INPLASY PROTOCOL

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Population-based incidence of all-cause anaphylaxis and its development over time: a systematic review and meta-analysis

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Review question / Objective: The aim of this study is to determine the current population-based incidence rates of anaphylaxis worldwide as well as per continent. It is also evaluated whether the incidence has increased during the past decades. Furthermore, the study analyses confounding factors to identify potential underlying reasons for the wide range of incidence rates discussed in previous articles.

Condition being studied: Anaphylaxis can be summarized as an acute, systemic and very severe type of allergic reaction. Similarly to other allergic reactions, anaphylaxis is characterized by an IgE-mediated immunologic mechanism. According to the criteria defined by the NIAID-FAAN Symposium, the clinical picture of anaphylaxis can vary significantly, however, it may involve a combination of cutaneous, respiratory, cardiovascular and gastrointestinal symptoms, as well as organ dysfunction and hypotension.

INTRODUCTION

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METHODS

Search strategy: A systematic query was performed using four electronic databases, namely MEDLINE (by OVID), CINAHL (by EBSCOhost), Web of Science™ Core Collection (by Clarivate Analytics) and LILACS.
The search strategy was designed for MEDLINE and was later adapted for use with the three other databases.
The search included terms related to anaphylaxis, incidence, prevalence and epidemiological methods as well as terms related to included study types. The search excluded terms referring to animal studies.
As the aim is to assess the development of anaphylaxis incidence over time, no limitation was set on the year of publication.
All articles that do not meet any of the exclusion criteria and that include relevant information on population-based incidence rates of all-cause anaphylaxis are included in this analysis.

Participant or population: All publications concerning cause-unspecific anaphylaxis incidence rates are included, i.e. studies where the authors stated the reactions were anaphylactic. Hence, publications which reported on non-IgE-mediated anaphylactic reactions - often referred to as "anaphylactoid reactions" - are excluded. The same is true for studies reporting on cause specific incidence rates or solely on anaphylaxis caused death. This study includes patients of all ages and genders. In cases where research was performed on a specific sub-population (e.g. age specific analyses), the publication is included if the size of the respective reference population is available.

Intervention: This systematic review and meta-analysis does not involve interventions.

Comparator: As one of the objectives, the study will compare population-based incidence rates of all-cause anaphylactic reactions between the investigated continents. Moreover, the results of studies with similar key characteristics (i.e. data source or population age range) are compared and analysed as confounding factors.

Study designs to be included: Included study designs: cohort studies, cross-sectional studies, case control studies, randomized controlled trials and pharmacovigilance studies. Excluded study designs: reviews, discussions, non-research letters, editorials, practice guidelines, study protocols, position articles, meeting reports, case reports, case studies, case series and animal studies.

Eligibility criteria: Studies that report only on prevalence or exposure based frequencies are excluded. As far as language is concerned, publications or abstracts written in English or German are included. In case of articles of other languages for which only the abstract is available in English, the article is included as long as all the necessary information is mentioned in the abstract.

Information sources: The four electronic databases MEDLINE (by OVID), CINAHL (by EBSCOhost), Web of Science™ Core Collection (by Clarivate Analytics) and LILACS were used to perform a systematic query searching for publications that report population-based incidence rates of all-cause anaphylaxis.

Main outcome(s): The main outcome of the study will be the current population-based incidence rate of all-cause anaphylaxis, which will be achieved by calculating the weighted approximate rate of all incidence values reported in the articles that involve the latest years of analysis. The result will

be expressed as cases per 100,000 population per year.

Additional outcome(s): Additionally, the weighted approximate incidence rates worldwide and per continent will be calculated similarly as done for the main outcome, however, all articles will be included with no restriction on the year of analysis.

The study also intends to determine whether the incidence of anaphylaxis has increased over the past decades. The development over time will be evaluated using a trend line in a bubble plot, which presents the incidence rates of all incorporated articles against the years of analysis. The yearly change will be calculated using Poisson regression and given in percent.

Besides that, confounding factors (i.e. data source and population age range) will be calculated to evaluate whether these factors related to the design of the incorporated studies could have an impact on the resulting approximate incidence rate. This could also help to identify a reason for the wide range of incidence rates discussed in previous articles.

Data management: The publications resulting from the database queries were imported into the Reference Manager program (version 11). Automatic and manual duplicate checks were performed to eliminate publications that were retrieved from multiple databases.

The following variables are extracted for all incorporated publications: period of analysis, country of analysis, age of population, size of reference population, data source, incidence per 100,000 population per year. Additionally, a risk of bias assessment is performed.

Quality assessment / Risk of bias analysis: The quality of the incorporated studies and the risk of bias will be analysed based on a publication by Hoy et al. in 2012 (Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012;65(9):934-939). The authors elaborated a method that involves ten questions concerning external as well as internal validity plus a summary risk of bias assessment. These eleven items will also be used for this systematic review and meta-analysis.

The risk of bias will be evaluated by two independent reviewers. Disagreement will be resolved by discussion and, if necessary, by a third assessor.

Strategy of data synthesis: The key characteristics of the incorporated studies (period of analysis, country of analysis, age of population, size of reference population, data source, incidence per 100,000 population per year) are extracted and summarized in a table.

Poisson regression will be applied to determine incidence rates. Random effects models will be used to allow for within and between study variability. Average event rates across all studies will be calculated using a plain random effects Poisson model. For data management and analyses MS Excel and Stata 14.2 are used.

Subgroup analysis: To determine the current incidence of all-cause anaphylaxis, all articles will be divided into subgroups based on their years of analysis, while only the subgroup involving the latest years of analysis will be used for the calculation.

In addition to the worldwide incidence rate of all-cause anaphylaxis, the weighted approximate incidence rates per continent will be calculated.

For the analysis of confounding factors, articles will be grouped based on the age ranges of the study population and the various reported data sources.

Sensitivity analysis: A sensitivity analysis will be used to evaluate whether the results are robust and consistent or whether they are influenced by potential outlier values . Additionally, an analysis of confounding factors will be performed.

Country(ies) involved: Austria.

Keywords: anaphylactic reaction; anaphylaxis; epidemiology; incidence; meta-analysis; systematic review.

Contributions of each author:
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