REVIEW

Incidence of Fatal Anaphylaxis: A Systematic Review of Observational Studies

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Abstract

Background: Fatal anaphylaxis is very rare, with an incidence ranging from 0.5 to 1 deaths per million person-years.
Objective: Based on a systematic review, we aimed to explain differences in the reported incidence of fatal anaphylaxis based on the methodological and demographic factors addressed in the various studies.
Methods: We searched PubMed/MEDLINE, EMBASE, and the Web of Science for relevant retrospective and prospective cohort studies and registry studies that had assessed the anaphylaxis mortality rate for the population of a country or for an administrative region. The research strategy was based on combining the term "anaphylaxis" with "death", "study design", and "main outcomes" (incidence).
Results: A total of 46 studies met the study criteria and included 16,541 deaths. The range of the anaphylaxis mortality rate for all causes of anaphylaxis was 0.002-2.51 deaths per million person-years. Fatal anaphylaxis due to food (range 0.002-0.29) was rarer than deaths due to drugs (range 0.004-0.56) or Hymenoptera venom (range 0.02-0.61). The frequency of deaths due to anaphylaxis by drugs increased during the study period (IRR per year, 1.02; 95%CI, 1.00-1.04). We detected considerable heterogeneity in almost all of the meta-analyses carried out.
Conclusion: The incidence of fatal anaphylaxis is very low and differs according to the various subgroups analyzed. The studies were very heterogeneous. Fatal anaphylaxis due to food seems to be less common than fatal anaphylaxis due to drugs or Hymenoptera venom.

Key words: Anaphylaxis. Drugs. Food. Hymenoptera. Systematic review. Death. Incidence

Resumen

Antecedentes: La muerte por anafilaxia es un evento muy excepcional, con una incidencia que varía de 0,5 a 1 muerte por millón de personas/año.
Objetivo: Usando las técnicas de una revisión sistemática, nuestro objetivo ha sido explicar las diferencias en la incidencia informada de la muerte por anafilaxia atendiendo a diversos factores metodológicos y demográficos empleados en los diversos estudios de la revisión.
Métodos: Se realizaron búsquedas en PubMed/MEDLINE, EMBASE y Web of Science, con el fin de obtener estudios de cohortes y registros prospectivos y retrospectivos relevantes que hubieran evaluado la tasa de muerte por anafilaxia en la población de un país o una región administrativa. La estrategia de investigación se basó en combinar "anafilaxia" con "muerte", "diseño del estudio" y "resultados principales" (incidencia).
Resultados: Un total de 46 estudios cumplieron con los criterios del estudio. Los estudios incluyeron 16.541 muertes. El rango de la tasa de mortalidad por anafilaxia para todas las causas de anafilaxia fue de 0,002 a 2,51 muertes por millón de personas/año. La anafilaxia mortal debida a los alimentos (rango 0,002-0,29) fue más rara que las muertes debidas a medicamentos (rango 0,004-0,56) o veneno de himenópteros (rango 0,02-0,61). La frecuencia de muertes por anafilaxia por fármacos aumentó durante el período de estudio (IRR por año, 1,02; IC del 95%: 1,00-1,04). Se detectó una heterogeneidad considerable en casi todos los metaanálisis realizados.
Conclusión: La incidencia de anafilaxia mortal es muy baja y difiere según los distintos subgrupos analizados. Los estudios fueron muy heterogéneos. La muerte por anafilaxia debida a alimentos parece ser menos común que la anafilaxia mortal debida a fármacos o por veneno de himenópteros.

Palabras clave: Anafilaxia. Medicamentos. Alimentos. Himenóptera. Revisión sistemática. Muerte. Incidencia.

Introduction

Fatal anaphylaxis is a very rare event, to the extent that it can be classed as a microevent [1-3], with the crude anaphylaxis mortality rate ranging from 0.5 to 1 death per million person-years [3-5]. Food-induced fatal anaphylaxis is even more infrequent, usually lower than 0.1 [3-5], while that of fatal anaphylaxis due to drugs or venoms ranges between 0.2 and 0.5 per million person-years. Almost all studies on the epidemiology of anaphylaxis show that older age is associated with a higher risk of death due to drugs or insect venom [6-15], while fatal food anaphylaxis more frequently affects persons aged under 35 years [3-5,16,17].

Worldwide, results differ in several aspects, such as temporal trends [16-25] and incidence by country [12,14,17,19,20,22,26]. These discrepancies could probably be explained by the small number of cases of fatal anaphylaxis in the literature, the heterogeneity of study populations in terms of age [6-11,12,14,15,24], the type of health system, and the prevalence of atopic disease [12,15,17,19,20,22], as well as the diverse methodologies applied to collect cases (national clinical registries, national death certificates database [16,19,20,22,26,27], forensic series [15,17,18], pharmacovigilance programs [8,28-30]).

We performed a systematic review on fatal anaphylaxis in order to assess differences in the reported incidence of anaphylaxis according to the continent of origin, design used, diagnostic criteria, settings, and periods of publication.

Methods

The systematic review was registered in the PROSPERO database (No. CRD42020156968). The article was drafted following the PRISMA statement for systematic reviews [31].

Search Strategy

We performed a search of PubMed/MEDLINE, EMBASE, and Web of Science. The search was based on titles and abstracts from studies in humans with no language restrictions. The last search was run on 31 June 2019 by 2 investigators (MATA and SPC). In order not to overlook published material, the articles cited in the selected articles and in review papers on the epidemiology of fatal anaphylaxis were reviewed to find other, missing articles not selected using our review strategy.

The search strategy followed that of Umasunthar et al [32]. We combined the term "anaphylaxis" with "death", "study design", and "main outcomes" (incidence) (Annex 1). This strategy was developed with the support of the librarian of Hospital Universitario Fundación Alcorcon (EGC).

Two investigators (SPC, MATA) performed the search independently. The abstract and title of each article were examined during identification and screening in order to choose articles that met the study criteria. Disagreements between reviewers were resolved by consensus and discussion.

Selection Criteria

The study population assessed was the whole population of a country or administrative region with no restrictions on age or sex. The types of studies reviewed were observational studies, cohort studies, cross-sectional studies, and registry studies that had assessed the incidence of death due to anaphylaxis. The series included studies with all the major causes of anaphylaxis (food, drugs, Hymenoptera venom, and unknown) or series involving only a major cause of anaphylaxis.

We excluded studies with duplicate dates, studies in which quantitative data for the general population were missing, systematic reviews ± meta-analysis, nonoriginal studies (eg, reviews, letters, editorials, case reports, guidelines, and book chapters), qualitative studies, animal studies, studies assessing the crude anaphylaxis mortality rates of a very specific cause of death (eg, penicillin, peanuts, general anesthetics), studies where deaths were not reported, and studies from a single hospital or several hospitals or forensic series that were not representative of the population of a large geographic area (at least a state, province, or administrative region).

We did not extend the analysis to the most specific frequent causes (milk, egg, peanuts, fish, penicillin, nonsteroidal anti-inflammatory drugs), because this would have dramatically increased the number of studies and the length of the paper. We believed our research needed to maintain its generalist perspective and not enter into the problems of very specific causes of anaphylaxis, which could prove controversial, as is the case with cross-reactivity and underlying mechanisms. In our opinion, each specific cause of fatal anaphylaxis would need a purpose-designed specific meta-analysis.

