004;8:85-6
7. McRae A, Weijer C. U.S. Federal Regulations for emergency research: a practical guide and commentary. *Acad Emerg Med* 2008;15:88-97
8. Weijer C. The ethical analysis of risk. *J Law Med Ethics* 2000;28:344-61
9. Kassam-Adams N, Newman E. The reactions to research participation questionnaires for children and for parents (RRPQ-C and RRPQ-P). *Gen Hosp Psychiatry* 2002;24:336-42 doi: S0163834302002001 [pii]published Online First: Epub Date]|.
10. Kassam-Adams N, Newman E. Child and parent reactions to participation in clinical research. *Gen Hosp Psychiatry* 2005;27:29-35 doi: S0163-8343(04)00106-9 [pii]
10.1016/j.genhosppsych.2004.08.007published Online First: Epub Date]|.
11. Barakat LP, Patterson CA, Mondestin V, et al. Initial development of a questionnaire evaluating perceived benefits and barriers to pediatric clinical trials participation. *Contemp Clin Trials* 2013;34:218-26
12. Chu AT, DePrince AP, Weinzierl KM. Children's perception of research participation: Examining trauma exposure and distress. *Journal of Empirical Research on Human Research Ethics* 2008;.3:pp doi: 10.1525/jer.2008.3.1.49 19385782published Online First: Epub Date]|.
13. Staphorst MS, Hunfeld JA, Timman R, et al. Hearing the voices of children: self-reported information on children's experiences during research procedures: a study protocol. *BMJ Open* 2015;5:e009053 doi: bmjopen-2015-009053 [pii]
10.1136/bmjopen-2015-009053published Online First: Epub Date]|.
14. Staphorst MS, Timman R, Passchier J, et al. The development of the 'Children's Discomfort During Research Procedures Questionnaire' (CDRPQ). Manuscript submitted for publication. 2016
15. Staphorst MS, Hunfeld JAM, van de Vathorst S, et al. Children's self reported discomforts as participants in clinical research. *Soc Sci Med* 2015;142:154-62 doi: 10.1016/j.socscimed.2015.08.019published Online First: Epub Date]|.
16. Verhulst F, Van der Ende J, Koot H. Manual for the Child Behavior Checklist (in Dutch). Rotterdam: Department of Child and Adolescent Psychiatry, Erasmus Medical Centre/Sophia, 1996.

17. Seligman LD, Ollendick TH, Langley AK, et al. The utility of measures of child and adolescent anxiety: a meta-analytic review of the Revised Children's Manifest Anxiety Scale, the State–Trait Anxiety Inventory for Children, and the Child Behavior Checklist. *Journal of Clinical Child and Adolescent Psychology* 2004;33:557-65
18. Kendall PC, Puliafico AC, Barmish AJ, et al. Assessing anxiety with the child behavior checklist and the teacher report form. *Journal of Anxiety Disorders* 2007;21:1004-15
19. Spielberger C. *Manual for the state-trait anxiety inventory for children*. Palo Alto, California, USA: Consulting Psychologists Press, 1973.
20. Bakker F, Wieringen Pv, Ploeg Hvd, et al. *Handleiding bij de Zelf- Beoordelings Vragenlijst voor Kinderen, ZBV-K [Manual for the Self-Evaluation Questionnaire for Children, STAIC]*. Lisse, Netherlands: Swets & Zeitlinger, 1989.
21. Shah S, Whittle A, Wilfond B, et al. How do institutional review boards apply the federal risk and benefit standards for pediatric research? *JAMA* 2004;291:476-82
22. Janofsky J, Starfield B. Assessment of risk in research on children. *J Pediatr* 1981;98:842-6
23. US Department of Health and Human Services. Code of Federal Regulations. Human Subjects Research (45 CFR 46). 102 (i). , Revised July 14, 2009.
24. European Parliament CotEC. *Directive 2001*. Luxembourg: Office for Official Publications of the European Communities, 2001.
25. Alvarez C, Fernández Marcos A. Psychological treatment of evoked pain and anxiety by invasive medical procedures in paediatric oncology. *Psychology in Spain* 1997;1:17-36
26. Uman L, Birnie K, Noel M, et al. Psychological interventions for needle-related procedural pain and distress in children and adolescents. *Cochrane Database of Systematic Reviews* 2013:CD005179
27. Broome ME, Rehwaldt M, Fogg L. Relationships between cognitive behavioral techniques, temperament, observed distress, and pain reports in children and adolescents during lumbar puncture. *J Pediatr Nurs* 1998;13:48-54
28. Dahlquist LM, Busby SM, Slifer KJ, et al. Distraction for children of different ages who undergo repeated needle sticks. *J Pediatr Oncol Nurs* 2002;19:22-34
29. Nguyen TN, Nilsson S, Hellstrom AL, et al. Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial. *J Pediatr Oncol Nurs* 2010;27:146-55
30. DeMore M, Cohen LL. Distraction for pediatric immunization pain: A critical review. *Journal of Clinical Psychology in Medical Settings* 2005;12:281-91 doi: DOI 10.1007/s10880-005-7813-1published Online First: Epub Date]|.
31. Tromp K, Vathorst Svd. Gatekeeping by professionals in recruitment of pediatric research participants: Indeed an undesirable practice. *The American Journal of Bioethics* 2015;15:30-32

Table 1. Description of the medical procedures

Procedure	Description
Buccal swab test	Taking mucosal epithelial cells from the inner cheek lining using a small brush.
MRI-scan	Magnetic Resonance Imaging of different parts of the body, particularly of the head. The MRI-scans lasted between 30 and 60 minutes and were performed without sedation.
Pulmonary function test	Regular pulmonary function test that lasted between 15 and 30 minutes.
Skin prick test	Children were tested for 20 allergens. A droplet of each allergen was placed on the inner forearm and penetrated through to the skin using a specially modified lancet.
Ultrasound imaging	Ultrasound imaging used for research purposes was an echocardiogram. For clinical care purposes, ultrasound imaging was particularly an echocardiography and in some cases ultrasounds were made of the lymph nodes, the head or the abdomen.
Venepuncture	One to three 10ml tubes of blood were collected. In one of the two studies children could choose to have EMLA-cream applied before the venepuncture. None of the children had a local anaesthetic.
Dental check-up	During the dental check-up a general check was carried out, dental plaque was removed and children were given instructions on how to brush their teeth correctly. A new appointment was made for dental caries or other abnormalities.

Table 2. Demographics

Demographics	Research (N=307)	Dentist (N=50)	Total (N=357)
Gender (%)			
Boy	158 (51.5%)	27 (54%)	185 (51.8%)
Girl	149 (48.5%)	23 (46%)	172 (48.2%)
Age (%)			
Mean ± SD	10.5 ± 1.8	10.8 ± 1.5	10.6 ± 1.7
< 12 years	273 (88.9%)	38 (76%)	311 (87.1%)
≥ 12 years	34 (11.1%)	12 (24%)	46 (12.9%)
Procedure (%)			
Buccal Swab	25 (8.1%)	-	25 (7.0%)
MRI	89 (29.0%)	-	89 (24.9%)
Pulmonary function test	9 (2.9%)	-	9 (2.5%)
Skin prick test	75 (24.4%)	-	75 (21.0%)
Ultrasound imaging	77 (25.1%)	-	77 (21.6%)
Venepuncture	32 (10.4%)	-	32 (9.0%)
Check-up visit at dentist	-	50 (100%)	50 (14.0%)
Medical condition (%)			
ADHD/ADD	4 (1.3%)	-	4 (1.1%)
Cystic Fibrosis	6 (2.0%)	-	6 (1.7%)
Healthy (i.e. no known illness)	254 (82.7%)	50 (100%)	304 (85.2%)
Inflammatory Bowel Disease	36 (11.7%)	-	36 (10.1%)
Oncological condition	1 (0.3%)	-	1 (0.3%)
Primary ciliary dyskinesia	4 (1.3%)	-	4 (1.1%)
Other condition	2 (0.7%)	-	2 (0.6%)
Previous experience with procedure (%)	148 (48.2%)	50 (100%)	198 (55.5%)
Trait-anxiety - STAI-C*	**N=82**	**N=36**	**N=118**
Mean ± SD	29.3 ± 5.7	28.9 ± 5.7	29.2 ± 5.9
Range	20-44	22-42	20-44
Trait-anxiety - CBCL*	**N=192**	**N=0**	**N=192**
Mean ± SD	1.0 ± 1.4	-	1.0 ± 1.4
Range	0-6	-	0-6

* STAI-C = State Trait Anxiety Inventory for Children CBCL = Child Behaviour Check List

