BMJ Open Sibship size, birth order and risk of asthma and allergy: protocol for a systematic review and meta-analysis

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ABSTRACT

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Introduction The hygiene hypothesis suggests that reduced exposure to microbes might have contributed to the increase in prevalence and incidence of asthma and allergy observed during the second half of the last century. Following this proposal, several studies have investigated the role of sibship size and birth order in the development of asthma and allergic diseases, but the underlying evidence is conflicting. The objective of the present systematic review will be to identify, critically appraise and synthesise previous primary studies investigating the association of sibship size and birth order with the risk of asthma and allergic diseases.

Methods and analysis The following databases will be searched: AMED, CABI, CINAHL, Embase, Google Scholar, OAlster, Open Access Theses and Dissertations, Open Grey, ProQuest Dissertations & Theses Global, PsycINFO, PubMed, SciELO, Scopus, Web of Science and WHO Global Index Medicus. Studies published up until 31 December 2020 will be eligible. There will be no restrictions by language and geographical location. Risk of bias in the included studies will be assessed using the Effective Public Health Practice Project quality assessment tool. The produced evidence will be synthesised narratively, and studies that present comparable numerical data will be included in meta-analyses using random effects model. Ethics and dissemination Only data from the published literature will be included in this systematic review. Therefore, no ethical approval is required. The final review paper will be published in a peer-reviewed journal. PROSPERO registration number CRD42020207905.

INTRODUCTION

The incidence and prevalence of asthma, along with allergic diseases such as allergic rhinitis and atopic eczema, were observed to have increased during the second half of the last century, in particular in the developed world.^{1 2} More recent trends remain unclear, as both increase³ and levelling off^{1 4 5} have been suggested. Around 300 million people have asthma globally.¹ For allergic diseases, evidence indicates that there is still a global increase in prevalence.^{5 6} Asthma and allergic diseases account for significant morbidity for

Strengths and limitations of this study

- This will be the first systematic review encompassing a comprehensive spectrum of the most common allergic and respiratory outcomes, in relation to sibship size and birth order.
- Inclusion of the leading databases, including search of the grey literature, enables a comprehensive identification of the relevant studies addressing the research question.
- The reproducibility of our work is enhanced through a priori outline of the review processes before the actual review starts.
- Self-reported diagnoses of the study outcomes are expected to make up a significant source of data from included studies, which gives the possibility of assessment bias.

individuals, as well as a substantial socioeconomic burden on the society.² Asthma results in roughly 14 million missed school days each year in the USA alone, and the morbidity is even higher for adults.⁷ Allergic rhinitis is also associated with significant loss in productivity.⁸ Furthermore, the WHO estimates that roughly 250 000 cases of death annually, worldwide, are due to asthma.⁷ Identifying risk factors for asthma and allergy is therefore of great interest in order to reduce the burden associated with these diseases.

Over the last five decades, numerous hypotheses have been proposed to explain the observed increase in the prevalence of these diseases, a substantial part of the studies focusing on the role of environmental factors. One of the main hypotheses is the hygiene hypothesis, which was first proposed by Strachan⁹ in 1989, and suggests that reduced microbial exposure during childhood increases the risk of developing asthma and allergy. One of the first proposed underlying biological mechanisms to the hygiene hypothesis was the observed skewing of balance towards T helper 2 cells (which have been associated with allergic sensitisation) in subjects lacking microbial stimuli and conversely a T helper 1 cell domination in subjects exposed to greater quantities of microbes.¹⁰ Further research has broadened the explanatory model with additional factors, such as T regulatory cells and T helper 17 cells,¹¹ but the pathophysiology is yet to be fully understood.¹² Connected to the hygiene hypothesis is the proposed sibling effect, which suggests that the number of siblings and/or the birth order of a child in a family may play a role in the development of asthma and allergy, as a result of varying degrees of microbial exposure during childhood, depending on the number of siblings.¹³

While several studies have investigated the association of sibship (group of individuals sharing the same pair of parents) size and birth order (the sequence in which members of a sibship are born) with risk of asthma and allergic diseases, findings are conflicting.¹⁴ Karmaus and Botezan have estimated the proportion of cases attributable to the sibling effect to be 34% for atopic dermatitis, 56% for allergic rhinitis and 28% for asthma. Karmaus and Botezan have also argued that at least 30% of cases of asthma and allergy could be prevented if the causal factors for these conditions were better understood,¹⁵ further indicating warranty for elucidating the sibling effect in relation to asthma and allergy. So far, there are no systematic reviews synthesising evidence from previous studies on the topic. A systematic synthesis of previous studies investigating the association of sibship size and birth order with risk of asthma and allergy will provide a clearer appreciation of the strength, magnitude and quality of the underlying evidence.