Data Collection and Extraction

We recorded the following: first author, country, year, criteria for establishing anaphylaxis as the cause of the death, cause of anaphylaxis, institutions and other settings where cases were collected, age groups, sex, codes used (both *International Classification of Diseases, Ninth Revision [ICD-9]* and *ICD-10* codes were used to define all causes of anaphylaxis), study design, population number, duration of data collection, mortality incidence rate, and quality of studies (or risk of bias). One author obtained all the information (SPC) and the other checked its accuracy (MATA). Disagreement was resolved by consensus.

When the same group published several reports on the same exposure in different studies, duplication was ruled out if the study period was different and without overlaps.

Given that our study was a systematic review of published literature, it was not necessary to request approval from the local ethics committee.

Risk of Bias in Individual Studies

The quality of the studies and the presence of bias were assessed using the score designed by Hoy et al [33] for prevalence studies. The 10 questions of the tool assessed both external and internal validity.

Summary Measures

The crude anaphylaxis death rate was calculated as the number of deaths per million person-years with the 95%CI. When articles gave this rate, we included it. However, we frequently had to calculate this rate using the official web

pages of the national statistics office of the country where the study was carried out. The denominator of this rate was the product of the number of people in the country for the year in the middle of the study period multiplied by the number of years comprising this period. The web pages were accessed between September and December, 2019.

We compared crude anaphylaxis mortality rates for all types of anaphylaxis, major causes of anaphylaxis, anaphylaxis in different geographical areas, age ranges, grade of risk of bias, and origin of cases. We were unable to classify settings where the database was collected from various origins (national death certificates, forensic data, clinical registries), as some articles pooled data from several settings. Therefore, we report bivariate variables whose positive result depends on whether the publication states that the data originated in a specific setting, independently of whether data in the same article came from several sources. In the case of temporal trend studies, where data were grouped based on an arithmetic progression, the results were homogenized into a single scale that increased in steps of 1 year.

We attempted to perform a meta-analysis to calculate pooled statistics. However, we observed considerable heterogeneity, which was almost always higher than 90%. Therefore, we only report descriptive statistics (median, range, minimum, and maximum), which were calculated using the statistical software application STATA-16.1. The crude anaphylaxis death rates were transformed into their natural logarithms, and the standard error of the transformed rate was estimated using the inverse of the square root of the events in each study ($1/\sqrt{events}$). The heterogeneity of the studies was measured using the I^2 statistic (inconsistency) [25,30]. Given the very probable heterogeneity of the epidemiologic studies, we performed the meta-analysis using a random-effects model, following the approach of DerSimonian and Laird [34]. We plotted quantiles of estimates of crude anaphylaxis death rates against the quantiles of the normal distribution (Q–Q plot) to detect outliers.

Likewise, in order to ascertain the heterogeneity of the studies, we used the same methodology in different subgroups.

Publication bias was determined by graphical analysis of the symmetry of the funnel plot [34,35].

Finally, after recording a heterogeneity (I^2) lower than 50% in the principal causes of anaphylaxis (drugs, food, Hymenoptera venom), we carried out another systematic review and meta-analysis, in which we assessed the trends of the crude anaphylaxis death rate for the main causes in the last 35 years using a logarithmic transformation of the crude anaphylaxis mortality rate and its standard error. The risk ratios were calculated as a division of crude anaphylaxis death rates for exposure and nonexposure, and their 95%CI was calculated as a Poisson distribution using a tool in STATA-16.1.

Results

Selection of Studies

Our literature search revealed 2888 publications on fatal anaphylaxis (Figure 1). After exclusion of duplicate studies, the number of publications decreased to 1565. A further 1345 articles were excluded during the screening phase because

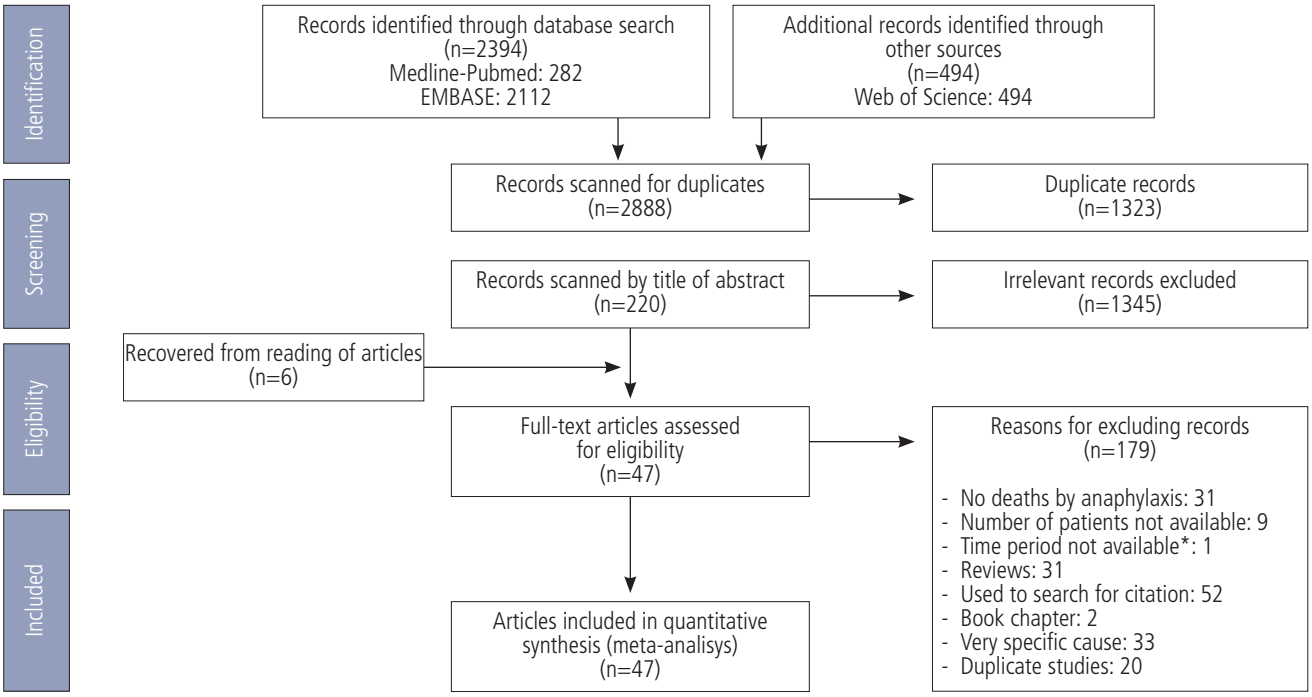

Figure 1. PRISMA flow diagram summarizing the process for selecting studies on the crude fatal anaphylaxis death rate. *The study by Barnard JH (Studies of 400 Hymenoptera sting deaths in the United States. J Allergy Clin Immunol 1973;52:259-64) was published 45 years ago and was subject to methodological problems, namely, omission of the time period of the study, the method used to collect data, and the inclusion criteria.