Table 3. Discomfort from child's perspective

Example. *"Were you bored while undergoing the MRI-scan?"*

1 = not
2 = slightly
3 = somewhat
4 = very
5 = extremely

	Nervous		**Annoyed**		**Pain**		**Frightened**		**Bored**		**Tired**		**Average discomfort score**	
	Mean	4+5*	Mean	4+5*	Mean	4+5*	Mean	4+5*	Mean	4+5*	Mean	4+5*	Mean	4+5**
Research														
Buccal swab	1.1	0	1.2	0	1.0	0	1.1	0	2.2	12	1.0	0	1.3	12
MRI	1.8	5	1.4	1	1.1	0	1.3	0	1.7	5	2.3	19	1.6	21
Pulmonary function test	1.2	0	2.1	11	1.2	0	1.0	0	2.6	22	2.4	11	1.8	33
Skin prick test	1.6	3	1.4	1	1.3	0	1.2	0	1.3	1	1.3	1	1.3	7
Ultrasound imaging	1.5	5	1.4	3	1.1	0	1.2	0	1.7	7	1.2	1	1.4	14
Venepuncture	1.9	6	2.1	6	1.9	0	1.5	6	1.8	3	1.3	0	1.7	9
Dentist check-up	1.6	0	1.6	6	1.4	0	1.2	2	2.0	8	1.5	2	1.6	10

* Percentage of children that answered 'very' or 'extremely' on a question

** On at least one discomforting aspect

Table 4. Suggestions to reduce discomforts

Suggestion	Number of children	Percentage (%)
(Distraction total)	(192)	(62.6)
- Movie	185	60.3
- Music	1	0.3
- Small talk	2	0.7
- Other form of distraction	4	1.3
Less noise (MRI)	24	7.8
Fewer physical sensations	11	3.6
Warm gel (echoscope)	4	1.3
Warmer room temperature (MRI)	3	1.0
Shorter duration	1	0.3
Receiving present	1	0.3
Other	11	3.6
No suggestion	60	19.5
Total	**307***	**100.0**

* Only children in clinical research

AUTHORS' CONTRIBUTIONS

MS conceptualized and designed this study, carried out the data collection, drafted the initial manuscript, and approved the final manuscript as submitted. JH, JP, and HG conceptualized and designed this study, supervised the study, reviewed and revised the manuscript, and approved the final manuscript as submitted. RT assisted with the statistical analyses of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. SV and JB conceptualized and designed this study, reviewed and revised the manuscript, and approved the final manuscript as submitted. MAB, MB, IB, KD, EH, VJ, KJ, JJ, AK, MK, JO, MP, LR, LdR, GHT, HT assisted with acquisition of data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

FUNDING

This work was supported by ZonMw (The Netherlands Organization for Health Research and Development), grant number 113203202.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

The dataset is available by contacting the corresponding author.

Appendix A. Children's Discomfort during Research Procedures Questionnaire (CDRPQ)

1. Were you nervous while undergoing procedure X?
   - ☐ I was **not** nervous
   - ☐ I was **slightly** nervous
   - ☐ I was **somewhat** nervous
   - ☐ I was **very** nervous
   - ☐ I was **extremely** nervous

2. Was procedure X annoying?
   - ☐ Procedure X was **not** annoying
   - ☐ Procedure X was **slightly** annoying
   - ☐ Procedure X was **somewhat** annoying
   - ☐ Procedure X was **very** annoying
   - ☐ Procedure X was **extremely** annoying

3. Was procedure X painful?
   - ☐ Procedure X was **not** painful
   - ☐ Procedure X was **slightly** painful
   - ☐ Procedure X was **somewhat** painful
   - ☐ Procedure X was **very** painful
   - ☐ Procedure X was **extremely** painful

4. Were you frightened while undergoing procedure X?
   - ☐ I was **not** frightened
   - ☐ I was **slightly** frightened
   - ☐ I was **somewhat** frightened
   - ☐ I was **very** frightened
   - ☐ I was **extremely** frightened

5. Were you bored while undergoing procedure X?
   - ☐ I was **not** bored
   - ☐ I was **slightly** bored
   - ☐ I was **somewhat** bored
   - ☐ I was **very** bored
   - ☐ I was **extremely** bored

6. Did you find procedure X tiring?
   - ☐ It was **not** tiring
   - ☐ It was **slightly** tiring
   - ☐ It was **somewhat** tiring
   - ☐ It was **very** tiring
   - ☐ It was **extremely** tiring

7. Do you have any suggestions for making procedure X **less discomforting**?

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes
Methods			
Study design	4	Present key elements of study design early in the paper	Yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes
Bias	9	Describe any efforts to address potential sources of bias	Yes. In the limitation section, we describe the potential selection bias of our study sample. However, this bias cannot be addressed because children in

			clinical research are already a biased group (i.e. they gave assent for participating in research).
Study size	10	Explain how the study size was arrived at	Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes
		(*b*) Describe any methods used to examine subgroups and interactions	Yes
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A → we used a convenience sample
		(*e*) Describe any sensitivity analyses	N/A
Results			Yes
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Yes
		(c) Consider use of a flow diagram	No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes
		(b) Indicate number of participants with missing data for each variable of interest	Yes
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	Yes
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes
		(*b*) Report category boundaries when continuous variables were categorized	N/A

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes
Discussion			
Key results	18	Summarise key results with reference to study objectives	Yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The child's perspective on discomfort during medical research procedures: a descriptive study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016077.R1
Article Type:	Research
Date Submitted by the Author:	23-May-2017
Complete List of Authors:	Staphorst, Mira; Erasmus University Medical Center, Psychiatry, section Medical Psychology and Psychotherapy; Emma Kinderziekenhuis AMC, Paediatrics Benninga, Marc; Emma Kinderziekenhuis AMC, Pediatrics Bisschoff, Margriet; Erasmus University Medical Center, Pediatrics and Child Psychiatry Bon, Irma; VU University Medical Center (VUmc), Pediatrics Busschbach, Jan; Erasmus University Medical Center, Psychiatry, section Medical Psychology and Psychotherapy Diederen, Kay; Emma Kinderziekenhuis AMC, Pediatrics van Goudoever, Johannes; VU University Medical Center (VUmc), Pediatrics; Emma Kinderziekenhuis AMC Haarman, Eric; VU University Medical Center (VUmc), Pediatrics Hunfeld, Joke; Erasmus University Medical Center, Psychiatry, section Medical Psychology and Psychotherapy Jaddoe, Vincent; Erasmus University Medical Center, Pediatrics and Child Psychiatry de Jong, Karin; Academic Center Dentistry Amsterdam (ACTA), Pedodontology de Jongste, Johan; Erasmus University Medical Center, Pediatrics and Child Psychiatry Kindermann, Angelika; Emma Kinderziekenhuis AMC, Pediatrics Königs, Marsh; VU University, Section of Clinical Neuropsychology Oosterlaan, Jaap; VU University, Section of Clinical Neuropsychology Passchier, Jan; VU University, Clinical Psychology/EMGO+ Pijnenburg, Marielle; Erasmus University Medical Center, Pediatrics and Child Psychiatry Renemna, Liesbeth; Emma Kinderziekenhuis AMC, Pediatrics de Ridder, Lissy; Erasmus University Medical Center, Pediatrics and Child Psychiatry Tamminga, Hyke; Emma Kinderziekenhuis AMC, Pediatrics Tiemeier, Henning; Erasmus University Medical Center, Pediatrics and Child Psychiatry Timman, Reinier; Erasmus University Medical Center, Psychiatry, section Medical Psychology and Psychotherapy van de Vathorst, Suzanne; Erasmus University Medical Center, Ethics and Philosophy
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Ethics, Evidence based practice

Keywords:	ETHICS (see Medical Ethics), MEDICAL ETHICS, PAEDIATRICS

The child's perspective on discomfort during medical research procedures: a descriptive study

Mira S. Staphorst[1,2] on behalf of the BURDEN-group

The BURDEN-group:

Marc A. Benninga[2], Margriet Bisschoff[3], Irma Bon[4], Jan J.V. Busschbach[1], Kay Diederen[2], Johannes B. van Goudoever[2,4], Eric G. Haarman[4], Joke A.M. Hunfeld[1], Vincent V.W. Jaddoe[3], Karin J.M. de Jong[5], Johan C. de Jongste[3], Angelika Kindermann[2], Marsh Königs[6], Jaap Oosterlaan[6], Jan Passchier[7], Mariëlle W. Pijnenburg[3], Liesbeth Reneman[2], Lissy de Ridder[3], Hyke G. Tamminga[2], Henning W. Tiemeier[3], Reinier Timman[1], Suzanne van de Vathorst[8]

Affiliations

[1] Department of Psychiatry, section Medical Psychology and Psychotherapy, Erasmus University Medical Center, Rotterdam, the Netherlands

[2] Department of Pediatrics, Emma Children's Hospital, Academic Medical Canter (AMC), Amsterdam, the Netherlands

[3] Departments of Pediatrics and Child Psychiatry, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands

[4] Department of Pediatrics, VU University Medical Center (VUmc), Amsterdam, the Netherlands

[5] Department of Pedodontology, Academic Center Dentistry Amsterdam (ACTA), Amsterdam, the Netherlands

[6] Section of Clinical Neuropsychology, VU University, Amsterdam, the Netherlands

[7] Department of Clinical Psychology/EMGO+, VU University, Amsterdam, the Netherlands

[8] Department of Ethics and Philosophy, Erasmus University Medical Center, Rotterdam, the Netherlands

Corresponding author

Mira S. Staphorst, MSc.