Aim

To identify, critically appraise and synthesise previous primary studies investigating the association of sibship size and birth order with risk of asthma and allergic diseases.

METHODS AND ANALYSES

This protocol is reported according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P),¹⁶ which provides guidelines for a standardised, transparent and reproducible reporting of systematic review protocols. The PRISMA-P checklist is presented in online supplemental appendix 1. Updates to the protocol will be documented, and deviations from the protocol will be described in the final review paper. The protocol for this systematic review has been prospectively registered with the international prospective register of systematic reviews (PROSPERO, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=207905) with registration number CRD42020207905.

Study eligibility criteria Study types and publication status

We will include observational epidemiological studies, including prospective and retrospective cohort studies, case-control studies and cross-sectional studies. Randomised controlled studies, quasirandomised controlled studies, controlled before-after studies and controlled clinical trials will not be considered, as interventional studies are not relevant for this research question. Animal studies, reviews, case studies, case series, expert opinions will also be excluded. Studies of any publication status will be eligible, and data used from them if available.

Participants

Offspring of any age, gender, ethnic background and medical background, where the study context is that the participants are part of defined sibships. Studies with any amount of participants will be eligible.

Exposures

Sibship size, birth order (number of older siblings) and number of younger siblings in the studied sibships.

Outcome measures

Self-reported or objectively measured/diagnosed asthma and allergic disease in the sibships. For the purpose of encompassing all relevant literature on the topic, asthma and allergic disease will be defined broadly. Asthma will be defined as any type of asthma, including those based on symptom definition, such as wheezing, and those based on spirometry findings of variable expiratory airflow limitation.¹⁷ Allergic disease will encompass any of the following: (A) allergic rhinitis/(rhino)conjunctivitis, food allergy, atopic eczema, urticaria, angio-oedema, anaphylaxis¹⁸ and (B) indicators of hypersensitivity (and indirectly of allergic disease), which includes allergenspecific serum IgE test, skin prick test and provocation/ challenge test. Conditions with primarily a genetic aetiology, such as hereditary angioedema,¹⁹ will not be included in these definitions.

Search methods

The search queries were developed using the PEO model: population, exposure and outcome (PEO). PEO is a specific implementation of population, intervention, control, outcome (PICO), used as a framework to produce effective search queries from formulated research questions, especially befitting retrieval of interventional and observational studies.²⁰ Since the population (P) will be defined broadly, that is, including both studies in children and adults, the actual search queries will be composed of two blocks: exposure (E) and outcome (O). A scoping search was performed in PubMed to identify previous studies on the topic and map relevant search terms. The search terms identified were: Medical Subject Headings (MeSH) and their corresponding alternatives in other databases, entry terms, free-text words and phrases. Subsequent scoping searches were made in PubMed with Boolean operator 'NOT' between various MeSH and freetext terms, alternately, in order to identify more synonyms and related search terms. The developed search terms have been piloted and refined before they will be used to identify relevant studies. The search queries have been modified for each database to be searched in regards to, inter alia, support for controlled vocabulary and syntax. Peer Review of Electronic Search Strategies has been used to identify potential weaknesses in the search strategy. Details of the search strategy are presented in online supplemental appendix 2.

Studies will be retrieved from the following databases: AMED (via Ovid), CABI, CINAHL (via EBSCO), Embase (via Ovid), Google Scholar, PsycINFO (via ProQuest), PubMed, SciELO, Scopus, Web of Science and WHO Global Index Medicus. In addition, unpublished articles and grey literature will be retrieved through searches of OAIster, Open Access Theses and Dissertations, Open Grey and ProQuest Dissertations & Theses Global. Finally, studies will also be included from reference lists of the studies included in the review, as well as through contact with experts who have published in the field. All databases will be searched for articles published from inception of respective database up until 3 December 2020; an updated search will be performed at the completion of the review to ensure inclusion of studies published after the first search. There will be no language restrictions, and articles will be translated into English where possible. Articles that could not be translated will be reported in the final review paper. In Google Scholar, due to the fact that the amount of results is sometimes overwhelming, results will be retrieved from the first 300 hits.²¹ Furthermore, the search query for Google Scholar has been significantly simplified, including only the most important terms in each block, due to an upper limit of 256 characters for search strings.²²

Data management

EndNote will be used for deduplication, full-text retrieval, secondary screening and for general management of retrieved studies. For primary screening, the articles will be imported to Rayyan QCRI.

Screening/selection process

The first stage of screening will be based on the title and/ or abstract of the articles. Articles that are clearly not relevant to the research question or clearly meet any of the exclusion criteria will be excluded. Articles, where there is doubt about relevancy, will be included to the next step. In the second stage of screening, the full text of the articles will be retrieved and assessed for eligibility. The reason for each article not being included will be documented and presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram in the final review paper.²³ The screening/selection will be independently performed by two reviewers. A third reviewer will arbitrate any disagreement.

