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Unpublished clinical studies in pediatric emergence delirium – a cross sectional analysis

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emergence delirium, publication bias, research waste, clinical studies

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Abstract

Objectives: Emergence delirium (ED) is a frequent and potentially serious complication of general anesthesia in children. Although there are various treatment strategies, no general management recommendations can be made. Selective reporting of study results may impair clinical decision making. We therefore analyzed whether the results of completed registered clinical studies in patients with pediatric ED are publicly available or remain unpublished.

Design: Cross sectional analysis.

Setting: ClinicalTrials.gov and ClinicalTrialsRegister.eu

Participants and outcome measures: We determined the proportion of published and unpublished studies registered at ClinicalTrials.gov and ClinicalTrialsRegister.eu that were marked as completed by September 1st 2018. The major trial and literature databases were used to search for publications. In addition, the study investigators were contacted directly.

Results: Of the 44 registered studies on pediatric ED, only 24 (54%) have been published by September 2019. Published trials contained data from n=2556 patients, whereas n=1644 patients were enrolled in unpublished trials. Median time to publication was 19 months. Studies completed in recent years were published faster, but still only 9 of 25 trials were published within 12 months after completion.

Conclusion: There is a distinct publication gap in clinical research in pediatric ED that may have an impact on meta-analyses and clinical practice.

Strengths and limitations of this study

- This study quantitates the amount of research waste in pediatric emergence delirium assessed as a) the number and b) sample sizes of published and unpublished completed clinical studies
- The precise reasons for non-publication of the studies included in this analysis remain unknown
- Strengths of findings as well as directions of individual unpublished studies remain unknown
- Study registers other than ClinicalTrials.gov and ClinicalTrialsRegister.eu were not analyzed

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Introduction

Emergence delirium (ED) can be a very stressful event for both patients and caregivers during general anesthesia in children. Although it may also develop in adults, ED is much more common in pediatric patients, with prevalences between 25% and 80% depending on the definition of ED [1]. Symptoms usually begin shortly after emergence from anesthesia and can be very frightening including self-inflicted injury or accidental removal of catheters and other medical devices. Although episodes of ED are usually short lived, it has been suspected that ED may be associated with long-term behavioral disturbances such as eating disorders, sleeping disorders, and separation anxiety [2].

The exact pathophysiology of ED is not yet understood. However, several risk factors are known: young age, use of volatile anesthetics (especially sevoflurane), type of surgery (increased risk for otorhinolaryngeal and ophthalmological procedures), parental as well as patient anxiety, and pre-existing behavioral problems [3]. Whereas anxiety and behavioral problems can be addressed by non-pharmacological interventions, most of these risk factors cannot be modified and prompt the pre- and/or perioperative administration of various medications including benzodiazepines, alpha-2-agonists, propofol, opioids, and ketamine [4 5].

However, although it is evident that all of these drugs may have beneficial effects in specific settings to reduce the rates of ED, no universal recommendations can be derived from the existing literature for this very common and potentially serious complication. This is a typical situation in the treatment of pediatric patients, where many treatment decisions are still based on incomplete clinical data, and off-label use of various drugs is common. One important factor for the lack of clinical consensus data might be a publication bias. It is twice as likely that a positive outcome of an intervention is reported than a negative one [6]. Such selective reporting

of positive results is likely to influence clinical decision making. We therefore investigated potential publication bias and time to publication in registered clinical trials on ED in children.

Methods

Identification of clinical trials

Two databases were assessed to identify registered clinical trials on Pediatric Emergence Delirium reported as completed: 1) the ClinicalTrials.gov database provided by the U.S. National Library of Medicine and 2) the European Union Clinical Trials Register at ClinicalTrialsRegister.eu. Search criteria were: keywords "emergence delirium" and "emergence agitation" with the query selection parameters "completed studies" and "child (0-17 years)". Close of database was September 1st 2019. Data were downloaded for further analysis.

Search for publications of completed trials

To identify publications related to the registered and completed trials, ClinicalTrials.gov, PubMed and Google Scholar were searched for NCT number, EudraCT number, study title, principal investigator, study sponsor and keywords generated from the study title. If no respective publication was found, the principal investigators were contacted by email and/or ResearchGate and asked to provide information whether the study was published in a source not covered by PubMed or Google Scholar.

Data Analysis

The STROBE criteria (STrengthening the Reporting of OBservational studies in Epidemiology) were applied for design and analysis of this study [7]. Data were analyzed for age and number of participants, gender, study type, study design, condition, intervention, availability of study results, completion date, publication date, sponsor and country of sponsor. Trials were categorized into eight groups according to their main research topic. Time to publication was calculated as the difference in

months between study completion date and publication date and. Missing data were not imputed. All statistical analyses were performed in SPSS 20 (IBM Corporations, Armonk, New York) using standard methods for descriptive statistics. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Publication status of studies

We identified a total of 47 studies that were reported as completed in the two trial databases. Of these, three unpublished studies were completed less than one year before close of the database. Because the U.S. Food and Drug Administration (FDA) allows a time frame of one year between completion and publication of the study as specified in the in the FDA Drug Administration Amendments Act (FDAAA) [8], these three studies were excluded from the analysis. Of the remaining 44 studies, 29 were published and 19 were unpublished. Nine principal investigators of the unpublished studies could not be contacted by email or the ResearchGate social network. Of the remaining ten, two replied and confirmed that the study results had not been published yet (figure 1). Publication rates considerably varied between different countries of the sponsor (table 1) and main topics of the investigations (table 2).

The numbers of published and unpublished studies for each year of study completion (2007 – 2018) is shown in figure 2. An increasing number of publications over the years can be observed as well as an increasing proportion of unpublished studies which even exceeded the number of published studies in the last three years.

Patient numbers

All studies involved both genders. Published trials contained data from n=2556 patients, whereas n=1644 patients were enrolled in unpublished trials. Median size of published trials was 90 (IQR 68-136), range 40-418, whereas median size of unpublished trials was 80 (IQR 55-100), range 22-156 participants. Of note, the number of patients enrolled in unpublished studies significantly exceeded those in published studies during the last years (figure 3).

Time to publication

Median time to publication was 19 (IQR 12-27), range 3 to 104 months. More recent studies were published faster, but still only 9 of 25 trials were published within 12 months after completion as warranted by the FDAAA (figure 4).

Discussion

Almost every second completed registered clinical trial on pediatric ED remains unpublished, making results from 1644 enrolled study patients unavailable for clinical decision making. Given the high prevalence of ED and its potentially serious Manifestations, this significant publication bias is both surprising and unsatisfying.

This lack of study results may directly influence clinical practice. An illustrative example is the use of dexmedetomidine. Two published studies could show a reduction of incidence and degree of ED following premedication with intranasal dexmedetomidine [9] [10]. However, dexmedetomidine, like most potent sedatives, causes an unpleasant burning sensation when applied intranasally [11]. Oral application might therefore be a better choice for anxious children. One recent study showed that 1 µg per kg oral dexmedetomidine for premedication provided satisfactory sedation levels, but was not effective in preventing ED [12]. On the other hand, we identified an unpublished registered trial (NCT03357718) that used 2 µg/kg, so it is not known whether oral dexmedetomidine at higher doses might be as effective as intranasal application. Another unpublished study (NCT03171740) compared premedication with intranasal dexmedetomidine to oral midazolam. Intra- or postoperative dexmedetomidine application was investigated in five registered trials (NCT01901588, NCT03779282, NCT00857727, NCT01895023, NCT01535287) the results of which are not available (yet) to the public. Especially with regard to different doses and potential cardiocirculatory side-effects of intravenous dexmedetomidine, the data of these 482 patients would be very interesting.

Similar considerations can be made for several study topics summarized in table 2. Minimizing pain with intraoperative Fentanyl given at a mean dose of 2.5 µg/kg at the end of surgery reduced the incidence of ED in a study by Cohen et al. [13]. However, in

the context of postoperative delirium in the PICU we could recently show that fentanyl increases the risk for delirium in a dose-dependent way and that this could probably attributed to substance-specific anticholinergic effects [14]. Therefore it would be very interesting to see the results of the 322 patients from the three unpublished registered trials (NCT02753725, NCT03010540, NCT03062488) on intraoperative fentanyl given at different doses.