Table 1. Methodological Characteristics of the 46 Studies Included in the Meta-analyisis[a]

Author	Country	Year	Source of data/ Source of population	Study design	Coding of death due to anaphylaxis	Risk of bias
BOCK	USA	2001	NATIONAL MEDICAL REGISTRY https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	Clinical diagnosis	High 1-4,7,10,11
BOCK	USA	2007	NATIONAL MEDICAL REGISTRY https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	Clinical diagnosis	High 1-4,7,10.11
BORZUTZKY	CHILE	2011	NATIONAL DEATH CERTIFICATES https://datosmacro.expansion.com/paises/chile https://www.ine.cl	Retrospective cohort	*ICD-9-CM*	Low 4,7
BROWN	AUSTRALIA	2001	DATA OF EMERGENCY DEPARTMENT OF 1 HOSPITAL http://stat.data.abs.gov.au/Index.aspx?DataSetCode=ABS_ERP_LGA2018	Retrospective cohort	*ICD-10*	Moderate 1,4,7,9,11
CALVANI	LAZIO, ITALY	2008	ICD-9-CM CODES OF REGIONAL DATABASE OF LAZIO HOSPITAL SYSTEM AND EMERGENCY SYSTEM rates from the publication http://seriestoriche.istat.it/index.php?id=1&no_cache=1&L=1&tx_usercento_centofe%5Bcategoria%5D=32&tx_usercento_centofe%5Baction%5D=show&tx_usercento_centofe%5Bcontroller%5D=Categoria&cHash=04e5a2e51acfa92f173aac082f0d8872	Retrospective cohort	*ICD-9-CM*	Low 4,7
CHARFI	TUNISIA	2009	TUNISIAN PHARACOVIGILANCE DATABASE http://www.ins.tn/en/statistics-tunisia-national-institute-statistics	Retrospective cohort	Clinical diagnosis	High 1-4,6,7,10, 11
CLARKSON	UK	2002	VOLUNTARY REPORTS OF YELLOW CARD SCHEME DATABASE IN UK https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland	Retrospective cohort	Clinical diagnosis	High 1,3,4,6,7, 10,11
DA-YOU WANG	SWEDEN	1998	SWEDEN PHARMACOVIGILANCE DATABASE (SPD) https://www.scb.se/en/finding-statistics/statistics-by-subject-area/population/population-composition/population-statistics/pong/tables-and-graphs/yearly-statistics--the-whole-country/summary-of-population-statistics/; https://en.wikipedia.org/wiki/Demographics_of_Sweden;	Retrospective cohort	Codes for immediate hypersensitivity	Moderate 1,3,4,7
DESAY	USA-CANADA	2019	ICD-9-CM CODES OF A NATIONAL DATABASE OF THE US HOSPITAL SYSTEM https://datosmacro.expansion.com/paises/canada; https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	*ICD-9-CM*	Moderate 1,4,7,10
FORRESTER	USA	2012	NATIONAL DEATH CERTIFICATES https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	*ICD-10*	Low 4,7

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Table 1. Methodological Characteristics of the 46 Studies Included in the Meta-analyisis[a] *(continuation)*

Author	Country	Year	Source of data/ Source of population	Study design	Coding of death due to anaphylaxis	Risk of bias
FORRESTER	USA	2018	NATIONAL DEATH CERTIFICATES https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	*ICD-10*	Low 4,7
GIBBISON	UK	2012	NATIONAL MEDICAL REGISTRY OF CRITICAL CARE UNITS https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland	Prospective cohort	Clinical diagnosis	Moderate 1,4,7
HELBLING	SWITZERLAND	2004	NATIONAL DEATH CERTIFICATES https://www.bfs.admin.ch/bfs/fr/home/statistiques/population/effectif-evolution/population.html	Retrospective cohort	*ICD-10*	Low 4,7
JEPPESEN	DENMARK	2016	NATIONAL DEATH CERTICICATES AND CODES OF ICD-9-CM OF A NATIONAL DATABASE OF THE DANISH HOSPITAL SYSTEM https://www.statbank.dk/statbank5a/default.asp?w=2048	Retrospective cohort	*ICD-10*	Low 4,7
JERSCHOW	USA	2014	NATIONAL DEATH CERTIFICATES https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	*ICD-10*	Low 4,7
JOHANSON	SWEDEN	1991	NATIONAL DEATH CERTIFICATES https://www.scb.se/en/finding-statistics/statistics-by-subject-area/population/population-composition/population-statistics/pong/tables-and-graphs/yearly-statistics--the-whole-country/summary-of-population-statistics/; https://en.wikipedia.org/wiki/Demographics_of_Sweden	Retrospective cohort	*ICD-9*	Low 4,7
KIVISTÖ	FINLAND	2016	NATIONAL DEATH CERTIFICATES http://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/StatFin__vrm__vaerak/statfin_vaerak_pxt_11rc.px/	Retrospective cohort	SAMPSON	Low 4
KRMPOTIC	CANADA, ONTARIO	2019	PICUs ON CANADIAN ATLANTIC COAST, MEDICAL REPORTS https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/prof/details/Page.cfm?Lang=E&Geo1=PR&Code1=35&Geo2=&Code2=&Data=Count&SearchText=Ontario&SearchType=Begins&SearchPR=01&B1=All&GeoLevel=PR&GeoCode=35	Retrospective cohort	Clinical diagnosis	Moderate 1,4,7,10,11
LANGLEY	USA	1997	NATIONAL DEATH CERTIFICATES https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	*ICD-9*	Low 4,7
LANGLEY	USA	2005	NATIONAL DEATH CERTIFICATES https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	*ICD-9, ICD-10*	Low 4,7
LENLER-PETERSEN	DENMARK	1995	NATIONAL DEATH CERTIFICATES, VOLUNTARY REPORTS (NATIONAL MEDICAL REGISTER) https://www.statbank.dk/statbank5a/default.asp?w=2048	Retrospective cohort	*ICD-10* and *ICD-9*	Low 4

(continued)

Table 1. Methodological Characteristics of the 46 Studies Included in the Meta-analysis[a] *(continuation)*

Author	Country	Year	Source of data/ Source of population	Study design	Coding of death due to anaphylaxis	Risk of bias
LIU	TAIWAN	2017	ICD-9-CM CODES OF A NATIONAL DATABASE IN THE TAIWANESE HOSITAL SYSTEM rates from the publication https://eng.stat.gov.tw/public/data/dgbas04/bc6/census027e(final).html	Retrospective cohort	*ICD-9-CM*	Moderate 1,4,7,10
MA	USA	2014	NATIONAL DEATH CERTIFICATES https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	*ICD-10*	Low 4,7
MAC-DOUGALL	UK AND IRELAND	2002	NATIONAL DEATH CERTIFICATES, NATIONAL MEDICAL REGISTER, NATIONAL EPIDEMIOLOGIC SURVEY, ANAPHYLAXIS CAMPAIGN, AND SEARCH IN 2 NATIONAL NEWSPAPERS https://webarchive.nationalarchives.gov.uk/20180903180843/https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesfoΩrukenglandandwalesscotlandandnorthernireland; https://www.cso.ie/en/statistics/womenandmeninireland/womenandmeninireland2011/	Prospective and retrospective cohort	*ICD-9* and clinical diagnosis	Low 7
MIRANDA-MACHADO	COLOMBIA	2018	ICD-9-CM CODES A NATIONAL DATABASE OF THE COLOMBIAN PUBLIC HOSITAL SYSTEM https://www.dane.gov.co/index.php/estadisticas-por-tema	Retrospective cohort	*ICD-10*	Low 4,7
MOSBECK	DENMARK	1983	NATIONAL DEATH CERTIFICATES https://www.statbank.dk/statbank5a/default.asp?w=2048	Retrospective cohort	*ICD-9*	Low 4,7
MULLINS	AUSTRALIA	2016	NATIONAL DEATH CERTIFICATES http://stat.data.abs.gov.au/Index.aspx?DataSetCode=ABS_ERP_LGA2018	Retrospective cohort	*ICD-9* and *ICD-10*	Low 4,7
NGUYEN	VIETNAM	2019	PHARMACOVIGILANCE DATABASE https://www.gso.gov.vn/default_en.aspx?tabid=774	Retrospective cohort	SAMPSON	High 1,3,4,7,10
PENG	UK	2004	ICD-9-CM CODES OF A NATIONAL DATABASE FROM UK GENERAL PRACTICE https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland	Retrospective cohort	Clinical diagnosis	Low None
POUESSEL	FRANCE	2017	NATIONAL DEATH CERTIFICATES https://www.insee.fr/en/statistiques/2382599?sommaire=2382613	Retrospective cohort	*ICD-9* and *ICD-10*	Low 4,7
POUESSEL	FRANCE	2018	NATIONAL DEATH CERTIFICATES https://www.insee.fr/en/statistiques/2382599?sommaire=2382613	Retrospective cohort	*ICD-9* and *ICD-10*	Low 4,7
POUESSEL	FRANCE	2019	NATIONAL MEDICAL REGISTRY https://www.insee.fr/en/statistiques/2382599?sommaire=2382613	Registry	Clinical diagnosis	High 1-4,7,11
POUESSEL-PICU	FRANCE	2018	PICUs* IN FRANCE, MEDICAL REPORTS https://www.insee.fr/en/statistiques/2382599?sommaire=2382613	Retrospective cohort	*ICD-10* and clinical diagnosis	Moderate 1,4,7,10