Department of Psychiatry, section Medical Psychology and Psychotherapy

Erasmus University Medical Centre

PO box 2040

3000 CA Rotterdam

the Netherlands

Phone: +31 10 7038336

Email: mstaphorst@gmail.com

Keywords: child; discomfort; ethics; research participation; self report

Word count: 3352 words

ABSTRACT

Objective: the evaluation of discomfort in paediatric research is scarcely evidence-based. In this study, we make a start in describing children's self-reported discomfort during common medical research procedures and compare this with discomfort during dental check-ups which can be considered as a reference level of a 'minimal discomfort' medical procedure. We exploratory study whether there are associations between age, anxiety-proneness, gender, medical condition, previous experiences and discomfort. We also describe children's suggestions for reducing discomfort.

Design: cross-sectional descriptive study.

Setting: paediatric research at three academic hospitals.

Patients: 357 children with and without illnesses (8-18 years, mean=10.6 years) were enrolled: 307 from paediatric research studies and 50 from dental care.

Main outcome measures: we measured various generic forms of discomfort (nervousness, annoyance, pain, fright, boredom, tiredness) due to six common research procedures: buccal swabs, MRI-scans, pulmonary function tests, skin prick tests, ultrasound imaging and venepunctures.

Results: most children reported limited discomfort during the research procedures (means: 1.0-2.6 on a scale from 1-5). Compared with dental check-ups, buccal swab tests, skin prick tests and ultrasound imaging were less discomforting, while MRI-scans, venepunctures and pulmonary function tests caused a similar degree of discomfort. 60.3% of the children suggested providing distraction by showing movies to reduce discomfort. The exploratory analyses suggested a positive association between anxiety-proneness and discomfort.

Conclusions: the findings of this study support the acceptability of participation of children in the studied research procedures, which stimulates evidence-based research practice. Furthermore, the present study can be considered as a first step in providing benchmarks for discomfort of procedures in paediatric research.

Strengths and limitations of this study

- This is the first large-scale study on children's discomfort of research procedures.
- The findings of this study support the acceptability of participation of children in the studied research procedures, which stimulates evidence-based research practice.
- This study can help to establish benchmarks for discomfort of research procedures in paediatric research.
- We included a limited number of children for measuring discomfort, of which most were healthy 11-year-olds. For generalizability, future research should include larger numbers and more heterogeneous groups of children.
- Although this study gives insight into the degree of discomfort, it needs to be established whether these degrees correspond with the concepts of 'minimal discomfort', a 'minor increase over minimal discomfort', or 'more than minimal discomfort' that IRBs use in their evaluation of research protocols.
- A limitation of this study is the cross-sectional design for comparing discomfort during research procedures and dental check-ups. A design with paired measurements from the same child might have given a more accurate reference level (dental check-up) of discomfort.

INTRODUCTION

There is a need to improve treatments and licensed medication for children by conducting paediatric research.[1] For instance, it is estimated that 25 to 65% of all prescribed paediatric drugs are used off-label,[2] which exposes children to an increased risk of medication under- or overdose. Paediatric research, however, is complicated by the obligation to protect children against the risks and discomfort of research procedures. It is the responsibility of Institutional Review Boards (IRBs) to estimate the risks and discomfort of research procedures, and evaluate whether these are acceptable for the children. Primarily in case of discomfort, IRBs base this evaluation on their intuition and experiences, which may not necessarily give a representative view of children's experiences.[3-6] Consequently, this can lead to the rejection of studies when discomfort is expected to be excessive, and vice versa. Preferably, the estimation of discomfort is based on group-level data of children's discomfort during research procedures, but unfortunately, these data are scarce. In this study we therefore make a start in describing children's self-reported discomfort during research procedures. These data are an important first step in providing an empirical basis for the evaluation by IRBs and eventually providing benchmarks for the level of discomfort that might be expected for children with a given procedure.

We measured discomfort during research *procedures* instead of during a research study *as a whole* to make the results generalizable to children who undergo these procedures in future research and because IRBs often evaluate the research procedures of a study separately.[7-9] By addressing research procedures, this study provides a crucial complement to previous studies that have measured children's overall reactions to participation in research studies, such as the understanding of your rights of being a research participant.[10-13] We compared the outcomes to discomfort of children during routine dental check-ups. In several countries, like the United

States, IRBs have to establish whether discomfort of paediatric research activities is minimal in relation to children's 'daily life' activities or medical/psychological routine examinations that are regarded as minimal discomfort. Therefore, we compared discomfort in research to dental check-ups because regular dental check-ups are medical routine examinations that all children in our country encounter approximately twice a year (Note: dental check-ups for children 0-18 years are covered by basic health insurance). In this way, the dental check-ups could function as a 'reference level' of minimal discomfort. Furthermore, we exploratory studied whether there is an association between age, anxiety-proneness, gender, medical condition and previous experiences with the procedure, and children's discomfort. It is known that most of these factors are important for IRBs to consider when they estimate the discomfort of research procedures for the children. In addition, children were asked for suggestions to reduce discomfort.

MATERIALS AND METHODS

Participants

We used a convenience sample in which we aimed to include 50 children for each research procedure, or as much we could enrol within the timeframe of our study.[14] Due to the exploratory nature of our study and the absence of previous data using the CDRPQ on which to base the calculations, it was not possible to calculate a sample size needed for our study or to do a valid power analysis. The number of 50 children is an educated guess, based on the duration of our study and the availability of children undergoing the research procedure at the different locations during the inclusion period of our study. Children were eligible to participate if they met the following criteria: a) aged between 8-18 years, b) fluent in Dutch, c) no current psychological treatment for pain or anxiety disorders, d) no psychosocial problems as diagnosed

in the Diagnostic and Statistical Manual of Mental Disorders at the time of enrolment, and e) accompanied by a parent or caretaker. This information was determined by consultation of parent(s) or the child's medical record.

The children were recruited from research studies being conducted at three academic hospitals in the Netherlands. In addition, children without a known illness who had had a check-up visit to the dentist were included. The same inclusion criteria were applied to this group. Children were enrolled between March 2014 and June 2015.

Procedure

First, the researchers conducting the research studies approached children and their parents if they were willing to participate in our study. Interested children and parents were provided with more information about the study by the first author or a research assistant. After agreement, written consent from parents and written child assent (>12 years) were obtained. Children younger than twelve gave oral assent to participate. Directly after the research procedure, the children completed two questionnaires on an iPad mini tablet to measure discomfort and anxiety-proneness. We asked the children directly after they underwent the medical procedure because we thought this would correspond to the 'highest' level of discomfort for the children. From other research areas (for example pain research) we know that measures that are as close as possible to the event are considered to be more valid than delayed retrospective measures which bear the risk of recall bias. Parents provided demographic information. All children received a gift card (€7.50) after completing the questionnaires.

Instruments

Discomfort

We developed the Children's Discomfort during Research Procedures Questionnaire (CDRPQ) because no appropriate instrument existed for the aim of the current study.[15] Instruments that measure children's self-reported experiences in medical situations often focus on the measurement of pain, distress or anxiety. Discomfort - which is mentioned as an important assessment criterion for research participation in most ethics guidelines and regulations - also involves other aspects than pain, distress and anxiety, as was shown in an interview study we conducted about the face-validity of discomfort from the child's perspective.[16] Measuring various forms of discomfort therefore provides a more thorough measure of the child's discomfort than only focusing on anxiety or pain. We aimed for an instrument that measures forms of discomfort that are applicable to all kinds of research procedures. Therefore the CDRPQ can be considered as a generic questionnaire.

The CDRPQ contains: 1) six questions about generic types of discomfort (nervousness, annoyance, pain, fright, boredom, and tiredness), which are measured using Likert scales ranging from 1='not discomforting' to 5='extremely discomforting', and 2) one open question about suggestions for reducing discomfort (Appendix A. Note: the CDRPQ was developed in Dutch and then translated to English for this manuscript). Validity and test-retest reliability were acceptable.[15]

Anxiety-proneness

Anxiety-proneness was measured using the Dutch translation of the trait scale of the State-Trait Anxiety Inventory for Children (STAI-C),[17] or the anxiety scale of the Child Behaviour

Checklist (CBCL),[17] depending on which questionnaire was already being used by the participating studies. Previous research shows that there are little differences in measuring anxiety by the trait scale of the STAI-C and the anxiety scale of the CBCL when parent-reported,[18] and that these scales are highly correlated (r=0.77).[19] The trait scale of the STAI-C is self-reported and addresses the frequency and intensity of anxiety symptoms in general. It consists of 20 items (e.g. *"I worry about school"*).[20] The STAI-C trait scale has shown good internal consistency (Cronbach's α>0.80) and acceptable test–retest reliability (r>0.65).[21] The anxiety scale of the CBCL is parent-reported and includes six questions on anxiety problems (e.g. "fear of animals, situations or places"). The CBCL has shown good validity and reliability.[17]

Demographics

Parents provided information on demographics.