Unfortunately, the low publication rate for studies on ED that we found in our analysis is in line with other published observations. Anderson et al. recently reported that only 38.3% of all completed or prematurely terminated trials registered at ClinicalTrials.gov were published [15], and we came to similar conclusions when testing for publication bias in fields as diverse as pediatric liver transplantation [16] or autism [17]. Publication of the results gathered in clinical trials involving human subjects is considered an ethical imperative [18]. In 2007 it became a legal obligation in the U.S. to register all clinical trials in advance and publish its results within 12 months after completion [8]. Interestingly, the highest rate of unpublished study with regard to the country of the investigation was found for the U.S. despite of this federal law. Timely publication of the results is another issue that we investigated in our study. Only 9 of the 24 published studies were published within 12 months after completion, and we did not observe a trend to shorter publication intervals during recent years.

Limitations

Our study has several limitations. First, we only analyzed clinical trials that were registered either at ClinicalTrials.gov or ClinicalTrialsRegister.eu., therefore some studies registered in smaller national registers may have been missed. Second, our analysis relies on the accuracy of data input in the respective register. Third, we can only speculate about the reasons why half of the investigators chose not to publish

their results, because we did not receive respective information after contacting them directly. Last, it is likely that some of the recently completed studies will be published eventually, but still considerably later than the 12 months warranted by the FDAAA.

Conclusion

There is a distinct publication gap in clinical research in pediatric ED. Although this does not call into question the results of published studies, it should raise awareness that many aspects of the current treatment options are not exactly known and that larger numbers of published trials are immensely helpful to either support existing data or to challenge it thereby improving clinical practice. In addition, timely publication of study results helps to improve patient care and avoids unnecessary exposure to research if a similar research question in being investigated repeatedly.

Authors' contributions

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: JM, MR

Drafting the work or revising it critically for important intellectual content: JM, MR

Final approval of the version to be published: JM, MR

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: JM, MR

Data sharing statement

All relevant data are in the manuscript.

Competing interests statement

JM and MR report no conflict of interest

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Figure legends

Figure 1: Flowsheet: details of the study selection process

Figure 2: Distribution of published (n=24) and unpublished (n=20) trials by year of completion

Figure 3: Distribution of patient count stratified by publication status and year

Figure 4: Time to publication (time between completion of the trial and publication of results) in months by year of completion

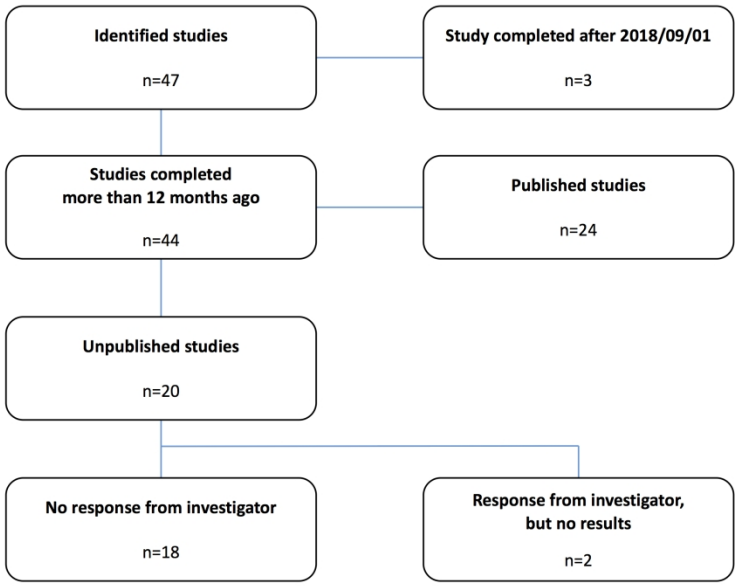
"FDAAA" = timeline mandated by the U.S. Food and Drug Administration Amendments Act of 2007

Table 1: Published (n=25) and unpublished (n=19) completed studies on pediatric emergence delirium by country

Countries	Published studies (n)	Unpublished studies (n)
Belgium	2	0
Brasil	0	1
Canada	1	0
China	0	2
Egypt	1	0
Greece	1	0
India	1	1
Italy	1	0
Kenya	0	1
South Korea	8	4
Thailand	2	1
Turkey	3	2
United States	4	8

Table 2: Publication status of studies registered as completed on ClinicalTrials.gov and ClinicalTrialsRegister.eu involving children with emergence delirium

Issue	Overall number of studies	Number and percentage of published studies	Number of patients enrolled in unpublished studies
Dexmedetomidin	13	5 (38%)	596
Diagnostic criteria	6	2 (33%)	326
Non-pharmacological interventions	5	4 (80%)	100
Opioids	5	2 (40%)	322
Other drugs	5	4 (80%)	66
Propofol	4	3 (75%)	105
Volatile anesthetics	3	1 (33%)	132
Midazolam	3	3 (100%)	0



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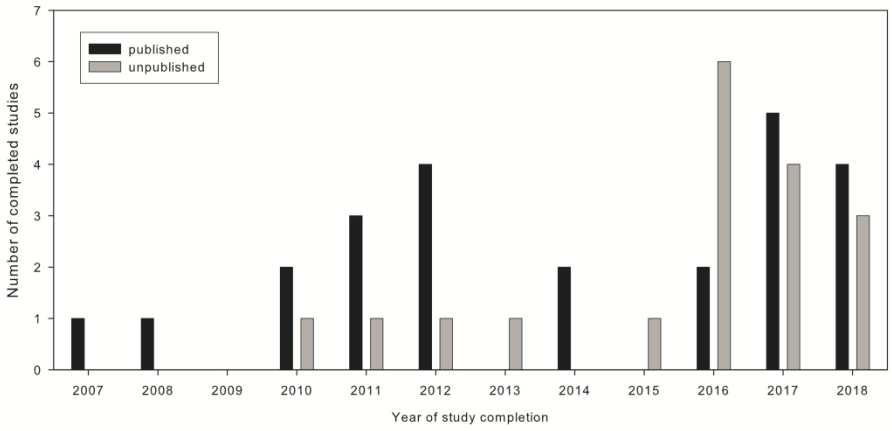

Figure 2: Distribution of published (n=24) and unpublished (n=20) trials by year of completion

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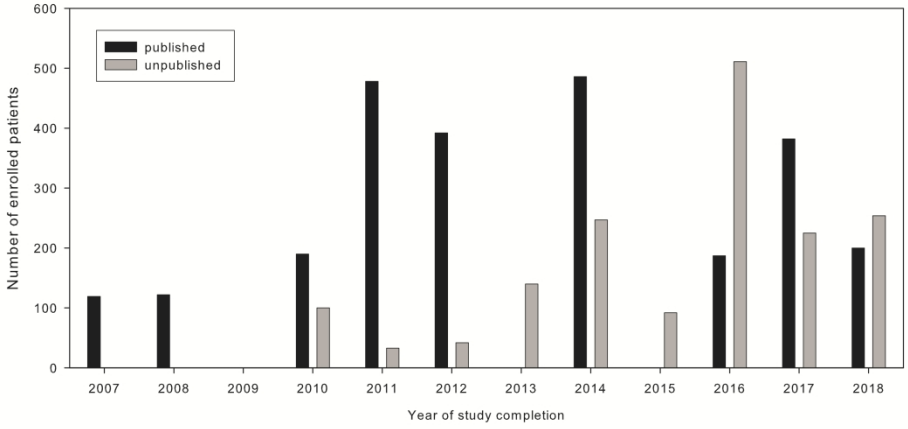

Figure 3: Distribution of patient count stratified by publication status and year

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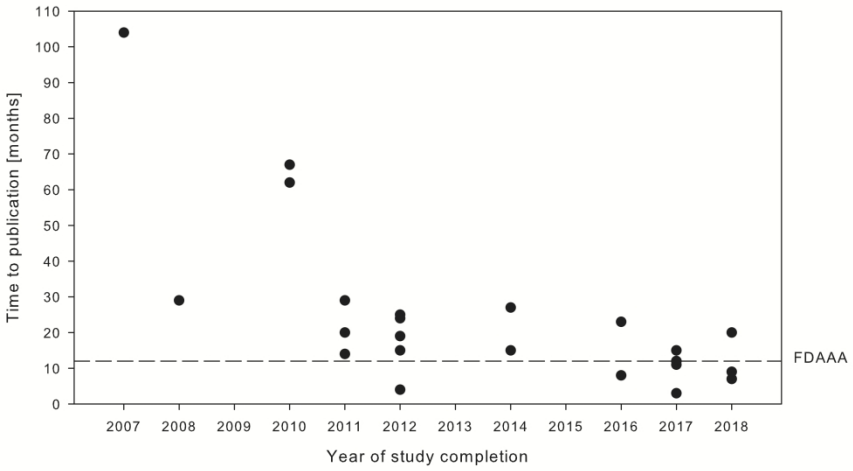