(continued)

Table 1. Methodological Characteristics of the 46 Studies Included in the Meta-analysis[a] *(continuation)*

Author	Country	Year	Source of data/ Source of population	Study design	Coding of death due to anaphylaxis	Risk of bias
RAMSEY	USA-CANADA	2019	ICD-10-CM CODES AND DATABASE OF PICUs* IN USA AND CANADA https://datosmacro.expansion.com/paises/canada; https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	*ICD-10*	Moderate 1,4,7,10
RIBEIRO-BAZ	PORTUGAL	2011	NATIONAL MEDICAL REGISTRY-PHARMACOVIGILANCE https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&contecto=pi&indOcorrCod=0008273&selTab=tab0	Prospective cohort	NIAID-FAAN	High 1-4,6,7,10, 11
RUIZ OROPEZA	DENMARK	2017	EMERGENCY CASES FROM A DANISH HOSPITAL https://www.statbank.dk/statbank5a/default.asp?w=2048	Retrospective cohort	*ICD-10*	Moderate 1,4,7,9,10
SIMON	FLORIDA, USA	2008	NATIONAL DEATH CERTIFICATES rates from the publication	Retrospective cohort	*ICD-10* and *ICD-9*	Low 4,7
TANNO	BRAZIL	2017	NATIONAL DEATH CERTIFICATES https://sidra.ibge.gov.br/Tabela/200	Retrospective cohort	*ICD-11*-beta-2016	Low 4,7
TEJEDOR	SPAIN	2019	ICD-9-CM CODES AND CASES FROM A NATIONAL FORENSIC INSTITUTION https://www.ine.es	Retrospective cohort	*ICD-9* and Forensic diagnosis	Moderate 1,4,7
TURNER	ENGLAND AND WALES	2015	NATIONAL MEDICAL REGISTRY rates from the publication	Retrospective cohort	Clinical diagnosis	Low 4
XU	CANADA, ONTARIO	2014	CASES FROM A NATIONAL FORENSIC INSTITUTION https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/prof/details/Page.cfm?Lang=E&Geo1 =PR&Code1=35&Geo2=&Code2=&Data=Count&SearchText=Ontario&SearchType=Begins&SearchPR=01&B1=All&GeoLevel=PR&GeoCode=35	Retrospective cohort	Forensic diagnosis	High 1-4,7.10,11
YILMAZ	TURKEY	2009	CASES FROM A NATIONAL FORENSIC INSTITUTION http://www.turkstat.gov.tr/UstMenu.do?metod=temelist	Retrospective cohort	Clinical diagnosis	Moderate 1,4,7
YOCUM	USA	1999	SANITARY AREA MEDICAL REGISTRY https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	Clinical diagnosis	Moderate 1,4,7
ZAFAR 2006	USA	2018	ICD-9-CM CODES FROM A NATIONAL DATABASE IN THE US HOSPITAL SYSTEM https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	*ICD-9-CM*	Moderate 4,7,9
ZAFAR 2015	USA	2018	ICD-9-CM CODES FROM A NATIONAL DATABASE IN THE US HOSITAL SYSTEM https://www.census.gov/data/tables/2011/demo/age-and-sex/2011-age-sex-composition.html; https://www.census.gov/data/tables/2003/demo/age-and-sex/2003-age-sex-composition.html; https://www2.census.gov/programs-surveys/demo/tables/p20/510/p20-510u.pdf	Retrospective cohort	*ICD-9-CM*	Moderate 4,7,9
ZHAO	CHINA-BEIJING	2018	BEIJING PHARMACOVIGILANCE DATABASE (BPD) http://tjj.beijing.gov.cn/nj/main/2014-en/content/mV40_0302.htm	Retrospective cohort	Clinical diagnosis	High 1-4,7,10.11

Abbreviations: *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification*; PICU, pediatric intensive care unit.
[a]We used the score of Hoy et al [33] to address risk of bias. The meaning of the numbers is explained in Annex 2.

they did not meet the inclusion criteria and the reviewers agreed that they contained no relevant data related to the objectives of the review. Six articles [6,9-11,30,36-37] were identified by checking the references of the excluded articles. Of the remaining 220 studies, 180 were excluded for various reasons (Figure 1). Therefore, 46 met our criteria [6-30,36-58] for the quantitative analysis (Table 1). Using a Q–Q plot with estimations of the model, we observed 2 outlier studies with very low values: Peng et al [42] and Pouessel et al [51] (Figure E1). The studies were published from 1983 to 2019. All studies were published in English.

In the studies that assessed the crude anaphylaxis death rate, we observed symmetry in the smaller or in the larger study areas, although findings were widely dispersed (Figure E2).

Characteristics of the Studies

The 46 studies on fatal anaphylaxis carried out for all causes of anaphylaxis reported 16 541 deaths (Table 2). Drugs were the most frequently reported cause of fatal anaphylaxis (4262), while foods were the least frequently reported cause (612). The authors did not estimate the accuracy of these data.

The country with highest number of articles was the USA (30.43%). Europe was the continent with the highest number of publications (43.48%) (Table 1). A clear increase in the number of publications was observed from 2016 onward (43.48% of all publications, Table 3).

As for origin, 43.48% of the articles were collected from national death certificate databases, while approximately each of the other origins (medical registries, hospital systems, and combinations of several databases) contained 19.57%, 15.22%, and 10.87% of data on fatal anaphylaxis, respectively (Table 3).

The cause of death was coded using *ICD-9*, *ICD-10*, or both in 58.70% of the studies. A clinical diagnosis was made in 26.09% of publications, whereas a forensic diagnosis was made in 2.17%. In 10.87% of articles, the authors used several methods (Table 3).

Age of death was not uniformly collected in 34 articles. Most publications collected data on all age groups (80%), and some studies focused only on the pediatric population (20%).