Medical procedures

Research procedures

We measured children's experiences during six research procedures: buccal swabs, MRI-scans, pulmonary function tests, skin prick tests, ultrasound imaging and venepunctures (Table 1). The research procedures were selected based on the following criteria: no general anaesthesia necessary, perceived by a consulted group of paediatric healthcare professionals as possibly causing discomfort, and performed in the participating hospitals during the timeframe of our study. Almost all children underwent the research procedures for non-therapeutic research purposes; the pulmonary function tests and some venepunctures were performed as part of

therapeutic research studies.

Dentist

We measured the experiences of a group of children without a known illness during regular check-up visits to a general academic dental centre (Table 1). Fifth-year dentistry students performed supervised dental check-ups on children at this academic dental centre.

Data analysis

The data were analysed using SPSS version 21. For each procedure, we calculated the means of the different forms of discomfort, the percentage who reported the research procedure as 'very' or 'extremely' discomforting, and an average discomfort score based on the six forms of discomfort. As most data were skewed, we used non-parametric statistics. A Kruskal-Wallis Test and Mann-Whitney U tests were used to explore differences between the procedures in the average discomfort score. We used Spearman correlations to explore the relation between the average discomfort score, and age and anxiety-proneness. Mann-Whitney U tests were used to explore differences in the average discomfort score between children with and without an illness, boys and girls, and children with and without previous experiences. Concerning the suggestions of the children to reduce discomfort, the first author coded the question 'What would you suggest to make *[procedure X]* less annoying?' into categories. A supervising researcher checked these categories (JH), and disagreements were discussed until consensus was reached.

Ethical approval

The IRB of the VU Medical Centre in Amsterdam (The Netherlands) indicated that there was no

risk or discomfort associated with this study (i.e. completing the questionnaires), and stated that it is exempt from requiring approval under Dutch Law (2014/010).

RESULTS

Participants

434 children were potentially suitable for participation in our study, of which 38 children (8.8%) did not meet the inclusion criteria (24 in research and 14 from the dental clinic): two children did not speak Dutch fluently, five children were not accompanied by a parent and 31 children were too young or too old. Of the 396 children who were invited to participate, 357 children agreed to participate (90.2%). The most frequently mentioned reason for declining was lack of time of the parents (56%), followed by 'no interest' (26%). 307 children were enrolled from clinical research, and 50 from an academic dental clinic. The majority of the children in research did not have a known illness (82.7%); their mean age was 10.5 years. Further characteristics of the children are presented in Table 2.

Discomfort during research procedures (CDRPQ)

Table 3 shows the means and standard deviations of the discomfort children experienced. The percentages of children's reports on the different levels of discomfort can be found in Appendix B.

The percentages of children who *did not* experience discomfort varied from 21.9% to 100%. Moreover, for three procedures (buccal swab, skin prick testing and ultrasound imaging), the percentage of children who reported 'no discomfort' was more than 50%. For the children who *did* experience discomfort, the mean discomfort scores generally were low: most reported

'slight' discomfort or sometimes 'somewhat' discomfort. An exception is that 18% of the children undergoing an MRI-scan experienced this as 'very' or 'extremely' tiring.

There were significant differences in discomfort between the procedures ($p<0.001$). Compared to check-up visits to the dentist, discomfort of buccal swab tests, skin prick tests and ultrasound imaging were less discomforting ($p=0.002$-0.007), while MRI-scans, venepunctures and pulmonary function tests caused a similar degree of discomfort ($p=0.05$-0.26).

Suggestions to reduce discomfort

A large group of the children in clinical research (62.6%) suggested that distraction during the research procedures, preferably in the form of a movie, would reduce discomfort (Table 4).

Exploring potential relations between discomfort and demographic factors

There was a significant correlation between anxiety-proneness, measured with the STAI-C ($p=0.004$), and discomfort. Anxiety-proneness, measured with the CBCL ($p=0.09$), and discomfort showed a trend for a correlation between these factors. There was no significant correlation between age and discomfort ($p=0.32$). There were no significant differences in discomfort between healthy children and children with a chronic condition ($p=0.78$), boys and girls ($p=0.89$), and children who had a previous experience or children who underwent the research procedure for the first time ($p=0.31$).

DISCUSSION

This is the first large-scale study investigating children's self-reported discomfort during research procedures. It is in line with the trend of actively involving children in expressing their

experiences in medical and research situations. Our study shows that a many children did not experience discomfort during the studied research procedures; and the level of discomfort for the children who did experience discomfort is limited.

Although the studied research procedures may not be the most invasive ones, it is important to have actual data on the discomfort children experience during these research procedures rather than making assumptions. Besides, research shows that there are significant differences in the evaluation of discomfort of some of these research procedures in similar children (i.e. healthy 11-year-olds) among IRB members,[22, 23] which supports the importance of self-reported data by children during the evaluation of study protocols.

Looking at the different forms of discomfort, it is remarkable that the scores of the children in our study on being bored and tired are higher than the scores on the other forms of discomfort. Although a boring or tiring research procedure may not be considered by IRBs as unacceptable in terms of discomfort, these are important forms of discomfort for children and can be a reason for them to refuse undergoing this procedure (in the future). For this reason, we believe it is important that these forms of discomfort are explicitly taken into account when evaluating discomfort by IRBs.

In several ethics codes and guidelines, minimizing discomfort is a requirement for paediatric research.[24, 25] According to the majority of the children in our study, distraction can help to achieve this. Distraction is proven to be (cost-)effective in reducing discomfort during medical procedures in children of all ages.[26-31] While children preferred to be distracted by movies, during some procedures it may be more feasible to distract children by providing music, toys, or decoration on walls and ceilings.

Strengths and limitations

The outcomes of this study can help to establish benchmarks for the discomfort of research procedures in children, and thereby assist IRBs, paediatric researchers, parents and children in their estimation of the acceptability of these procedures for research participation. Other strengths of the study are the multi-site enrolment for generalizability, the large number of children in some of the procedures, the exploratory comparison with a routine medical procedure that is regarded as causing minimal discomfort, the use of a specifically developed questionnaire to measure different forms of discomfort (CDRPQ), and the suggestions for reducing discomfort.

As we were dependent on the participating studies, we were unable to include the intended number of children for some procedures, because fewer children took part in these studies than expected, or were included at a later stage than initially planned. This has reduced the power of the outcomes of some research procedures (e.g. pulmonary function tests). On the other hand, for some procedures more children were included than initially planned (e.g. MRI-scans).

We used different groups of children to compare discomfort in clinical research with dental check-ups. A design with paired measurements from the same child might have given a more accurate reference level of discomfort.

For this study, we aimed to include both healthy and ill children. However, the majority of the participants in our research appeared to be healthy. Therefore the results might not be representative for ill children. However, the explorative analysis to investigate differences in discomfort between healthy and ill children did not show any differences in discomfort.

Furthermore, the degree of discomfort may be relative to the presence of other research procedures the children underwent in the studies. As there was little variation in their ratings of

discomfort, we assume that the other research procedures did not have much influence on children's reports.

All children included in our study assented to undergo the research procedures, which is why our study might be hampered by a selection bias (note: this is applicable to all studies investigating children's experiences in paediatric research). It may be possible that highly anxious children declined to undergo the research procedures because of expected discomfort or anxiousness, or that they may not have been approached to participate for this reason (i.e. gatekeeping by the researcher/paediatrician).[32] The fact that we did not have to exclude children with anxiety-disorders (i.e. one of the exclusion criteria) nor that children did have high scores on the anxiety-proneness measures, supports this. The findings of this study therefore cannot just be generalized to children in clinical care.

Implications and recommendations for those involved in paediatric research

Institutional Review Boards (IRBs)

We encourage IRBs to use self-reported data of the children when evaluating discomfort for reasons mentioned above. To be able to use children's self-reported information on discomfort of *all* kinds of research procedures and across children from all kinds of backgrounds, it is needed that these data are collected and disseminated. IRBs can play a key role in this by requiring these data as part of a study protocol and recommending paediatric researchers to register children's experiences.

Paediatric researchers

We recommend that paediatric researchers routinely include a brief assessment of the impact of the research procedures of their studies by asking the participating children, e.g. the CDRPQ, which we developed for this purpose. To avoid overloading paediatric researchers with extra work and responsibilities during a study visit, it would be ideal if children can report their experiences directly on a website/app. As such, paediatric researchers can limit their tasks to emphasizing the opportunity and importance of reporting these experiences to children (and their parents) and to refer them to the website/app concerned. Of course, this website/app need to be developed first.

During the informed consent procedure, we encourage researchers providing parents and children with information on expected discomfort of research procedures based on empirical data, in order to facilitate their decision-making for participation.

It is important that discomfort in paediatric research is reduced as much as possible. This can be achieved by standard asking children for their suggestions to reduce discomfort, and - if feasible - to apply these in their studies. As we showed in this study, many children suggested providing (more) distraction, for instance by showing short movies.