Figure 4: Time to publication (time between completion of the trial and publication of results) in months by year of completion
"FDAAA" = timeline mandated by the U.S. Food and Drug Administration Amendments Act of 2007

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract – done
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found – done
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported - done
Objectives	3	State specific objectives, including any prespecified hypotheses - done
Methods		
Study design	4	Present key elements of study design early in the paper - done
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection – done
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants - done
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable - done
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 - done
Bias	9	Describe any efforts to address potential sources of bias - done
Study size	10	Explain how the study size was arrived at - done
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why - done
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding - done
		(*b*) Describe any methods used to examine subgroups and interactions - done
		(*c*) Explain how missing data were addressed - done
		(*d*) If applicable, describe analytical methods taking account of sampling strategy – not applicable
		(*e*) Describe any sensitivity analyses – not applicable
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 - done
		(b) Give reasons for non-participation at each stage - done
		(c) Consider use of a flow diagram – done (Fig 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders - done
		(b) Indicate number of participants with missing data for each variable of interest – not applicable
Outcome data	15*	Report numbers of outcome events or summary measures -done
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 - done

		(*b*) Report category boundaries when continuous variables were categorized – not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period – not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses – done
Discussion		
Key results	18	Summarise key results with reference to study objectives – done
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 – done
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - done
Generalisability	21	Discuss the generalisability (external validity) of the study results – done
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 - done

*Give information separately for exposed and unexposed groups.

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.

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Publication bias in pediatric emergence delirium: almost half of registered clinical trials are not published

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Conclusion: There is a distinct publication gap in clinical research in pediatric ED that may have an impact on meta-analyses and clinical practice.

Strengths and limitations of this study

- This study quantitates the amount of research waste in pediatric emergence delirium assessed as a) the number and b) sample sizes of published and unpublished completed clinical studies
- The precise reasons for non-publication of the studies included in this analysis remain unknown
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- Study registers other than ClinicalTrials.gov and ClinicalTrialsRegister.eu were not analyzed

Funding statement:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Introduction

Emergence delirium (ED) can be a very stressful event for both patients and caregivers during general anesthesia in children. Although it may also develop in adults, ED is much more common in pediatric patients, with prevalences between 25% and 80% depending on the definition of ED [1]. Symptoms usually begin shortly after emergence from anesthesia and can be very frightening including self-inflicted injury or accidental removal of catheters and other medical devices. Although episodes of ED are usually short lived, it has been suspected that ED may be associated with long-term behavioral disturbances such as eating disorders, sleeping disorders, and separation anxiety [2].

The exact pathophysiology of ED is not yet understood. However, several risk factors are known: young age, use of volatile anesthetics (especially sevoflurane), type of surgery (increased risk for otorhinolaryngeal and ophthalmological procedures), parental as well as patient anxiety, and pre-existing behavioral problems [3]. Whereas anxiety and behavioral problems can be addressed by non-pharmacological interventions, most of these risk factors cannot be modified and prompt the pre- and/or perioperative administration of various medications including benzodiazepines, alpha-2-agonists, propofol, opioids, and ketamine [4 5].

However, although it is evident that all of these drugs may have beneficial effects in specific settings to reduce the rates of ED, no universal recommendations can be derived from the existing literature for this very common and potentially serious complication. This is a typical situation in the treatment of pediatric patients, where many treatment decisions are still based on incomplete clinical data, and off-label use of various drugs is common. One important factor for the lack of clinical consensus data might be a publication bias. It is twice as likely that a positive outcome of an intervention is reported than a negative one [6]. Such selective reporting of positive results is likely to influence clinical decision making. We therefore investigated

potential publication bias and time to publication in registered clinical trials on ED in children. This is a cross-sectional study.

Methods

Identification of clinical trials

Two databases were assessed to identify registered clinical trials on Pediatric Emergence Delirium reported as completed: 1) the ClinicalTrials.gov database provided by the U.S. National Library of Medicine and 2) the European Union Clinical Trials Register at ClinicalTrialsRegister.eu. Search criteria were: keywords "emergence delirium" and "emergence agitation" with the query selection parameters "completed studies" and "child (0-17 years)". Close of database was September 1st 2019. Data were downloaded for further analysis.

Search for publications of completed trials

To identify publications related to the registered and completed trials, ClinicalTrials.gov, PubMed and Google Scholar were searched for NCT number, EudraCT number, study title, principal investigator, study sponsor and keywords generated from the study title. If no respective publication was found, the principal investigators were contacted by email and/or ResearchGate and asked to provide information whether the study was published in a source not covered by PubMed or Google Scholar. The authors were contacted once more if they did not reply within four weeks.

Data Analysis

The STROBE criteria (STrengthening the Reporting of OBservational studies in Epidemiology) were applied for design and analysis of this study [7]. In order to analyze characteristics of published and unpublished clinical studies in pediatric emergence delirium, the following variables were analyzed: age, condition, number of participants (study population), condition and intervention (topic of investigation), availability of

study results (publication status), completion date, and publication date (time-to-publication), and country of sponsor (study localization). Trials were categorized into eight groups according to their main research topic. Time to publication was calculated as the difference in months between study completion date and publication date and. Missing data were not imputed. All statistical analyses were performed in SPSS 20 (IBM Corporations, Armonk, New York) using standard methods for descriptive statistics. No sensitivity analyses were conducted

Patient and Public involvement:

No patient involved

Results

Publication status of studies

We identified a total of 47 studies that were reported as completed in the two trial databases. Of these, three unpublished studies were completed less than one year before close of the database. Because the U.S. Food and Drug Administration (FDA) allows a time frame of one year between completion and publication of the study as specified in the in the FDA Drug Administration Amendments Act (FDAAA) [8], these three studies were excluded from the analysis. Of the remaining 44 studies, 29 were published and 19 were unpublished. Nine principal investigators of the unpublished studies could not be contacted by email or the ResearchGate social network. Of the remaining ten, two replied and confirmed that the study results had not been published yet (figure 1). Publication rates considerably varied between different countries of the sponsor (table 1) and main topics of the investigations (table 2).

The numbers of published and unpublished studies for each year of study completion (2007 – 2018) is shown in figure 2. An increasing number of publications over the years can be observed as well as an increasing proportion of unpublished studies which even exceeded the number of published studies in the last three years.

Patient numbers

All studies involved both genders. Published trials contained data from n=2556 patients, whereas n=1644 patients were enrolled in unpublished trials. Median size of published trials was 90 (IQR 68-136), range 40-418, whereas median size of unpublished trials was 80 (IQR 55-100), range 22-156 participants. Of note, the number of patients enrolled in unpublished studies significantly exceeded those in published studies during the last years (figure 3).

Time to publication

Median time to publication was 19 (IQR 12-27), range 3 to 104 months. More recent studies were published faster, but still only 9 of 25 trials were published within 12 months after completion as warranted by the FDAAA (figure 4).

Discussion

Almost every second completed registered clinical trial on pediatric ED remains unpublished, making results from 1644 enrolled study patients unavailable for clinical decision making. Given the high prevalence of ED and its potentially serious Manifestations, this significant publication bias is both surprising and unsatisfying.

This lack of study results may directly influence clinical practice. An illustrative example is the use of dexmedetomidine. Two published studies could show a reduction of incidence and degree of ED following premedication with intranasal dexmedetomidine [9 10]. However, dexmedetomidine, like most potent sedatives, causes an unpleasant burning sensation when applied intranasally [11]. Oral application might therefore be a better choice for anxious children. One recent study showed that 1 µg per kg oral dexmedetomidine for premedication provided satisfactory sedation levels, but was not effective in preventing ED [12]. On the other hand, we identified an unpublished registered trial (NCT03357718) that used 2 µg/kg, so it is not known whether oral dexmedetomidine at higher doses might be as effective as intranasal application. For three of the 19 unpublished studies, preliminary results are available at ClinicalTrials.gov, and all three studies compared dexmedetomidine to placebo. However, their preliminary results are as conflicting as the published ones: no positive effects of intramuscular (NCT01535287) and intravenous (NCT01901588) dexmedetomidine, respectively, but reduction of ED when 8-fold higher intravenous doses had been used (NCT00857727). Another unpublished study (NCT03171740) compared premedication with intranasal dexmedetomidine to oral midazolam. Intra- or postoperative dexmedetomidine application was investigated in five registered trials (NCT01901588, NCT03779282, NCT00857727, NCT01895023, NCT01535287) the results of which are not available (yet) to the public. Especially with regard to different

doses and potential cardiocirculatory side-effects of intravenous dexmedetomidine, the data of these 482 patients would be very interesting.