The median study period was 10 years (range, 1-37 years) (Table 2). Eight publications [13,15,18-24] reported temporal trends in fatal anaphylaxis during the study periods.

Almost all studies were retrospective cohort studies (91.30%) (Table 3). Thirteen publications (26.07%) performed only 1 study, while the remaining articles had 2 or more substudies, depending on the main cause of anaphylaxis or the subgroup analyzed (age, sex, temporal trends) (Table 3).

Risk of Bias

According to the score of Hoy et al [33], 51.06% of publications had a low risk of bias, 29.53% a moderate risk, and 19.15% a high risk. The items for which the conditions were not fulfilled in most of the studies were the minimal likelihood of nonresponse (95.65%) and the length of the shortest period prevalence for the parameter of interest (91.30%) (Table 2).

Incidence of Fatal Anaphylaxis According to All the Main Causes

Twenty-five studies assessed the crude anaphylaxis death rate according to all the main causes, revealing a range of 0.002 to 2.51 deaths per million person-years, with a median of 0.50. Six studies overcame the crude anaphylaxis mortality rate of 1 death per million person-years.

The crude anaphylaxis death rate was higher in studies from Australia than in studies from Europe, North America, and Asia. The probability of differences was statistically significant ($P<.01, \chi^2$) for the crude anaphylaxis mortality rate on the different continents (Figure 2A). The meta-analysis of the total group on the different continents revealed considerable heterogeneity (higher than 95%).

Incidence of Fatal Anaphylaxis in Studies Assessed According to Subgroups

The range of the crude anaphylaxis mortality rate was 0.08-1.13 (median, 0.60) in articles that reported data from national death certificate databases and 0.002-2.51 (median, 0.35) in articles from the remaining settings, with nonsignificant results in the test of probability of differences ($P=.24, \chi^2$). Within subgroups, heterogeneity was greater than 98%. The remaining studies, which were carried out in several settings (forensic series, hospital systems, other settings), also revealed considerable heterogeneity and nonsignificant differences between groups (Table 4). Likewise, for the other different subgroups (use of *ICD-9, ICD-10*, or both and subgroups according to whether the risk of bias was low or moderate-high) also revealed marked heterogeneity within subgroups and no differences between them, although studies with a low risk of bias had higher median (0.56) than those with a moderate-to-high risk of bias (0.39) (Table 4).

On the other hand, the studies carried out in pediatric and adolescent populations revealed lower crude anaphylaxis death rates (median, 0.08; range 0.002-0.43) than studies involving all age groups (median, 0.59; range, 0.03-2.28), with statistically significant differences ($P=.03$). Studies based only on adult populations were not available (Figure 2B). Heterogeneity was very high in both age ranges for both subgroups.

We performed an additional assessment by grouping the different causes of anaphylaxis. Deaths caused by drugs and Hymenoptera venom ranged from 0.004 to 0.56 (median, 0.2) and from 0.02 to 0.61 (median, 0.14), respectively. The crude anaphylaxis mortality rate for foods was much lower than that of the other 2 causes (median, 0.04; range, 0.002-0.29). The difference was statistically significant ($P<.01, \chi^2$). Intragroup heterogeneity was higher than 98% (Figure 3).

Temporal Trends for Fatal Anaphylaxis

We observed considerable heterogeneity (higher than 90%) in anaphylaxis overall and in the subgroup of fatal anaphylaxis due to unknown causes. Heterogeneity was lower than 50% for the remaining causes. We noted a positive trend in the crude fatal anaphylaxis rate for drugs, in which the IRR for fatal episodes increased during the study period (1.02 per year of

Table 2. Crude Anaphylaxis Death rate in the 46 Studies Collected for the Meta-analysis

No. of substudies performed	Author	Country	Year of publication	Follow-up period	No. of deaths	Duration of follow-up in years	General Population	Person-years	Rate	95% CI Lower Limit	95% CI Upper Limit
4	BOCK	USA	2001	1994-1999	32	6	262976000	1577856000	0.02	0.01	0.03
4	BOCK	USA	2007	2000-2006	31	7	290223757	2031566301	0.02	0.01	0.02
1	BORZUTZKY	CHILE	2011	1991-2008	82	18	15186389	273355000	0.30	0.24	0.37
1	BROWN	AUSTRALIA	2001	1998-1999	1	1	397843	397843	2.51	0.35	17.84
8	CALVANI	LAZIO, ITALY	2008	2000-2003	1	4	863552	3454208	0.29	0.04	2.06
1	CHARFI	TUNISIA	2009	1990-2006	2	17	754890	12833127	0.16	0.02	0.25
1	CLARKSON	UK	2002	1964-2000	9	37	56662051	2096495894	0.004	0.002	0.008
4	DA-YOU WANG	SWEDEN	1998	1972-1995	51	16	8410627	134570039	0.25	0.19	0.33
1	DESAY	USA-CANADA	2019	2007-2014	5650	8	310234375	2481874996	2.28	2.14	2.34
4	FORRESTER	USA	2012	1999-2007	509	8	285933000	2287464000	0.22	0.20	0.23
4	FORRESTER	USA	2018	2008-2015	478	8	306110000	2448880000	0.20	0.18	0.21
4	GIBBISON	UK	2012	2005-2009	107	5	61563565	307817827	0.35	0.29	0.42
20	HELBLING	SWITZERLAND	2004	1996-1998	24	3	7096465	21289395	1.13	0.76	1.68
4	JEPPESEN	DENMARK	2016	1995-2012	50	18	5417501	97515018	0.51	0.39	0.68
20	JERSCHOW	USA	2014	1999-2010	2458	12	294337614	3532051364	0.70	0.67	0.72
4	JOHANSON	SWEDEN	1991	1975-1984	20	10	8200000	82000000	0.24	0.16	0.38
20	KIVISTÖ	FINLAND	2016	1996-2013	56	18	5267473	94814518	0.59	0.45	0.78
1	KRMPOTIC	CANADA, ONTARIO	2019	2007-2016	2	10	469205	4692050	0.43	0.11	1.70
4	LANGLEY	USA	1997	1979-1990	527	12	282162411	3385948932	0.16	0.14	0.17
4	LANGLEY	USA	2005	1991-2001	533	11	282162411	3103786521	0.17	0.16	0.19
4	LENLER-PETERSEN	DENMARK	1995	1968-1990	30	23	5071682	116648678	0.26	0.18	0.37
8	LIU	TAIWAN	2017	2005-2012	24	7	23058125	161406875	0.13	0.09	0.19
20	MA	USA	2014	1999-2009	2229	11	282162411	3103786521	0.72	0.69	0.75
4	MAC-DOUGALL	UK AND IRELAND	2002	1991-1999	8	10	13028933	130289330	0.06	0.03	0.12
1	MIRANDA-MACHADO	COLOMBIA	2018	2010-2105	37	6	46853833	281123000	0.13	0.09	0.18
1	MOSBECK	DENMARK	1983	1960-1980	21	21	4913758	103188918	0.20	0.13	0.31
20	MULLINS	AUSTRALIA	2016	1997-2013	324	17	20609294	350358000	0.92	0.83	1.03
1	NGUYEN	VIETNAM	2019	2010-2106	111	7	89782000	628474000	0.18	0.15	0.21
4	PENG	UK	2004	1994-1999	1	6	58339483	350036898	0.003	0.003	0.016
20	POUESSEL	FRANCE	2017	2005-2011	1603	33	59794608	1973222054	0.60	0.53	0.63
20	POUESSEL	FRANCE	2018	1979-2014	43	36	60317959	2171446537	0.08	0.06	0.10
3	POUESSEL	FRANCE	2019	2002-2018	18	16	59794608	956713723	0.004	0.002	0.008
20	POUESSEL-PICU	FRANCE	2018	2003-2013	3	11	64270738	706978120	0.002	0.002	0.002
20	RAMSEY	USA-CANADA	2019	2010-2015	19	6	349949985	2099699912	0.04	0.03	0.06
1	RIBEIRO-BAZ	PORTUGAL	2011	2000-2010	24	11	10494990	115444886	0.21	0.14	0.31