Data extraction

A data extraction form (online supplemental appendix 3) has been developed to extract data from included studies in a standardised and reproducible fashion. The form will be piloted and revised before being used in the review. If a study does not present needed data, authors of the study will be contacted. Extracted data will be presented in table form. The extraction will be independently conducted by two reviewers. A third reviewer will arbitrate any disagreement.

Data items

The following data items will be summarised from each study: author of publication; country of origin of study; publication year; type of study design; sample size of study; source from where study participants were recruited; definition and assessment of sibship and birth order; duration of follow-up; confounding factors adjusted included in studies; study outcomes and their assessment; analysis methods; and main results.

Quality assessment

Quality and risk of bias in the individual, included studies will be assessed using the Effective Public Health Practice Project Quality Assessment Tool (EPHPP).²⁴ The EPHPP contains six domains of assessment for each study, including study design, selection bias, confounding, blinding, study collection, withdrawals and dropouts. Based on the grading of each of the six domains, a global quality grading will be derived for each study. Detailed results will be presented in a separate table in the final review paper. Appraisal of quality and risk of bias will be independently performed by two reviewers. A third reviewer will arbitrate any disagreement.

Data synthesis

Descriptive tables will be generated to present the key characteristics of the included studies. The produced evidence will be synthesised narratively. In addition, studies that present numerically comparable and reasonably homogenous (in terms of clinical and epidemiological settings of study participants) data will be synthesised quantitatively with meta-analyses in RevMan V.5 to produce pooled effect size estimates. Random effects model will be applied in the meta-analyses, because the included studies, solely based on published literature, are anticipated to not be similar in every aspect and thus do not estimate the same effect. This model is more conservative and provides a realistic scenario in the context of studies gathered solely from published literature.²⁵ Separate meta-analyses will be undertaken for each of the factors investigated (sibship size and birth order) in relation to each asthma and allergy outcome. The results of the meta-analyses will be presented in forest plots.

Risk ratio (RR) will be used as the outcome measure in the meta-analyses, because of its intuitive interpretative feature.²⁶ Data from studies presenting effect measures as OR, incidence rate ratio (IRR) or HR will be converted to estimates of RR before combining with other studies, using the following formulas:

- b. RR \approx HR or OR (if outcome is <15% by the end of follow-up).
- c. RR $\approx \sqrt{OR}$ or $\frac{1 0.5\sqrt{HR}}{1 0.5\sqrt{\frac{1}{HR}}}$ (if outcome is $\ge 15\%$ by the end of follow-up).

Calculation of I^2 will quantify heterogeneity between the included studies.²⁸ Consideration will be taken, regarding that this statistic can be biased in meta-analyses with few studies.²⁹ Subgroup analysis will be performed to explore potential reasons for heterogeneity between studies with the following subgroup variables: (A) study design; (B) quality appraisal of studies; (C) classification of the study country into 'high-income', 'upper-middle-income', 'lower-middle-income' and 'low-income' economy, as defined by the World Bank³⁰; (D) time during which the study was conducted, grouped into <1990, 1990-1999, 2000-2009 and 2010-2020; (E) participant age, grouped arbitrarily into <1 year, 1–6 years, 7–14 years and ≥ 15 years; and (F) gender, grouped into 'male' and 'female'. Subgroup analysis will be performed if there will be at least four (arbitrarily chosen cut-off³¹) studies in at least two subgroups. In addition, if more than 10 included studies present comparable numerical data,³² meta-regression will be performed to explore the impact of explanatory variables (covariates) on the observed heterogeneity in estimates across studies.

To investigate whether the conclusions of the review are independent of arbitrary decisions, sensitivity analysis will be performed by only including studies that: (A) reach either 'strong' or 'moderate' global rating of quality in accordance to EPHPP and (B) have objectively verified diagnosis of asthma or allergic disease as outcome, with either ICD codes or verified medical examination as the basis for diagnosis. The sensitivity analysis will be reported in a summary table.

Publication bias

Publication bias will be assessed with Funnel plot, as well as Begg's rank test and Egger's regression test,^{33 34} with p<0.05 being defined as statistically significant. In case of (significant) publication bias, the trim-and-fill method will be implemented to analyse its influence on the review results.³⁵

Patient and public involvement

No patients or participants were involved in the development of this protocol or the design of this study.

DISCUSSION

The conclusions that will potentially be drawn from this systematic review will be limited by the quality of the included studies. For this research question, the fact that all included studies will be observational limits the establishment of causality between sibship size, birth order and risk of asthma and allergic diseases.³⁶

A strength of this study is the comprehensiveness of the search strategy, including 15 of the leading databases of formally published literature, as well as grey literature. There will be no restrictions in terms of language or geographical location. All these enable comprehensive identification of relevant studies for this research question. Furthermore, this systematic review will encompass a comprehensive spectrum of the most common asthma and allergic outcomes in relation to sibship size and birth order, thereby contributing to a broad overview of the existing evidence on the topic.