Similar considerations can be made for several study topics summarized in table 2. Minimizing pain with intraoperative Fentanyl given at a mean dose of 2.5 µg/kg at the end of surgery reduced the incidence of ED in a study by Cohen et al. [13]. However, in the context of postoperative delirium in the PICU we could recently show that fentanyl increases the risk for delirium in a dose-dependent way and that this could probably attributed to substance-specific anticholinergic effects [14]. Therefore it would be very interesting to see the results of the 322 patients from the three unpublished registered trials (NCT02753725, NCT03010540, NCT03062488) on intraoperative fentanyl given at different doses.

Unfortunately, the low publication rate for studies on ED that we found in our analysis is in line with other published observations. Anderson et al. recently reported that only 38.3% of all completed or prematurely terminated trials registered at ClinicalTrials.gov were published [15], and we came to similar conclusions when testing for publication bias in fields as diverse as pediatric liver transplantation [16] or autism [17]. Publication of the results gathered in clinical trials involving human subjects is considered an ethical imperative [18]. In 2007 it became a legal obligation in the U.S. to register all clinical trials in advance and publish its results within 12 months after completion [8]. Interestingly, the highest rate of unpublished study with regard to the country of the investigation was found for the U.S. despite of this federal law. Timely publication of the results is another issue that we investigated in our study. Only 9 of the 24 published studies were published within 12 months after completion, and we did not observe a trend to shorter publication intervals during recent years.

Limitations

Our study has several limitations. First, we only analyzed clinical trials that were registered either at ClinicalTrials.gov or ClinicalTrialsRegister.eu., therefore some studies registered in smaller national registers may have been missed. Second, our analysis relies on the accuracy of data input in the respective register. Third, we can only speculate about the reasons why half of the investigators chose not to publish their results, because we did not receive respective information after contacting them directly. Last, it is likely that some of the recently completed studies will be published eventually, but still considerably later than the 12 months warranted by the FDAAA.

Conclusion

There is a distinct publication gap in clinical research in pediatric ED. Although this does not call into question the results of published studies, it should raise awareness that many aspects of the current treatment options are not exactly known and that larger numbers of published trials are immensely helpful to either support existing data or to challenge it thereby improving clinical practice. In addition, timely publication of study results helps to improve patient care and avoids unnecessary exposure to research if a similar research question in being investigated repeatedly.

Authors' contributions

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: JM, MR

Drafting the work or revising it critically for important intellectual content: JM, MR

Final approval of the version to be published: JM, MR

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: JM, MR

Data sharing statement

All relevant data are in the manuscript.

Competing interests statement

JM and MR report no conflict of interest.

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Figure legends

Figure 1: Flowsheet: details of the study selection process

Figure 2: Distribution of published (n=24) and unpublished (n=20) trials by year of completion

Figure 3: Distribution of patient count stratified by publication status and year

Figure 4: Time to publication (time between completion of the trial and publication of results) in months by year of completion

"FDAAA" = timeline mandated by the U.S. Food and Drug Administration Amendments Act of 2007

Table 1: Published (n=25) and unpublished (n=19) completed studies on pediatric emergence delirium by country

Countries	Published studies (n)	Unpublished studies (n)
Belgium	2	0
Brasil	0	1
Canada	1	0
China	0	2
Egypt	1	0
Greece	1	0
India	1	1
Italy	1	0
Kenya	0	1
South Korea	8	4
Thailand	2	1
Turkey	3	2
United States	4	8

Table 2: Publication status of studies registered as completed on ClinicalTrials.gov and ClinicalTrialsRegister.eu involving children with emergence delirium

Topic of investigation	Overall number of studies	Number and percentage of published studies	Number of patients enrolled in unpublished studies
Dexmedetomidin	13	5 (38%)	598
Diagnostic criteria	6	2 (33%)	326
Non-pharmacological interventions	5	4 (80%)	160
Opioids	5	2 (40%)	322
Other drugs	5	4 (80%)	66
Propofol	4	3 (75%)	100
Volatile anesthetics	3	1 (33%)	132
Midazolam	3	3 (100%)	0

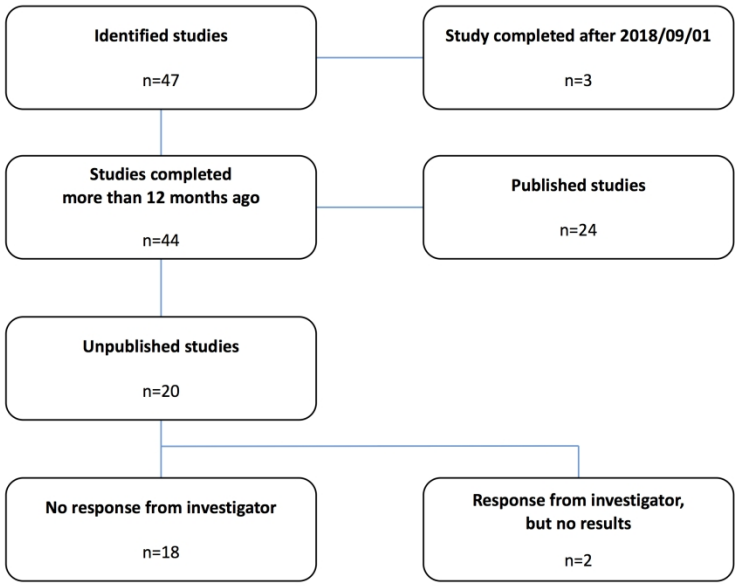

Figure 1: Flowsheet: details of the study selection process

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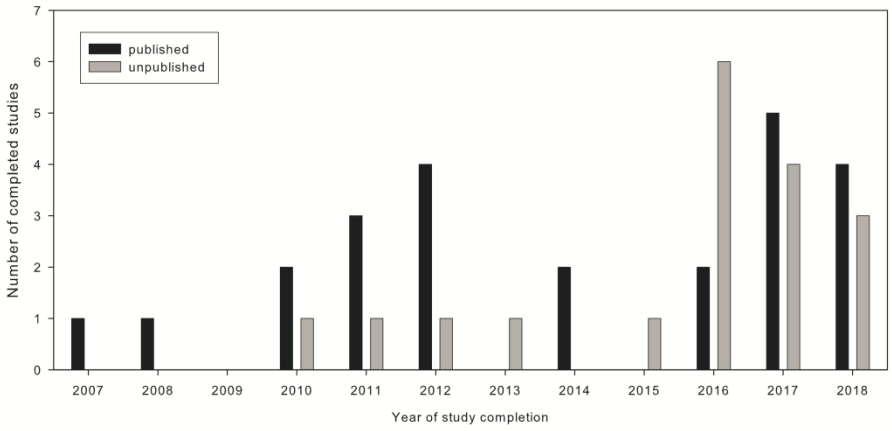

Figure 2: Distribution of published (n=24) and unpublished (n=20) trials by year of completion

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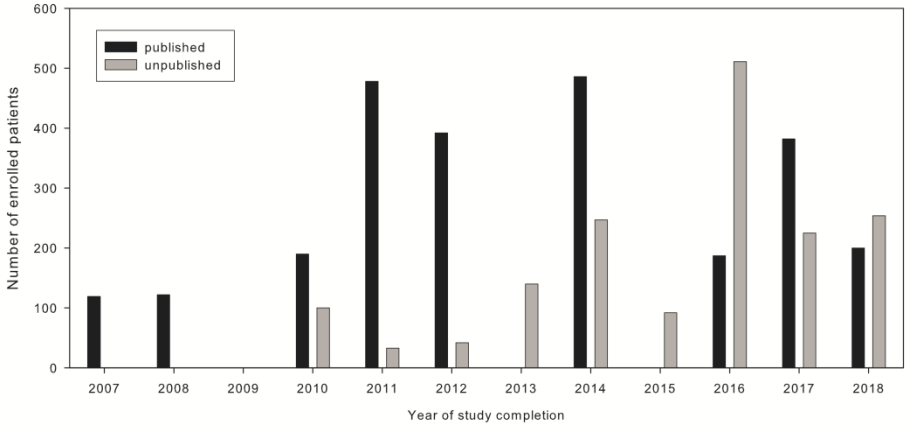