Children and parents

For children (and parents) who are approached for research participation, it can be helpful when they have access to information on discomfort of research procedures of children in previous research. It provides them with additional information on what to expect from undergoing research procedures from the perspective of their peers. This information can facilitate decision-making for (parts of) research participation, as they will be better informed. For instance, if the

majority of children do not experience a specific research procedure as discomforting, it may be a reason for others to agree with undergoing this procedure too.

The availability of children's self-reported data on discomfort is dependent on the willingness of children to report on their experiences during research participation. As we learned from this study, most children are willing to report these experiences as long as it does not require much extra time.

Future research

For generalizability, future research should include larger numbers and more heterogeneous groups of children, in particular during pulmonary function tests. Future research is also needed to describe children's discomfort during other (more invasive) research procedures. We therefore recommend paediatric researchers to include measures in their studies (e.g. CDRPQ) to investigate discomfort related to the research procedures involved, and also disseminate these results (note: since March 2017 in the Netherlands an addition to the law on research participation was implemented which requires to define and monitor discomfort in paediatric research [http://www.ccmo.nl/nl/verruiming-mogelijkheden-medisch-wetenschappelijk-onderzoek-met-minderjarige-en-wilsonbekwame-proefp].

For IRBs and paediatric researchers who evaluate the level of discomfort of (non-therapeutic) research procedures, it is important to know which research procedures involve minimal, a minor increase over minimal discomfort, or more than minimal discomfort. Unfortunately, there are no clear guidelines for this. Future research - in which IRBs, paediatric researchers, children and their parents are consulted - is therefore needed to determine cut-off levels for this.

CONCLUSION

Our findings support the acceptability of participation of children in the studied procedures for research purposes because children experienced limited discomfort. The results are an important first step in providing benchmarks for discomfort of research procedures in paediatric research, and contribute to the evidence-based evaluation of discomfort in research.

REFERENCES

1. Kaplan W, Wirtz V, Mantel-Teeuwisse A, et al. Priority Medicines for Europe and the World 2013 Update. Geneva: World Health Organization in collaboration with Utrecht University and Boston University, 2013.
2. Kimland E, Odlind V. Off-label drug use in pediatric patients. *Clin Pharmacol Ther* 2012;91:796-801
3. Chambers CT, Giesbrecht K, Craig KD, et al. A comparison of faces scales for the measurement of pediatric pain: children's and parents' ratings. *Pain* 1999;83:25-35 doi: S030439599900086X [pii]published Online First: Epub Date]|.
4. McCarthy AM, Kleiber C, Hanrahan K, et al. Factors explaining children's responses to intravenous needle insertions. *Nurs Res* 2010;59:407-16 doi: 10.1097/NNR.0b013e3181f80ed5published Online First: Epub Date]|.
5. Rid A, Emanuel EJ, Wendler D. Evaluating the risks of clinical research. *JAMA* 2010;304:1472-9 doi: 10.1001/jama.2010.1414published Online First: Epub Date]|.
6. Romsing J, Moller-Sonnergaard J, Hertel S, et al. Postoperative pain in children: comparison between ratings of children and nurses. *J Pain Symptom Manage* 1996;11:42-6 doi: 0885392495001360 [pii]published Online First: Epub Date]|.
7. Weijer C. The ethical analysis of risk in intensive care unit research. *Crit Care* 2004;8:85-6
8. McRae A, Weijer C. U.S. Federal Regulations for emergency research: a practical guide and commentary. *Acad Emerg Med* 2008;15:88-97
9. Weijer C. The ethical analysis of risk. *J Law Med Ethics* 2000;28:344-61
10. Kassam-Adams N, Newman E. The reactions to research participation questionnaires for children and for parents (RRPQ-C and RRPQ-P). *Gen Hosp Psychiatry* 2002;24:336-42 doi: S0163834302002001 [pii]published Online First: Epub Date]|.
11. Kassam-Adams N, Newman E. Child and parent reactions to participation in clinical research. *Gen Hosp Psychiatry* 2005;27:29-35 doi: S0163-8343(04)00106-9 [pii]
10.1016/j.genhosppsych.2004.08.007published Online First: Epub Date]|.
12. Barakat LP, Patterson CA, Mondestin V, et al. Initial development of a questionnaire evaluating perceived benefits and barriers to pediatric clinical trials participation. *Contemp Clin Trials* 2013;34:218-26
13. Chu AT, DePrince AP, Weinzierl KM. Children's perception of research participation: Examining trauma exposure and distress. *Journal of Empirical Research on Human Research Ethics* 2008;.3:pp doi: 10.1525/jer.2008.3.1.49 19385782published Online First: Epub Date]|.
14. Staphorst MS, Hunfeld JA, Timman R, et al. Hearing the voices of children: self-reported information on children's experiences during research procedures: a study protocol. *BMJ Open* 2015;5:e009053 doi: bmjopen-2015-009053 [pii]
10.1136/bmjopen-2015-009053published Online First: Epub Date]|.
15. Staphorst MS, Timman R, Passchier J, et al. The development of the 'Children's Discomfort During Research Procedures Questionnaire' (CDRPQ). Manuscript submitted for publication. 2016
16. Staphorst MS, Hunfeld JAM, van de Vathorst S, et al. Children's self reported discomforts as participants in clinical research. *Soc Sci Med* 2015;142:154-62 doi: 10.1016/j.socscimed.2015.08.019published Online First: Epub Date]|.

17. Verhulst F, Van der Ende J, Koot H. Manual for the Child Behavior Checklist (in Dutch). Rotterdam: Department of Child and Adolescent Psychiatry, Erasmus Medical Centre/Sophia, 1996.
18. Seligman LD, Ollendick TH, Langley AK, et al. The utility of measures of child and adolescent anxiety: a meta-analytic review of the Revised Children's Manifest Anxiety Scale, the State–Trait Anxiety Inventory for Children, and the Child Behavior Checklist. *Journal of Clinical Child and Adolescent Psychology* 2004;33:557-65
19. Kendall PC, Puliafico AC, Barmish AJ, et al. Assessing anxiety with the child behavior checklist and the teacher report form. *Journal of Anxiety Disorders* 2007;21:1004-15
20. Spielberger C. *Manual for the state-trait anxiety inventory for children*. Palo Alto, California, USA: Consulting Psychologists Press, 1973.
21. Bakker F, Wieringen Pv, Ploeg Hvd, et al. *Handleiding bij de Zelf- Beoordelings Vragenlijst voor Kinderen, ZBV-K [Manual for the Self-Evaluation Questionnaire for Children, STAIC]*. Lisse, Netherlands: Swets & Zeitlinger, 1989.
22. Shah S, Whittle A, Wilfond B, et al. How do institutional review boards apply the federal risk and benefit standards for pediatric research? *JAMA* 2004;291:476-82
23. Janofsky J, Starfield B. Assessment of risk in research on children. *J Pediatr* 1981;98:842-6
24. US Department of Health and Human Services. Code of Federal Regulations. Human Subjects Research (45 CFR 46). 102 (i). , Revised July 14, 2009.
25. European Parliament CotEC. *Directive 2001*. Luxembourg: Office for Official Publications of the European Communities, 2001.
26. Alvarez C, Fernández Marcos A. Psychological treatment of evoked pain and anxiety by invasive medical procedures in paediatric oncology. *Psychology in Spain* 1997;1:17-36
27. Uman L, Birnie K, Noel M, et al. Psychological interventions for needle-related procedural pain and distress in children and adolescents. *Cochrane Database of Systematic Reviews* 2013:CD005179
28. Broome ME, Rehwaldt M, Fogg L. Relationships between cognitive behavioral techniques, temperament, observed distress, and pain reports in children and adolescents during lumbar puncture. *J Pediatr Nurs* 1998;13:48-54
29. Dahlquist LM, Busby SM, Slifer KJ, et al. Distraction for children of different ages who undergo repeated needle sticks. *J Pediatr Oncol Nurs* 2002;19:22-34
30. Nguyen TN, Nilsson S, Hellstrom AL, et al. Music therapy to reduce pain and anxiety in children with cancer undergoing lumbar puncture: a randomized clinical trial. *J Pediatr Oncol Nurs* 2010;27:146-55
31. DeMore M, Cohen LL. Distraction for pediatric immunization pain: A critical review. *Journal of Clinical Psychology in Medical Settings* 2005;12:281-91 doi: DOI 10.1007/s10880-005-7813-1published Online First: Epub Date]|.
32. Tromp K, Vathorst Svd. Gatekeeping by professionals in recruitment of pediatric research participants: Indeed an undesirable practice. *The American Journal of Bioethics* 2015;15:30-32

Table 1. Description of the medical procedures

Procedure	Description
Buccal swab test	Taking mucosal epithelial cells from the inner cheek lining using a small brush.
MRI-scan	Magnetic Resonance Imaging of different parts of the body, particularly of the head. The MRI-scans lasted between 30 and 60 minutes and were performed without sedation.
Pulmonary function test	Regular pulmonary function test that lasted between 15 and 30 minutes.
Skin prick test	Children were tested for 20 allergens. A droplet of each allergen was placed on the inner forearm and penetrated through to the skin using a specially modified lancet.
Ultrasound imaging	Ultrasound imaging used for research purposes was an echocardiogram. For clinical care purposes, ultrasound imaging was particularly an echocardiography and in some cases ultrasounds were made of the lymph nodes, the head or the abdomen.
Venepuncture	One to three 10ml tubes of blood were collected. In one of the two studies children could choose to have EMLA-cream applied before the venepuncture. None of the children had a local anaesthetic.
Dental check-up	During the dental check-up a general check was carried out, dental plaque was removed and children were given instructions on how to brush their teeth correctly. A new appointment was made for dental caries or other abnormalities.