(continued)

Table 2. Crude Anaphylaxis Death rate in the 46 Studies Collected for the Meta-analysis *(continuation)*

No. of substudies performed	Author	Country	Year of publi-cation	Follow-up period	No. of deaths	Duration of follow-up in years	General Population	Person-years	Rate	95% CI Lower Limit	95% CI Upper Limit
1	RUIZ OROPEZA	DENMARK	2017	2013-2014	1	2	288587	577174	1.73	0.24	12.30
20	SIMON	FLORIDA-USA	2008	1996-2005	91	10	17716308	177163075	0.50	0.41	0.62
20	TANNO	BRAZIL	2017	2008-2010	639	3	192960667	578882000	1.10	1.02	1.120
20	TEJEDOR	SPAIN	2019	1998-2011	152	14	43197684	604767576	0.25	0.21	0.29
20	TURNER	ENGLAND AND WALES	2015	1992-2012	519	21	65379044	1372959924	0.47	0.43	0.51
20	XU	CANADA, ONTARIO	2014	1986-2011	92	21	13448494	282418374	0.31	0.25	0.38
1	YOCUM	USA	1999	1983-1987	1	5	126667	633333	1.58	0.22	11.21
1	ZAFAR 2006	USA	2018	2005-2014	55	10	298379912	2983799120	0.14	0.14	0.24
1	ZAFAR 2015	USA	2018	2005-2014	75	10	320896618	3208966180	0.19	0.19	0.26
4	ZHAO	CHINA-BEIJING	2018	2005-2015	18	11	2929000	32219000	0.56	0.33	0.88
2	YILMAZ	TURKEY	2009	2001-2006	36	6	67632165	371976908	0.10	0.06	0.13

Abbreviation: PICU, pediatric intensive care unit.

Table 3. Source of Data, Study Design, Code and Type of Diagnosis, and Year of Publication in the 46 Studies in the Systematic Review

Source of data of health care setting	N	%	Diagnosis	N	%
Death certificates	20	43.48%	ICD 9 and/or 10	27	58.70%
Medical registries	9	19.57%	Clinical diagnosis	12	26.09%
Hospital system	7	15.22%	ICD-9	12	26.09%
Mixed setting	5	10.87%	ICD-10	10	21.74%
Pharmacovigilance	5	10.87%	ICD-9 and 10	5	10.87%
Forensic series	3	6.52%	Several methods	5	10.87%
Clinical practice data from a health district	2	4.35%	Forensic diagnosis	1	2.17%
Total	51		ICD-11. beta	1	2.17%
			Total	46	
Study design	N	%	Year of publication	N	%
Retrospective cohort	42	91.30%	1981-1990	1	2.17%
Prospective cohort	2	4.35%	1991-1995	1	2.17%
Registry	1	2.17%	1996-2000	4	8.70%
Prospective and retrospective cohort	1	2.17%	2001-2005	6	13.04%
Total	46		2005-2010	6	13.04%
			2011-2015	7	15.22%
			2016-2019	21	45.65%
			Total	46	100

Abbreviation: *ICD-9, International Classification of Diseases, Ninth Revision.*

follow-up). Differences in the IRR of the trend were observed between the different causes of fatal anaphylaxis (P=.014, χ^2) (Figure 4). According to the GRADE assessment, the level of evidence was moderate (possible values of scale: poor, low, moderate, high) (Table E1).

Discussion

Our systematic review seems to confirm the extremely low frequency of fatal anaphylaxis. The high heterogeneity that we observed for studies assessing all causes of anaphylaxis was maintained in the different subgroups (sources, ages, continents). Probably, one of the more reliable findings is that fatal anaphylaxis due to food is especially rare. We detected a slight increase in the crude rate of fatal anaphylaxis induced by drugs, as reported in recent years. The considerable heterogeneity of the meta-analyses prevented us from obtaining pooled estimated fatal anaphylaxis rates.

Incidence of Fatal Anaphylaxis and Its Causes

The crude anaphylaxis mortality rate ranged from 0.002 per million person-years to 2.51 per million person-years [42,57], although these figures probably underestimate and overestimate, respectively, the incidence of death due to anaphylaxis. However, they do show how uncommon fatal anaphylaxis actually is.

It is difficult to determine the reliability of the data we collected for review. Experts agree that studies underestimate the true crude fatal anaphylaxis rate. In cases where coding systems such as the *ICD-9* or the *ICD-10* are used, Tanno et al [27] showed that the codes for anaphylaxis in these systems are not reliable because they include only anaphylactic shock and omit other mechanisms of death [38]. Likewise, the use of *ICD-9* for coding of anaphylaxis is subject to variability between coders, low internal validity, and intermediate positive predictive value [59]. Furthermore, knowledge of anaphylaxis is very poor among professionals not working directly in allergy. Finally, unidentified cases of fatal anaphylaxis may include persons dying from acute asthma due to food allergy or sudden death from unrecognized insect stings [26]. Our data highlight the need for an improvement in how national death certificates are completed. Despite improvements in the coding of anaphylaxis in *ICD-11* [27], it seems unlikely that, outside the focus on allergic diseases, physicians' knowledge of the condition will improve or physicians will complete death certificates more appropriately.

It is also important to determine the most reliable source of data. However, we found crude anaphylaxis death rates to be very similar in meta-analyses of national death certificates and hospital systems. We also found that these sources overlapped with other sources of data. Our findings are limited by the fact that we cannot analyze groups from a single source (eg, only