Figure 3: Distribution of patient count stratified by publication status and year

296x209mm (300 x 300 DPI)

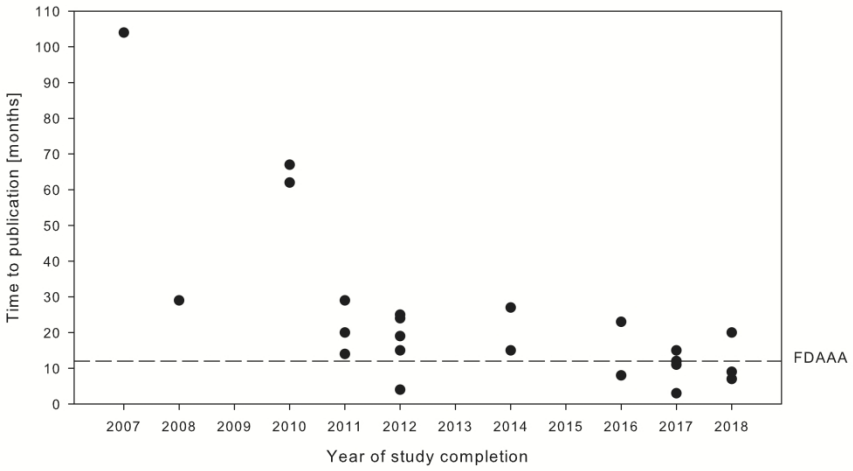

Figure 4: Time to publication (time between completion of the trial and publication of results) in months by year of completion
"FDAAA" = timeline mandated by the U.S. Food and Drug Administration Amendments Act of 2007

296x209mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2, line 34
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2, lines 27-48
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4, line 63 to page 5 line 90
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 2, lines 28-33 Page 4, line 88 to page 5 line 90
Methods			
Study design	4	Present key elements of study design early in the paper	Page 2 line 34, page 5 line 89
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6 lines 91-109
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 6 lines 111-118
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6 lines 111-118
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	Page 6 lines 91-109
Bias	9	Describe any efforts to address potential sources of bias	Page 6 lines 105-109
Study size	10	Explain how the study size was arrived at	Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6 line 113 to page 7 line 123
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7 lines 122-123
		(*b*) Describe any methods used to examine subgroups and interactions	No applicable

		(*c*) Explain how missing data were addressed	Page 7 line 121
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Page 7 line 123
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	Page 8, lines 130-140, Figure 1
		(b) Give reasons for non-participation at each stage	Page 8 line 136 -139
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1 and 2, Figures 2 and 3
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Tables 1 and 2, Figures 2,3, and 4
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	Not applicable
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10 lines 159-162
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	Page 11 line 208 to page 12 line 216
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12 lines 194 to 206
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 12 lines 219 to 225
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	Page 3 lines 60-62

*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.

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Publication bias in pediatric emergence delirium – a cross-sectional analysis of ClinicalTrials.gov and ClinicalTrialsRegister.eu

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Publication bias in pediatric emergence delirium – a cross-sectional analysis of ClinicalTrials.gov and ClinicalTrialsRegister.eu

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emergence delirium, publication bias, research waste, clinical studies

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Number of tables: 2
Number of figures: 4

Abstract

Objectives: Emergence delirium (ED) is a frequent and potentially serious complication of general anesthesia in children. Although there are various treatment strategies, no general management recommendations can be made. Selective reporting of study results may impair clinical decision making. We, therefore, analyzed whether the results of completed registered clinical studies in patients with pediatric ED are publicly available or remain unpublished.

Design: Cross-sectional analysis.

Setting: ClinicalTrials.gov and ClinicalTrialsRegister.eu

Participants and outcome measures: We determined the proportion of published and unpublished studies registered at ClinicalTrials.gov and ClinicalTrialsRegister.eu that were marked as completed by September 1st 2018. The major trial and literature databases were used to search for publications. In addition, the study investigators were contacted directly. For published trials, time to publication was calculated as the difference in months between study completion date and publication date.

Results: Of the 44 registered studies on pediatric ED, only 24 (54%) were published by September 2019. Published trials contained data from n=2556 patients, whereas n=1644 patients were enrolled in unpublished trials. Median time to publication was 19 months. Studies completed in recent years were published faster, but still only 9 of 25 trials were published within 12 months of completion.

Conclusion: There is a distinct publication gap in clinical research in pediatric ED that may have an impact on meta-analyses and clinical practice.

Strengths and limitations of this study

- This study quantitates the amount of research waste in pediatric emergence delirium assessed as a) the number and b) sample sizes of published and unpublished completed clinical studies
- The precise reasons for non-publication of the studies included in this analysis remain unknown
- Strengths of findings as well as directions of individual unpublished studies remain unknown
- Study registers other than ClinicalTrials.gov and ClinicalTrialsRegister.eu were not analyzed

Funding statement:

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Introduction

Emergence delirium (ED) can be a very stressful event for both patients and caregivers during general anesthesia in children. Although it may also develop in adults, ED is much more common in pediatric patients, with prevalences between 25% and 80% depending on the definition of ED [1]. Symptoms usually begin shortly after emergence from anesthesia and can be very frightening including self-inflicted injury or accidental removal of catheters and other medical devices. Although episodes of ED are usually short lived, it has been suspected that ED may be associated with long-term behavioral disturbances such as eating disorders, sleeping disorders, and separation anxiety [2].

The exact pathophysiology of ED is not yet understood. However, several risk factors are known: young age, use of volatile anesthetics (especially sevoflurane), type of surgery (increased risk for otorhinolaryngeal and ophthalmological procedures), parental as well as patient anxiety, and pre-existing behavioral problems [3]. Whereas anxiety and behavioral problems can be addressed by non-pharmacological interventions, most of these risk factors cannot be modified and prompt the pre- and/or perioperative administration of various medications including benzodiazepines, alpha-2-agonists, propofol, opioids, and ketamine [4 5].

However, although it is evident that all of these drugs may have beneficial effects in specific settings to reduce the rates of ED, no universal recommendations can be derived from the existing literature for this very common and potentially serious complication. This is a typical situation in the treatment of pediatric patients, where many treatment decisions are still based on incomplete clinical data, and off-label use of various drugs is common. One important factor for the lack of clinical consensus data might be a publication bias. It is twice as likely that a positive outcome of an intervention is reported than a negative one [6]. Such selective reporting of positive results is likely to influence clinical decision making. We, therefore, investigated

potential publication bias and time to publication in registered clinical trials on ED in children. This is a cross-sectional study.

Methods

Purpose of this study

The purpose of this analysis is to characterize publication status, patient numbers, topics of investigation, study localization, and time-to-publication of completed clinical trials in pediatric emergence ED, with the ultimate goal to obtain an insight into transparency and potential research waste in this important area of medicine.

Research reporting guideline

The STROBE criteria (STrengthening the Reporting of OBservational studies in Epidemiology) were applied for design, analysis, and reporting of this study [7].

Identification of clinical trials

Two databases were assessed to identify registered clinical trials on Pediatric ED reported as completed by September 1st 2018: 1) the ClinicalTrials.gov database provided by the U.S. National Library of Medicine and 2) the European Union Clinical Trials Register at ClinicalTrialsRegister.eu. Search criteria were: keywords “emergence delirium” and “emergence agitation” with the query selection parameters “completed studies” and “child (0-17 years)”. Close of database was September 1st 2019. Data were downloaded for further analysis.

Search for publications of completed trials

To identify publications related to the registered and completed trials, ClinicalTrials.gov, PubMed and Google Scholar were searched for NCT number, EudraCT number, study title, principal investigator, study sponsor and keywords generated from the study title. If no respective publication was found, the principal investigators were contacted by email and/or ResearchGate and asked to provide

information about whether the study was published in a source not covered by PubMed or Google Scholar. The authors were contacted once more if they did not reply within four weeks.