Table 2. Demographics

Demographics	Research (N=307)	Dentist (N=50)	Total (N=357)
Gender (%)			
Boy	158 (51.5%)	27 (54%)	185 (51.8%)
Girl	149 (48.5%)	23 (46%)	172 (48.2%)
Age (%)			
Mean ± SD	10.5 ± 1.8	10.8 ± 1.5	10.6 ± 1.7
< 12 years	273 (88.9%)	38 (76%)	311 (87.1%)
≥ 12 years	34 (11.1%)	12 (24%)	46 (12.9%)
Procedure (%)			
Buccal Swab	25 (8.1%)	-	25 (7.0%)
MRI	89 (29.0%)	-	89 (24.9%)
Pulmonary function test	9 (2.9%)	-	9 (2.5%)
Skin prick test	75 (24.4%)	-	75 (21.0%)
Ultrasound imaging	77 (25.1%)	-	77 (21.6%)
Venepuncture	32 (10.4%)	-	32 (9.0%)
Check-up visit at dentist	-	50 (100%)	50 (14.0%)
Medical condition (%)			
ADHD/ADD	4 (1.3%)	-	4 (1.1%)
Cystic Fibrosis	6 (2.0%)	-	6 (1.7%)
Healthy (i.e. no known illness)	254 (82.7%)	50 (100%)	304 (85.2%)
Inflammatory Bowel Disease	36 (11.7%)	-	36 (10.1%)
Oncological condition	1 (0.3%)	-	1 (0.3%)
Primary ciliary dyskinesia	4 (1.3%)	-	4 (1.1%)
Other condition	2 (0.7%)	-	2 (0.6%)
Previous experience with procedure (%)	148 (48.2%)	50 (100%)	198 (55.5%)
Trait-anxiety - STAI-C*	**N=82**	**N=36**	**N=118**
Mean ± SD	29.3 ± 5.7	28.9 ± 5.7	29.2 ± 5.9
Range	20-44	22-42	20-44
Trait-anxiety - CBCL*	**N=192**	**N=0**	**N=192**
Mean ± SD	1.0 ± 1.4	-	1.0 ± 1.4
Range	0-6	-	0-6

* STAI-C = State Trait Anxiety Inventory for Children CBCL = Child Behaviour Check List

Table 3. Discomfort from child's perspective

Example. *"Were you bored while undergoing the MRI-scan?"*

1 = not
2 = slightly
3 = somewhat
4 = very
5 = extremely

	Nervous		**Annoyed**		**Pain**		**Frightened**		**Bored**		**Tired**		**Average discomfort score**	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Research														
Buccal swab	1.1	0.33	1.2	0.37	1.0	0.00	1.1	0.28	2.2	1.26	1.0	0.20	1.3	0.26
MRI	1.8	0.88	1.4	0.74	1.1	0.30	1.3	0.56	1.7	0.93	2.3	1.28	1.6	0.45
Pulmonary function test	1.2	0.44	2.1	1.05	1.2	0.44	1.0	0.00	2.6	1.01	2.4	1.01	1.8	0.48
Skin prick test	1.6	0.83	1.4	0.74	1.3	0.47	1.2	0.45	1.3	0.66	1.3	0.58	1.3	0.35
Ultrasound imaging	1.5	0.82	1.4	0.74	1.1	0.31	1.2	0.42	1.7	0.96	1.2	0.60	1.4	0.32
Venepuncture	1.9	1.04	2.1	0.98	1.9	0.59	1.5	0.95	1.8	0.92	1.3	0.46	1.7	0.54
Dentist check-up	1.6	0.67	1.6	0.97	1.4	0.61	1.2	0.56	2.0	1.04	1.5	0.81	1.6	0.48

* Percentage of children that answered 'very' or 'extremely' on a question ** On at least one discomforting aspect

Table 4. Suggestions to reduce discomforts

Suggestion	Number of children	Percentage (%)
(Distraction total)	(192)	(62.6)
- Movie	185	60.3
- Music	1	0.3
- Small talk	2	0.7
- Other form of distraction	4	1.3
Less noise (MRI)	24	7.8
Fewer physical sensations	11	3.6
Warm gel (echoscope)	4	1.3
Warmer room temperature (MRI)	3	1.0
Shorter duration	1	0.3
Receiving present	1	0.3
Other	11	3.6
No suggestion	60	19.5
Total	**307***	**100.0**

* Only children in clinical research

AUTHORS' CONTRIBUTIONS

MS conceptualized and designed this study, carried out the data collection, drafted the initial manuscript, and approved the final manuscript as submitted. JH, JP, and HG conceptualized and designed this study, supervised the study, reviewed and revised the manuscript, and approved the final manuscript as submitted. RT assisted with the statistical analyses of the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. SV and JB conceptualized and designed this study, reviewed and revised the manuscript, and approved the final manuscript as submitted. MAB, MB, IB, KD, EH, VJ, KJ, JJ, AK, MK, JO, MP, LR, LdR, GHT, HT assisted with acquisition of data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

FUNDING

This work was supported by ZonMw (The Netherlands Organization for Health Research and Development), grant number 113203202.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

The dataset is available by contacting the corresponding author.

Appendix A. Children's Discomfort during Research Procedures Questionnaire (CDRPQ)

1. Were you nervous while undergoing procedure X?
   - ☐ I was **not** nervous
   - ☐ I was **slightly** nervous
   - ☐ I was **somewhat** nervous
   - ☐ I was **very** nervous
   - ☐ I was **extremely** nervous

2. Was procedure X annoying?
   - ☐ Procedure X was **not** annoying
   - ☐ Procedure X was **slightly** annoying
   - ☐ Procedure X was **somewhat** annoying
   - ☐ Procedure X was **very** annoying
   - ☐ Procedure X was **extremely** annoying

3. Was procedure X painful?
   - ☐ Procedure X was **not** painful
   - ☐ Procedure X was **slightly** painful
   - ☐ Procedure X was **somewhat** painful
   - ☐ Procedure X was **very** painful
   - ☐ Procedure X was **extremely** painful

4. Were you frightened while undergoing procedure X?
   - ☐ I was **not** frightened
   - ☐ I was **slightly** frightened
   - ☐ I was **somewhat** frightened
   - ☐ I was **very** frightened
   - ☐ I was **extremely** frightened

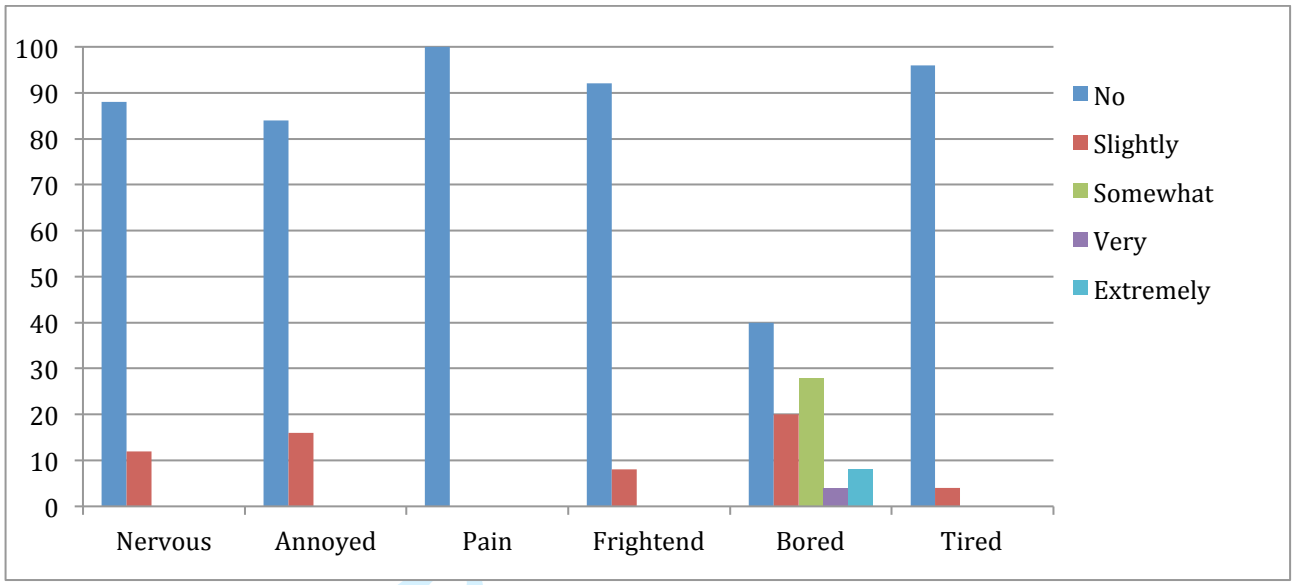
5. Were you bored while undergoing procedure X?
   - ☐ I was **not** bored
   - ☐ I was **slightly** bored
   - ☐ I was **somewhat** bored
   - ☐ I was **very** bored
   - ☐ I was **extremely** bored