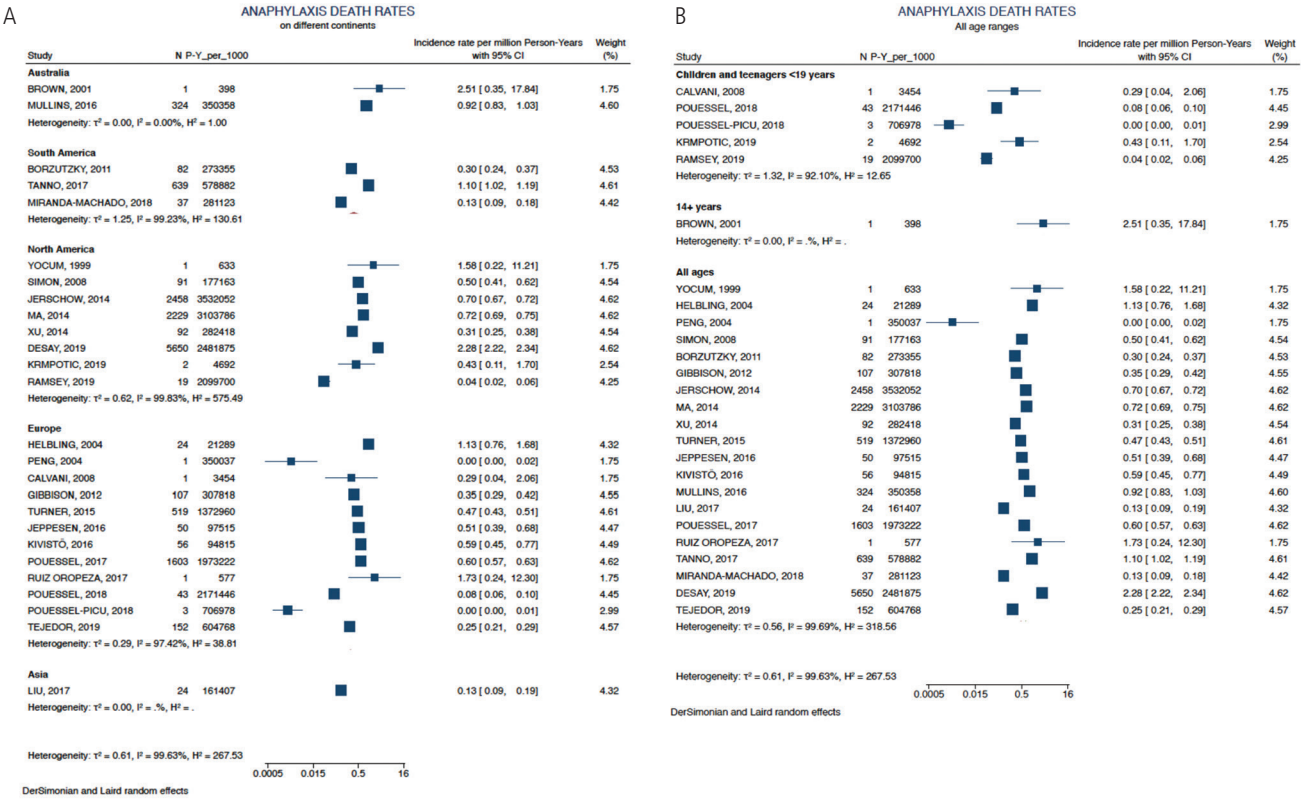

Figure 2. A, Meta-analysis of the crude anaphylaxis death rate in terms of its distribution on different continents.
B, The studies carried out in the pediatric and adolescent populations showed a lower crude anaphylaxis death rate than studie involving all ages, with the test of group differences yielding statistically significant differences (P=.04). Studies based only on the adult population were not available. N indicates number of deaths; P-Y, person-years.

Table 4. Ranges of Crude Anaphylaxis Death Rates According to the Setting or Source of the Studies, Age Ranges, and Risk of Bias[a]

Settings compared/ICD/ Risk of bias	Groups	No. of studies	Range	Hetero-geneity I^2	Hetero-geneity, *P*	Test of group differences
Death certificates of a state or administrative territory	Yes	12	0.08-1.13	98.14%	<.01	0.71
	No	14	0.0002- 2.51	63.34%	<.01	
Forensic studies	Yes	2	0.25-0.31	96.62%	<.01	0.53
	No	24	0.0002- 2.51	99.63%	<.01	
Hospital system series	Yes	4	0.13-2.28	99.67%	<.01	0.89
	No	22	0.002- 2.51	98.01%	<.01	
From several clinical settings	Yes	3	0.13-0.51	99.64%	<.01	0.31
	No	21	0.002.51	95.10%	<.01	
ICD used	*ICD-10*	8	0.04-2.51	97.53%	<.01	
	ICD-10 and *ICD-9-CM*	4	0.08-0.92	98.77%	<.01	1
	ICD-9-CM	4	0.13-2.28	99.43%	<.01	
Decade of publication	1990s	1	1.58			
	2000s	5	0.003-2.51	90.77%		
	2010	20	0.002-2.28	99.71%		
Risk of bias according to Hoy et al [33]	Low	15	0.003 -1.13	97.89%	<.01	0.79
	Moderate-High	11	0.002-2.51	99.52%	<.01	
All age groups and only children and adolescents	Children and adolescents	5	0.002-0.43	82.37%	<.01	
	All age groups	20	0.003-2.28	99.69%	<.01	<0.01
	Older than 12 years	1	2.51			

Abbreviation: *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.*
[a]Except for the review of the *ICD* used, we report bivariate variables whose positive result depends on whether the publication states that the data originated from a specific setting, independently of whether data in the same article came from several sources. In the case of the ICD, the studies used are limited to those that were based exclusively on these coding (eg, *ICD-10* and forensic series or clinical diagnosis).

hospitals, only forensic reports). Likewise, we did not observe differences in the ranges of crude anaphylaxis mortality rates for the different decades of publication.

According to the groups of studies reported in our review, it seems that studies carried out with people aged <19 years will always have a lower crude anaphylaxis death rate than studies performed in people of all ages (including children and adults). This finding of our review is associated with the finding that old age is a clear risk factor for severe and fatal anaphylaxis [1-5].

Our systematic review revealed significant differences between continents, with the highest crude anaphylaxis mortality rates in Australia and closer crude anaphylaxis death rates between North America and Europe. It is noteworthy that in Australia, studies on fatal anaphylaxis have traditionally reported high rates [18,22].

Our systematic review also found the crude anaphylaxis mortality rate to differ widely according to the main cause. The lower crude anaphylaxis death incidence rates for foods compared with the remaining main causes of anaphylaxis may be the most reliable finding of our review, owing to the fact that it is routinely repeated in studies on the incidence of fatal anaphylaxis. Oral intake may be less dangerous than parenteral intake, probably because lower human tryptase-containing mast cells from the small bowel mucosa [61] or younger age may better compensate for the hemodynamic changes induced by anaphylaxis in older patients [62,63].

In their meta-analysis, Umasunthar et al [32] found that the crude anaphylaxis mortality rate due to food was 1.81 per million person-years with food allergy when the prevalence of food allergy was 3%. The extrapolated estimation of the crude anaphylaxis death rate in the general population was 0.045, which is well within the range of food-induced fatal anaphylaxis studies in our review (0.02-0.29). However, the meta-analysis of Umasunthar et al [32] also revealed considerable heterogeneity (I^2>85%), which would also limit the reliability of a pooled estimation of fatal anaphylaxis due to foods in this study.

Temporal Trends

Our meta-analysis only revealed a slight increase in the crude anaphylaxis mortality rate by year during the study period among people who died from anaphylaxis induced by drugs, but not other causes. Our meta-analysis did not reveal considerable heterogeneity in the known causes of anaphylaxis (under 50%). However, several recent studies have reported a positive trend towards an increase in the anaphylaxis mortality rate for food [22] and the frequency of fatal anaphylaxis in the adult population [23]. Negative trends were reported in France [13] and Ontario (Canada) [17]. It is possible that the pooled crude anaphylaxis death rate in known causes of anaphylaxis is more influenced by older studies than by the most recent publications.