Data Analysis

The following variables were analyzed: age of participants, condition, number of participants, intervention, availability of study results, completion and publication dates (time-to-publication), and country of sponsor. The variables “age of participants” and “condition” refers to the inclusion criteria of a respective clinical study. Both variables were reviewed categorially in order to ensure that only pediatric studies with patients with emergence delirium were considered in the present analysis. The variable “number of participants” refers to the sample size of a given clinical study. Numbers and population sizes were calculated for both published and unpublished studies. The variable “intervention” provided information about the main research tropic of a respective clinical study. Time-to-publication was calculated as the difference in months between study completion date and publication date in order to ascertain when results were made publicly available after completion of the study. The variable “country of sponsor” provided information about the geographic localization of the study. A detailed overview of the data is provided in the referenced supplemental table. Trials were categorized into eight groups according to their main research topic. Missing data were not imputed. All statistical analyses were performed in SPSS 20 (IBM Corporations, Armonk, New York) using standard methods for descriptive statistics. No sensitivity analyses were conducted.

Patient and Public involvement:

No patient involved.

Results

Publication status of studies

We identified a total of 47 studies that were reported as completed in the two trial databases. Of these, three unpublished studies were completed less than one year before close of the database. Because the U.S. Food and Drug Administration (FDA) allows a time frame of one year between completion and publication of the study as specified in the FDA Drug Administration Amendments Act (FDAAA) [8], these three studies were excluded from the analysis. Of the remaining 44 studies, 29 were published and 19 were unpublished. Nine principal investigators of the unpublished studies could not be contacted by email or through the ResearchGate social network. Of the remaining ten, two replied and confirmed that the study results had not been published yet (figure 1). Publication rates varied considerably with the country of the sponsor (table 1) and the main topic of the investigation (table 2).

The numbers of published and unpublished studies for each year of study completion (2007 – 2018) is shown in figure 2. An increasing number of publications over the years can be observed as well as an increasing proportion of unpublished studies which even exceeded the number of published studies in the last three years.

Patient numbers

All studies involved both genders. Published trials contained data from n=2556 patients, whereas n=1644 patients were enrolled in unpublished trials. Median size of published trials was 90 (IQR 68-136), range 40-418, whereas median size of unpublished trials was 80 (IQR 55-100), range 22-156 participants. Of note, the number of patients enrolled in unpublished studies significantly exceeded those in published studies during the last years (figure 3).

Time-to-publication

Median time-to-publication was 19 (IQR 12-27), range 3 to 104 months. More recent studies were published faster, but still only 9 of 25 trials were published within 12 months after completion as warranted by the FDAAA (figure 4).

Discussion

Almost every second completed registered clinical trial on pediatric ED remains unpublished, making results from 1644 enrolled study patients unavailable for clinical decision making. Given the high prevalence of ED and its potentially serious manifestations, this significant publication bias is both surprising and unsatisfying.

This lack of study results may directly influence clinical practice. An illustrative example is the use of dexmedetomidine. Two published studies could show a reduction of incidence and degree of ED following premedication with intranasal dexmedetomidine [9 10]. However, dexmedetomidine, like most potent sedatives, causes an unpleasant burning sensation when applied intranasally [11]. Oral application might therefore be a better choice for anxious children. One recent study showed that 1 µg per kg oral dexmedetomidine for premedication provided satisfactory sedation levels, but was not effective in preventing ED [12]. On the other hand, we identified an unpublished registered trial (NCT03357718 [13]) that used 2 µg/kg, so it is not known whether oral dexmedetomidine at higher doses might be as effective as intranasal application. For three of the 19 unpublished studies, preliminary results are available at ClinicalTrials.gov, and all three studies compared dexmedetomidine to placebo. However, their preliminary results are as conflicting as the published ones: no positive effects of intramuscular (NCT01535287 [14]) and intravenous (NCT01901588 [15]) dexmedetomidine, respectively, but reduction of ED when 8-fold higher intravenous doses had been used (NCT00857727 [16]). Another unpublished study (NCT03171740 [17]) compared premedication with intranasal dexmedetomidine to oral midazolam. Intra- or postoperative dexmedetomidine application was investigated in five registered trials (NCT01901588 [15], NCT03779282 [18], NCT00857727 [16], NCT01895023 [19], NCT01535287 [14]) the results of which are not available (yet) to the public. Especially

with regard to different doses and potential cardiocirculatory side-effects of intravenous dexmedetomidine, the data of these 482 patients would be very interesting.

Similar considerations can be made for several study topics summarized in table 2. Minimizing pain with intraoperative Fentanyl given at a mean dose of 2.5 µg/kg at the end of surgery reduced the incidence of ED in a study by Cohen et al. [20]. However, in the context of postoperative delirium in the PICU, we could recently show that fentanyl increases the risk for delirium in a dose-dependent way and that this could probably be attributed to substance-specific anticholinergic effects [21]. Therefore, it would be very interesting to see the results of the 322 patients from the three unpublished registered trials (NCT02753725 [22], NCT03010540 [23], NCT03062488 [24]) on intraoperative fentanyl given at different doses.

Unfortunately, the low publication rate for studies on ED that we found in our analysis is in line with other published observations. Anderson et al. recently reported that only 38.3% of all completed or prematurely terminated trials registered at ClinicalTrials.gov were published [25], and we came to similar conclusions when testing for publication bias in fields as diverse as pediatric liver transplantation [26] or autism [27]. Publication of the results gathered in clinical trials involving human subjects is considered an ethical imperative [28]. In 2007 it became a legal obligation in the U.S. to register all clinical trials in advance and publish its results within 12 months of completion [8]. Interestingly, despite this federal law, the US was the country of investigation found to have the highest rate of unpublished studies. Timely publication of the results is another issue that we investigated in our study. Only 9 of the 24 published studies were published within 12 months of completion, and we did not observe a trend to shorter publication intervals during recent years.

Limitations

Our study has several limitations. First, we only analyzed clinical trials that were registered either at ClinicalTrials.gov or ClinicalTrialsRegister.eu. Therefore, some studies registered in smaller national registers may have been missed. Second, our analysis relies on the accuracy of data input in the respective register. Third, we can only speculate about the reasons why half of the investigators chose not to publish their results, as we did not receive respective information after contacting them directly. Last, it is likely that some of the recently completed studies will be published eventually, but still considerably later than the 12 months warranted by the FDAAA.

Conclusion

There is a distinct publication gap in clinical research in pediatric ED. Although this does not call into question the results of published studies, it should raise awareness that many aspects of the current treatment options are not exactly known. Larger numbers of published trials are immensely helpful to either support or challenge existing data which would further improve clinical practice. In addition, timely publication of study results helps to improve patient care and avoids unnecessary exposure to research, in particular, if a similar research question is being investigated repeatedly due to a lack of transparency.

Authors' contributions

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: JM, MR

Drafting the work or revising it critically for important intellectual content: JM, MR

Final approval of the version to be published: JM, MR

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: JM, MR

Data sharing statement

All relevant data are in the manuscript.

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Competing interests statement

JM and MR report no conflict of interest.

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Figure legends

Figure 1: Flowsheet: details of the study selection process

Figure 2: Distribution of published (n=24) and unpublished (n=20) trials by year of completion

Figure 3: Distribution of patient count stratified by publication status and year

Figure 4: Time to publication (time between completion of the trial and publication of results) in months by year of completion

"FDAAA" = timeline mandated by the U.S. Food and Drug Administration Amendments Act of 2007

Table 1: Published (n=25) and unpublished (n=19) completed studies on pediatric emergence delirium by country

Countries	Published studies (n)	Unpublished studies (n)
Belgium	2	0
Brasil	0	1
Canada	1	0
China	0	2
Egypt	1	0
Greece	1	0
India	1	1
Italy	1	0
Kenya	0	1
South Korea	8	4
Thailand	2	1
Turkey	3	2
United States	4	8

Table 2: Publication status of studies registered as completed on ClinicalTrials.gov and ClinicalTrialsRegister.eu involving children with emergence delirium

Topic of investigation	Overall number of studies	Number and percentage of published studies	Number of patients enrolled in unpublished studies
Dexmedetomidin	13	5 (38%)	598
Diagnostic criteria	6	2 (33%)	326
Non-pharmacological interventions	5	4 (80%)	160
Opioids	5	2 (40%)	322
Other drugs	5	4 (80%)	66
Propofol	4	3 (75%)	100
Volatile anesthetics	3	1 (33%)	132
Midazolam	3	3 (100%)	0