6. Did you find procedure X tiring?
   - ☐ It was **not** tiring
   - ☐ It was **slightly** tiring
   - ☐ It was **somewhat** tiring
   - ☐ It was **very** tiring
   - ☐ It was **extremely** tiring

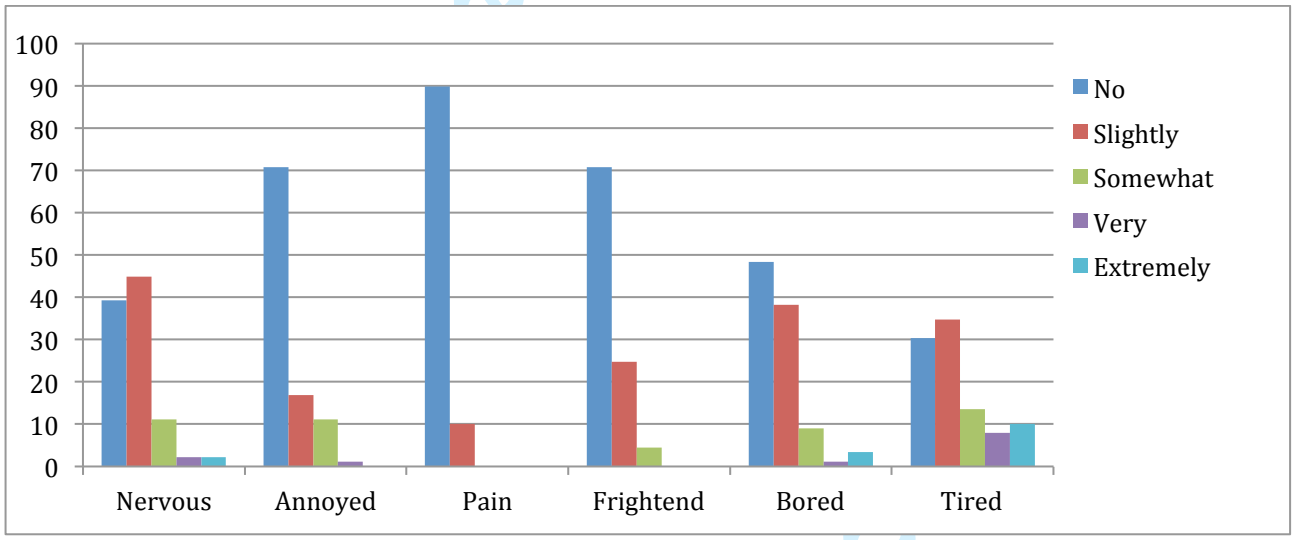
7. Do you have any suggestions for making procedure X **less discomforting**?