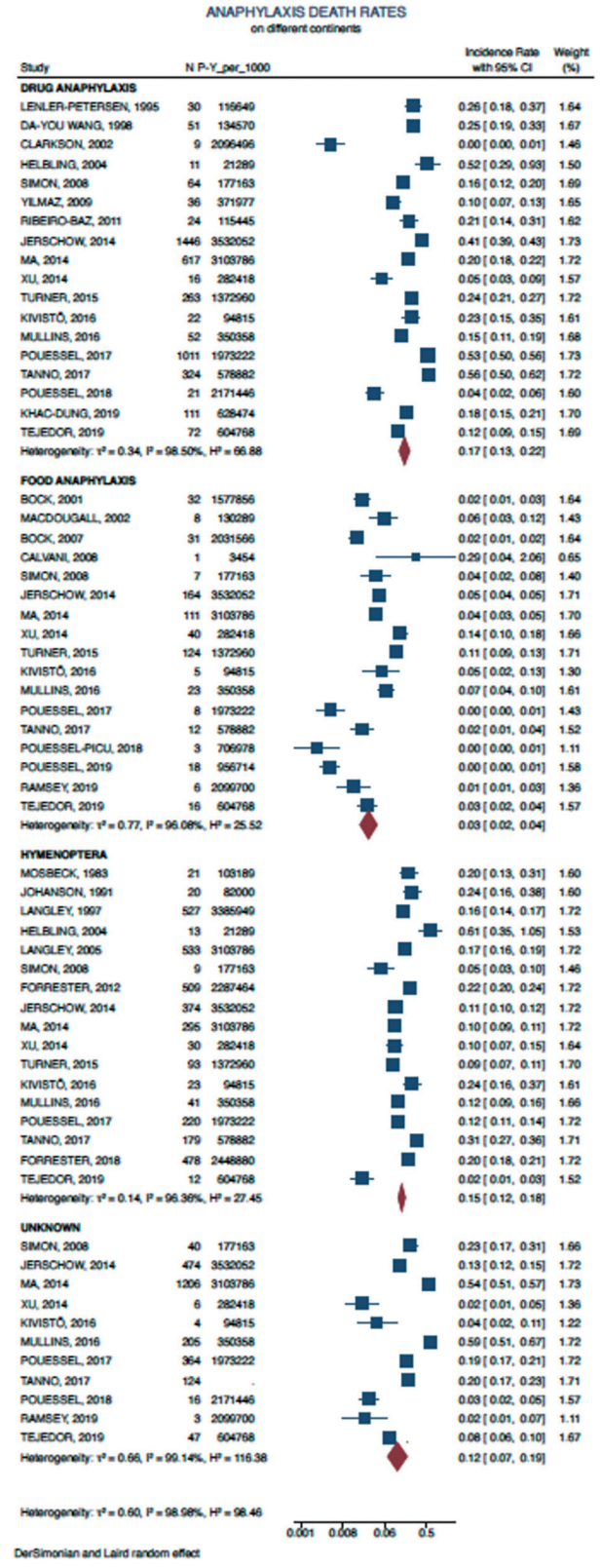

Figure 3. Systematic review of the crude anaphylaxis death rate according to the cause of anaphylaxis. The crude anaphylaxis death rate values on the x-axis (per 1 000 000 person-years) are real. N indicates number of deaths; P-Y, person-years.

On the other hand, the increase in fatal anaphylaxis due to drugs can be explained by the frequency of polymedication among elderly patients (antibiotics, nonsteroidal anti-inflammatory drugs, iodinated contrast media, and cancer treatments).

Limitations and Conclusions

The main limitation of our study, as previously mentioned, is the marked heterogeneity in almost all of the meta-analyses carried out and reproduced by other previous meta-analyses on anaphylaxis [32,64]. This considerably limits the reliability of our study for estimation of a pooled crude anaphylaxis death rate. Despite the analysis of subgroups, we are not able to explain the reasons for this heterogeneity.

In addition, other causes not explored in our review may contribute to the heterogeneity of the studies, for example, different rules are applied to code the cause of death (even if *ICD-9* or *ICD-10* is used) in the different countries. In addition, geographic areas are too large and include countries with different allergens or populations with different ages [64].

It is interesting to consider whether we should have included studies with 0 deaths [65]. However, some studies with 0 deaths will not be as powerful for detection of cases of fatal anaphylaxis as studies from a single hospital. This high power is achieved in many of the studies recovered by our

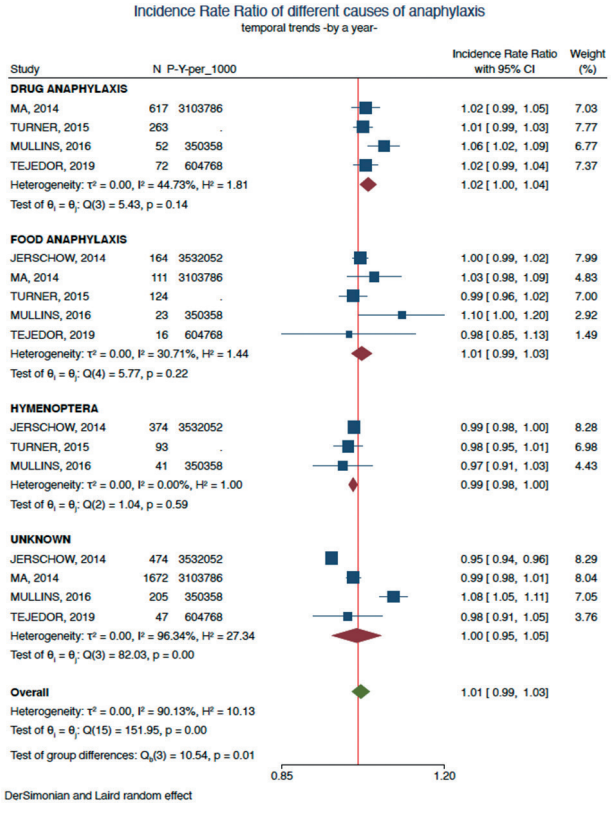

Figure 4. Meta-analysis of temporal trends in the crude anaphylaxis death rate (various causes). The vertical red line represents the value 1 of the different incidence risk ratios. N indicates number of deaths; P-Y, person-years.

search strategy, such as studies based on death certificates from a whole country or a large administrative territory. Consequently, studies from a single hospital or outpatient allergy clinic and insufficiently powered studies should be excluded if they do not report cases of deaths. For the small studies with cases of fatal anaphylaxis collected in our review, these cover the spectrum of high anaphylaxis mortality rates shown in the funnel plot (Figure E1), with a compensated distribution of large and small studies.

In summary, our findings are consistent with those reported in epidemiologic studies performed during the last 30 years. The considerable heterogeneity of our systematic review on the crude anaphylaxis death rates was maintained in the different subgroups we explored. Finally, the incidence of fatal anaphylaxis due to foods is lower than the incidence of fatal anaphylaxis due to other causes.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentations

- Sabela Pérez Codesido, Martina Privitera Torres, Jimena Laiseca García, Lucía González Bravo, Marianela Managua Brandoni Petrone, Miguel Ángel Tejedor Alonso. "Incidencia De Muerte Por Anafilaxia: Revisión Sistemática Y Metaanálisis De Estudios Observacionales". 32º CONGRESO DE LA SEAIC. Zaragoza, 4-7 November 2020,
- Sabela Pérez Codesido, Martina Privitera Torres, Lucía González Bravo, Jimena Laiseca García, Marianela Managua Brandoni Petrone, Miguel Ángel Tejedor Alonso. "Incidencia Y Análisis Demográfico De La Muerte Por Anafilaxia: Revisión Sistemática Y Metaanálisis De Estudios Observacionales". 32º CONGRESO DE LA SEAIC. Zaragoza, 4-7 November 2020.

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