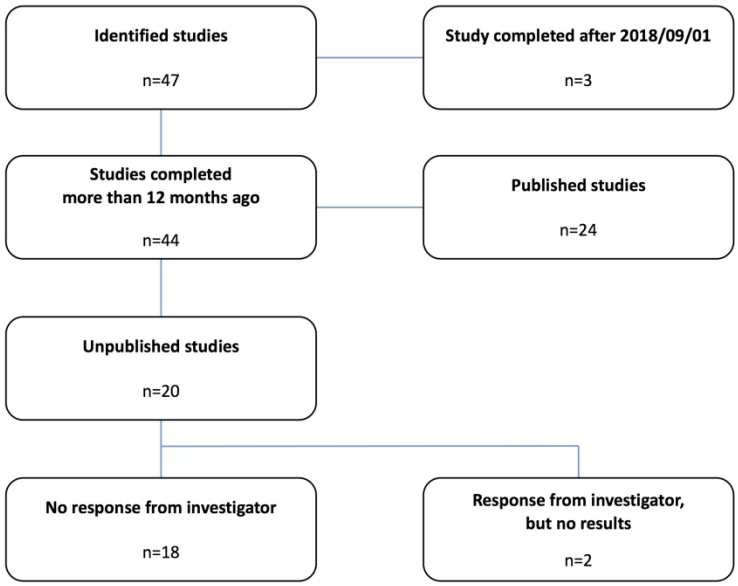

Figure 1: Flowsheet: details of the study selection process

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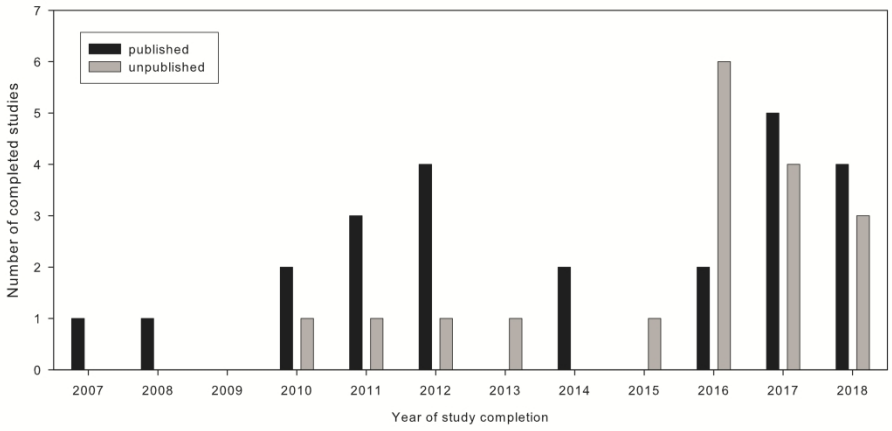

Figure 2: Distribution of published (n=24) and unpublished (n=20) trials by year of completion

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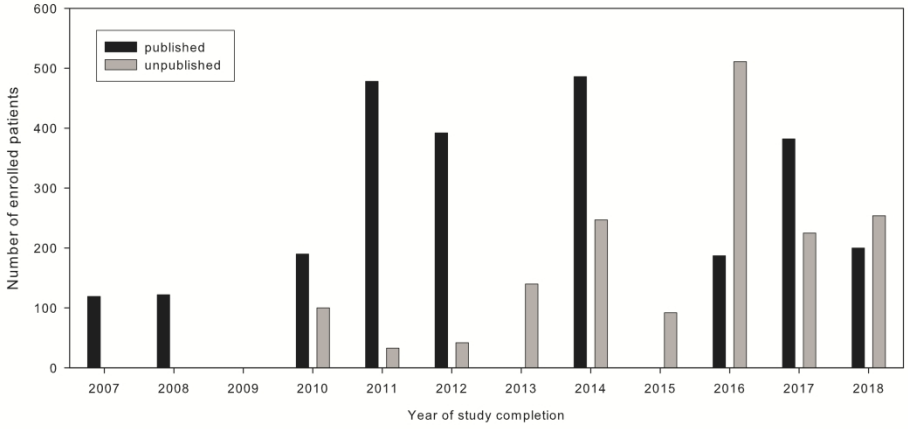

Figure 3: Distribution of patient count stratified by publication status and year

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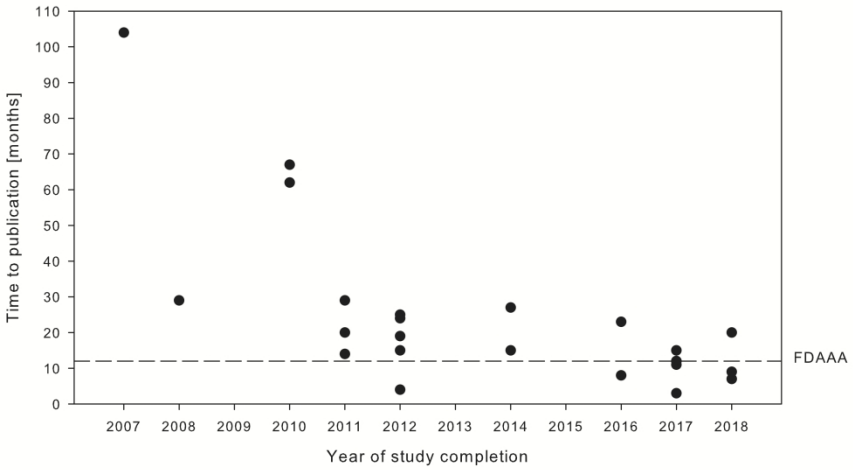

Figure 4: Time to publication (time between completion of the trial and publication of results) in months by year of completion
"FDAAA" = timeline mandated by the U.S. Food and Drug Administration Amendments Act of 2007

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Supplemental Table: Published and unpublished completed clinical studies in pediatric emergence delirium (Studies were completed before September 1st 2018, close of database was September 1st 2019)

Trial number	published	Date of completion [DD.MM.YY]	Date of publication [DD.MM.YY]	Time to Publication [months]	Study Title	Intervention	Patients enrolled [n]	Country
NCT00932685 [1]	yes	01.07.07	01.03.16	104	Does Distraction With a Hand Held Video Game Reduce Preoperative and Emergence Anxiety in Children?	Drug: Midazolam Device: Game Boy	119	United States
NCT00468052 [2]	yes	01.05.08	01.10.10	29	Decrease Emergence Agitation and Provide Pain Relief for Children Undergoing Tonsillectomy & Adenoidectomy	Drug: Dexmedetomidine Drug: Fentanyl	122	United States
NCT01096797 [3]	yes	01.03.10	01.05.15	62	Correlation Between Pain and Emergence Delirium After Adenotonsillectomy in Preschool Children	Drug: Sevoflurane	150	Italy
NCT00990769 [4]	yes	01.09.10	01.04.16	67	The Effect of Depth of Anesthesia as Measured by Bispectral Index (BIS) on Emergence Agitation in Children	Other: Depth of anesthesia	40	United States
NCT01440114 [5]	yes	01.07.11	01.12.13	29	The Effect of Intravenous Fentanyl Prior the End of Surgery on Emergence Agitation in Paediatric Patients After General Anesthesia	Drug: Fentanyl Drug: NSS	144	Thailand
NCT00885443 [6]	yes	01.08.11	01.04.13	20	Emergence Delirium in Children: Total Intravenous Anesthesia With Propofol and Remifentanil Versus Inhalational Sevoflurane Anesthesia	Drug: Propofol Drug: Sevoflurane	112	Kanada
NCT01506622 [7]	yes	01.12.11	01.02.13	14	Comparison Between Propofol and Fentanyl for Prevention of Emergence Agitation in Children After Sevoflurane Anesthesia	Drug: Propofol Drug: Fentanyl Drug: Saline	222	South Korea
NCT01512355 [8]	yes	01.03.12	01.03.14	24	The Effect of Dexmedetomidine on Decreasing Emergence Agitation and Delirium in Pediatric Patients Undergoing Strabismus Surgery	Drug: Dexmedetomidine	88	South Korea
NCT01235143 [9]	yes	01.08.12	01.11.13	15	Emergence Agitation Between	Drug: Desflurane	136	Thailand