Appendix B. Discomfort – percentages per procedure

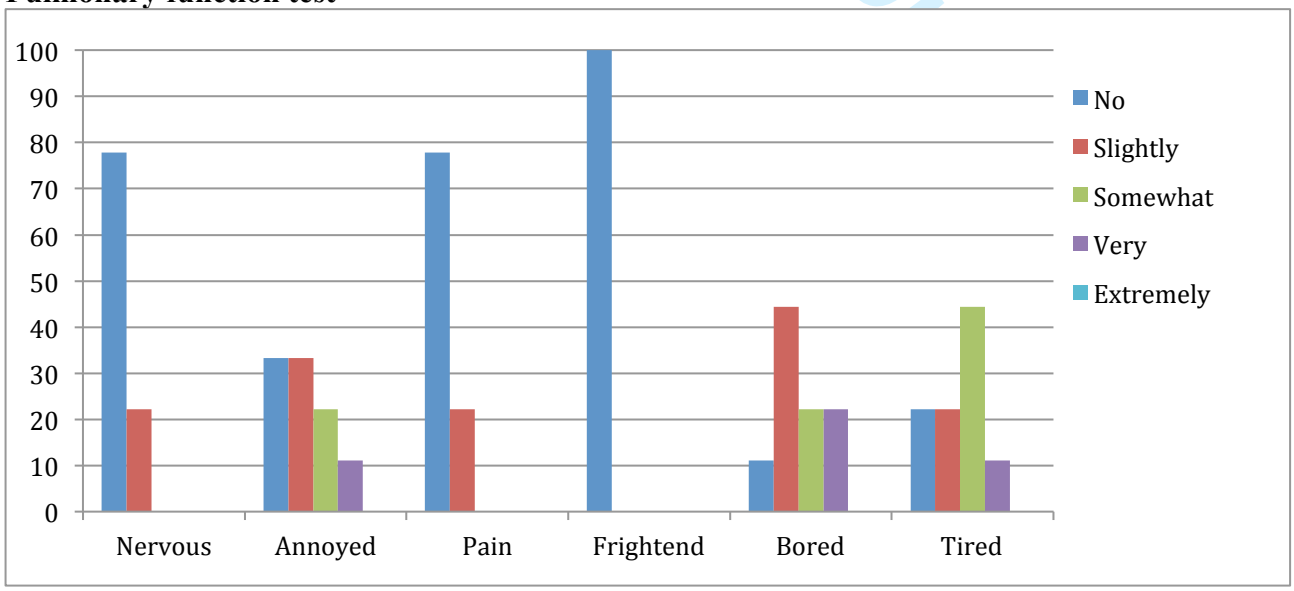
Buccal swab test



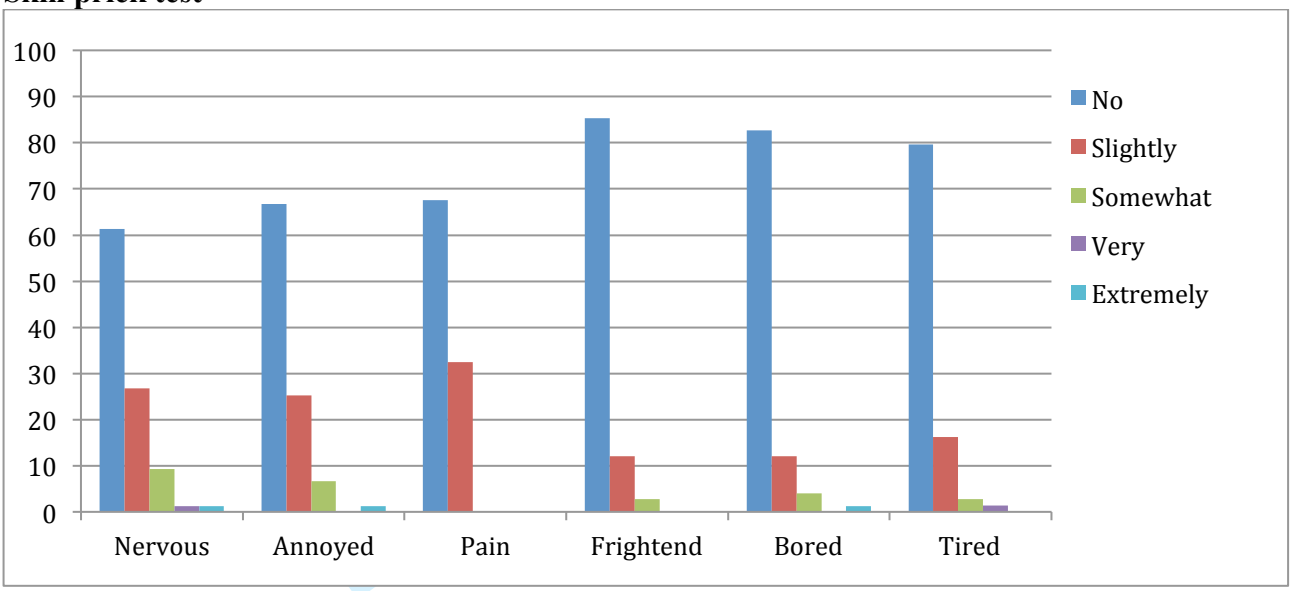
MRI-scan



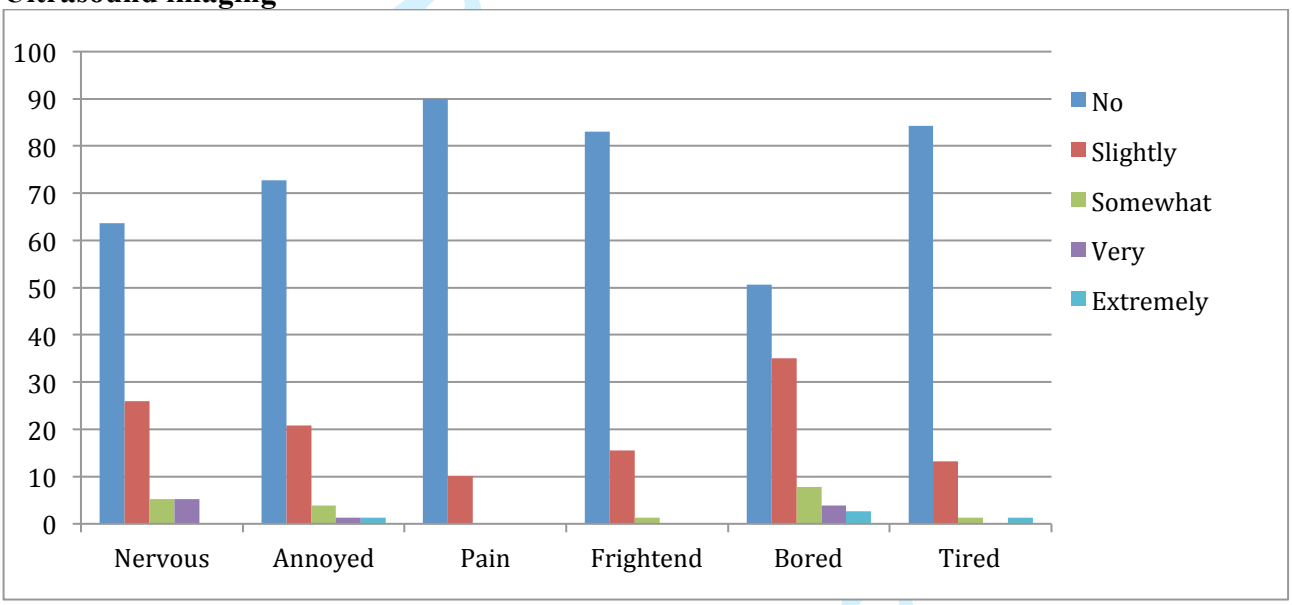
Pulmonary function test



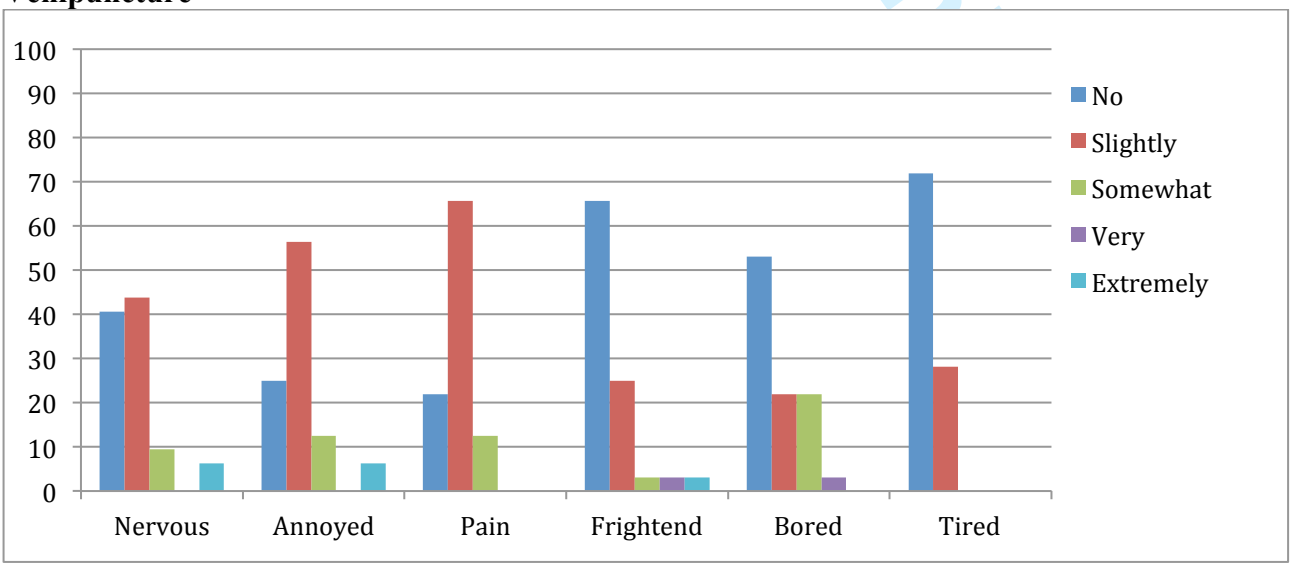
Skin prick test



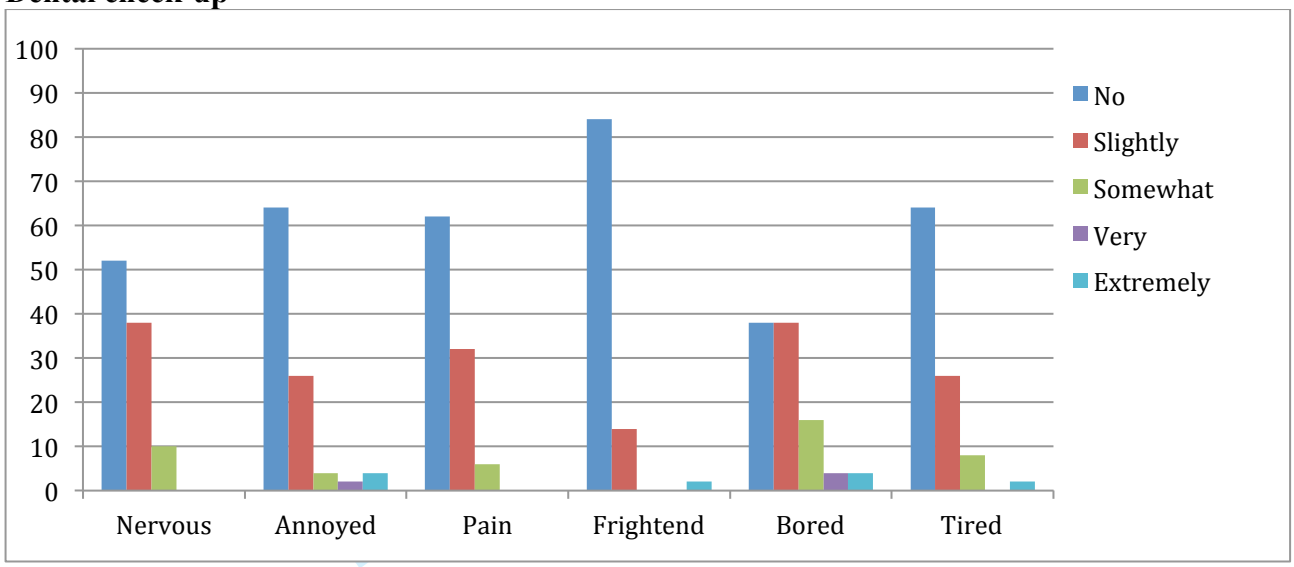
Ultrasound imaging



Venipuncture



Dental check-up



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Check	Page, line number(s)
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	p1, lines1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	p3-4, lines 43-49, 58-63
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	p6-7, lines 87-123
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	p6-7, lines 104-123
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	p8-9, lines 148-160
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	p7, lines 143-146 + abstract
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Yes	p7-8, lines 127-146
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	p9-11, lines 163-213
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	p9-11, lines 163-213
Bias	9	Describe any efforts to address potential sources of bias	Yes. In the limitation section, we describe the	

			potential selection bias of our study sample. However, this bias cannot be addressed because children in clinical research are already a biased group (i.e. they gave assent for participating in research).	
Study size	10	Explain how the study size was arrived at	Yes	p7-8, lines 126-133
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	p11, line 219
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	p11-12, lines 215-229
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	p11-12, lines 219-224
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A → we used a convenience sample	
		(*e*) Describe any sensitivity analyses	N/A	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Yes	p12, lines 237-243
		(b) Give reasons for non-participation at each stage	Yes	p12, lines 242-

				243
		(c) Consider use of a flow diagram	No	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Yes	p12, lines 243-246 + Table 2.
		(b) Indicate number of participants with missing data for each variable of interest	Yes	Table 2.
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A	
		Cross-sectional study—Report numbers of outcome events or summary measures	Yes	Table 2.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Yes	p13, lines 248-265
		(*b*) Report category boundaries when continuous variables were categorized	N/A	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Yes	p13-14, lines 267-278
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	p14-15, lines 283-308
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	p16-17, lines 319-344
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	p14-15, lines 284-308 p19-20, lines 405-408
Generalisability	21	Discuss the generalisability (external validity) of the study results	Yes	p16, lines 328-331 p19, lines 386-388
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Yes	p27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.