					Sevoflurane and Desflurane in Pediatric	Drug: Sevoflurane		
NCT02022488 [10]	yes	01.08.12	01.09.14	25	Sevoflurane Induced Emergence Agitation	Drug: Midazolam Drug: Alfentanil Drug: Ketamine	78	Turkey
NCT01680471 [11]	yes	01.11.12	01.06.14	19	A Study on the Effects of Midazolam on Delirium After Sevoflurane Anesthesia in Pediatric Strabismus Surgery	Drug: Midazolam 0.03mg/kg Drug: Midazolam 0.05mg/kg	90	South Korea
NCT02256358 [12]	yes	01.01.14	01.04.16	27	Comparison of Effects of Intravenous Midazolam and Ketamine on Emergence Agitation	Drug: Midazolam Drug: Ketamine	68	South Korea
NCT01528891 [13]	yes	01.08.14	01.11.15	15	Dexmedetomidine as a Rapid Bolus in Children for Emergence Agitation	Drug: Dexmedetomidine	418	United States
2015-002329-20 [14]	yes	31.03.16	01.12.17	20	Xenon as an adjuvant to sevoflurane anaesthesia in children younger than four, undergoing interventional or diagnostic cardiac catheterization: a pilot study	Drug: Xenon	40	Belgium
NCT02428283 [15]	yes	01.11.16	01.07.17	8	Scalp Nerve Block on Emergence Agitation	Drug: Ropivacaine Drug: Remifentanil Drug: Sevoflurane	44	South Korea
NCT02997124 [16]	yes	01.11.16	01.10.18	23	Transversus Abdominis Plane Block in Iliac Crest harvest-is it Beneficial?	Procedure: local infiltration and TAP block Procedure: local infiltration only	143	India
NCT03174678 [17]	yes	01.05.17	01.08.17	3	Dexmedetomidine Premedication in Children	Drug: Dexmedetomidine	100	Turkey
NCT03131375 [18]	yes	01.07.17	01.07.18	12	Dexmedetomidine Reduces Emergence Delirium in Children Undergoing Tonsillectomy With Propofol Anesthesia	Drug: Dexmedetomidine Drug: Normal saline Device: Bispectral index Device: Train of four ratio	60	Greece
NCT03197753 [19]	yes	01.08.17	01.08.18	12	Postoperative Discomfort After Dental General Anesthesia	Device: Laryngeal mask airway Device: Nasotracheal intubation	70	Turkey
NCT02955680 [20]	yes	01.09.17	01.08.18	11	Recorded Maternal Voice on the Emergence of General Anesthesia on Pediatric Patients	Procedure: recorded maternal voice Procedure: recorded stranger's voice	66	South Korea

NCT03172182 [21]	yes	01.10.17	01.01.19	15	Perioperative Effects of Operating Room Virtual Tour	Behavioral: 360-degree VR video tour	86	South Korea
2014-002510-23 [22]	yes	21.12.17	01.08.18	7	Xenon as an adjuvant to sevoflurane anaesthesia in children undergoing interventional or diagnostic catheterization: a randomized controlled clinical trial	Drug: Xenon	40	Belgium
NCT03179293 [23]	yes	01.06.18	06.03.19	9	Transition to Propofol After Sevoflurane Anaesthesia to Prevent Emergence Agitation	Drug: Propofol Drug: Saline	70	Egypt
NCT03807011 [24]	yes	01.10.18	01.08.18		Emergence Agitation in Pediatric Strabismus Surgery	Drug: Fentanyl Drug: Remifentanil	90	South Korea
NCT00535613 [25]	no	01.12.10			Propofol in Emergence Agitation	Drug: Propofol	100	United States
NCT00857727 [26]	no	01.12.11			Use of Dexmedetomidine to Reduce Emergence Delirium Incident in Children	Drug: Dexmedetomidine Drug: Saline	33	United States
NCT01748630 [27]	no	01.10.12			Effects of Dexmedetomidine on the Postoperative Experience in Children	Drug: dexmedetomidine Drug: Midazolam Drug: Fentanyl	42	Turkey
NCT01535287 [28]	no	01.10.13			Effect of Dexmedetomidine on Emergence Agitation in Children With or Without Tube Insertion Under General Anesthesia	Drug: Dexmedetomidine	140	United States
NCT03358069 [29]	no	01.06.14			Does Emergence Time Relate With Emergence Agitation in Pediatric Patients?	Diagnostic Test: Emergence agitation scale	91	Thailand
NCT01895023 [30]	no	01.08.14			Effects of Dexmedetomidine Premedication on Emergence Agitation After Strabismus Surgery in Children	Drug: Dexmedetomidine Drug: Midazolam Drug: Saline	156	China
NCT02489734 [31]	no	01.09.15			Post Extubation Delirium and End-tidal Sevoflurane Concentration	Drug: Sevoflurane	92	China
NCT02980549 [32]	no	01.01.16			How Common Are Sleep Disorders and Problems With Emergence From Anesthesia in Surgical Patients	Diagnostic Test: children's sleep habits questionnaire	100	United States
NCT02521259 [33]	no	01.04.16			Anesthetic Depth and the Incidence of Emergence Agitation in Children Undergoing Strabismus Surgery	Device: BIS	68	South Korea
NCT01901588 [34]	no	01.05.16			Efficacy of Single-Shot	Drug: Dexmedetomidine	63	United

					Dexmedetomidine Versus Placebo in Preventing Pediatric Emergence Delirium in Strabismus Surgery			States
NCT02753725 [35]	no	01.07.16			Effect of Fentanyl on Emergence Delirium (ED) on Children Undergoing Adeno-tonsilectomy at Kenyatta National Hospital (KNH)	Drug: Fentanyl Drug: Saline	110	Kenya
NCT02383004 [36]	no	01.11.16			Acupuncture for the Prevention of Emergence Delirium in Children Undergoing Myringotomy Tube Placement	Other: Acupuncture	100	United States
NCT03010540 [37]	no	01.12.16			Effect Of Combination of Morphine+Fentanyl on Emergence Delirium in Patients of Cleft Lip and Palate Repair	Drug: Morphine plus Fentanyl Drug: Fentanyl	70	India
NCT03134547 [38]	no	01.02.17			A Comparison of Emergence Agitation by Sevoflurane for Intraoperative Sedation Associated With Caudal Block	Drug: low dose Sevoflurane Drug: high dose Sevoflurane	40	South Korea
NCT03357718 [39]	no	01.06.17			Oral Dexmedetomidine vs Midazoam For Premedication	Drug: Precedex Drug: Midazolam	52	Turkey
NCT03332407 [40]	no	01.09.17			Does Preoperative Sleep Quality Affect the Postoperative Emergence Delirium in Children Undergoing Strabismus Surgery	Other: Sleep Quality	67	South Korea
NCT03132701 [41]	no	01.12.17			The Effect of Magnesium Supplementation During General Anesthesia on the Quality of Postoperative Recovery in Children	Drug: Magnesium Drug: Saline	66	South Korea
NCT03171740 [42]	no	01.01.18			Premedication With Intranasal Dexmedetomidine or Midazolam for Prevention of Emergence Agitation in Children	Drug: Dexmedetomidine Drug: Midazolam Drug: Oral saline Drug: Nasal saline	22	Brasil
NCT03062488 [43]	no	01.07.18			Emergence Agitation and Pain Scores in Pediatrics When Comparing Single-modal vs Multi-modal Analgesia for ENT Surgery	Drug: IV acetaminophen Drug: Fentanyl Drug: PO acetaminophen	142	United States
NCT03779282 [44]	no	01.09.18			KETODEX for Emergence Delirium in Children Undergoing Outpatient Strabismus Surgery	Drug: Dexmedetomidine	90	United States

Supplemental Table. List of published (n=24) and unpublished (n=20) trials in pediatric emergence delirium. Close of database was September 1st 2019.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title, Page 2, line 33
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2, lines 27-47
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4, line 63 to page 5 line 89
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 2, lines 27-33 Page 3, line 87 to page 5 line 89
Methods			
Study design	4	Present key elements of study design early in the paper	Page 2 line 33, page 5 line 89
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6 lines 91-108
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 6 lines 110 to page 7 line 118
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7 lines 120-138
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	Page 6 line 101 to page 7 line 138
Bias	9	Describe any efforts to address potential sources of bias	Page 6 line 114 to page 7 line 118
Study size	10	Explain how the study size was arrived at	Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7 line 120 - 138
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7 lines 136-138

		(*b*) Describe any methods used to examine subgroups and interactions	No applicable
		(*c*) Explain how missing data were addressed	Page 7 line 136
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Page 7 line 138
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	Page 8, lines 144-154, Figure 1
		(b) Give reasons for non-participation at each stage	Page 8 line 151 -154
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Tables 1 and 2, Figures 2 and 3
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures	Tables 1 and 2, Figures 2,3, and 4
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	Not applicable
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10 lines 173-177
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	Page 11 line 223 to page 12 line 231
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 12 lines 209 to 221
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 12 lines 233 to 241
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	Page 3 lines 59-61

*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.