Asthma and allergic diseases pose a significant burden on both individuals and society. While the role of sibship size and birth order in the development of these diseases have been investigated in several studies, although with conflicting evidence, a systematic review of existing studies is essential in providing a clearer appreciation of the underlying evidence. This protocol presents the methodology to perform a comprehensive systematic review and meta-analysis of existing literature on the topic.

ETHICS AND DISSEMINATION

Ethical approval will not be required due to the study being a systematic review of already published primary studies available in the public domain. Furthermore, patient consent will not be needed since data will stay aggregated.^{37,38}

Contributors BIN conceived the study idea. DL wrote the protocol, with review and suggestions for improvement from BIN, EG, GW, and SSÖE. All authors commented and approved the last version being submitted.

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Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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a. RR \approx IRR.

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Appendix to

Sibship Size, Birth Order and Risk of Asthma and Allergy: Protocol for a Systematic

Review and Meta-Analysis

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Appendix 1: PRISMA-P Checklist

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 4 (PROSPERO, registration number CRD420202079 05)
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	10
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			

Describe the rationale for the review in the context of	2-4			
what is already known				
Provide an explicit statement of the question(s) the				
review will address with reference to participants,	3-4			
interventions, comparators, and outcomes (PICO)				
METHODS				
Specify the study characteristics (such as PICO, study				
design, setting, time frame) and report characteristics	4.5			
(such as years considered, language, publication status)	4-5			
to be used as criteria for eligibility for the review				
Describe all intended information sources (such as				
electronic databases, contact with study authors, trial	4			
registers or other grey literature sources) with planned	0			
dates of coverage				
Present draft of search strategy to be used for at least one				
electronic database, including planned limits, such that it	5-6, Appendix 1			
could be repeated				
Describe the mechanism(s) that will be used to manage				
records and data throughout the review	6			
State the process that will be used for selecting studies				
(such as two independent reviewers) through each phase	- -			
of the review (that is, screening, eligibility and inclusion	6-7			
in meta-analysis)				
Describe planned method of extracting data from reports				
(such as piloting forms, done independently, in				
duplicate), any processes for obtaining and confirming	7, Appendix 2			
data from investigators				
List and define all variables for which data will be				
sought (such as PICO items, funding sources), any pre-	7			
planned data assumptions and simplifications				
List and define all outcomes for which data will be				
sought, including prioritization of main and additional	5			
outcomes, with rationale				
Describe anticipated methods for assessing risk of bias of				
individual studies, including whether this will be done at				
the outcome or study level, or both; state how this	4-5 6 5-6, Appendix 1 6 6 6-7 7, Appendix 2 7 5 9 8 8 8 8 8			
information will be used in data synthesis				
Describe criteria under which study data will be				
quantitatively synthesised	8			
If data are appropriate for quantitative synthesis, describe				
planned summary measures, methods of handling data	8			
and methods of combining data from studies, including				
any planned exploration of consistency (such as I^2 ,				
Kendall's τ)				
Describe any proposed additional analyses (such as				
sensitivity or subgroup analyses, meta-regression)	8-9			
If quantitative synthesis is not appropriate, describe the	Q			
type of summary planned	ð			
	Describe the rationale for the review in the context of what is already known Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated Describe the mechanism(s) that will be used to manage records and data throughout the review State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators List and define all variables for which data will be sought, including prioritization of main and additional outcomes, with rationale Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis Describe anticipated for which data will be quantitatively synthesised			

Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix to

Sibship Size, Birth Order and Risk of Asthma and Allergy: Protocol for a Systematic Review and Meta-Analysis

Daniil Lisik, Athina Ioannidou, Gregorio Paolo Milani, Sungkutu Nyassi, Saliha Selin Özuygur Ermis, Giulia Spolidoro, Emma Goksör, Göran Wennergren, Bright I Nwaru

Appendix 2: Search Strategies

Colorization Red: controlled vocabulary/thesaurus Blue: free-text Green: referral to search query component (table row; #)

AMED

#	Search term(s)
1	(birth order* or birth rank* or multiple birth* or parity).mp.
2	exp Family Characteristics/ or (family characteristic* or family size* or family structure* or family
	demograph* or family composition or household size* or household demograph* or household
	composition).mp.
3	exp Sibling Relations/ or (sibling* or sister* or brother* or sibship size* or sibship*).mp.
4	or/1-3
5	exp Asthma/ or (bronchial asthma* or exercise-induced asthma* or exercise-induced bronchospasm*
	or asthma* or respiratory hypersensitivit* or airway hyper responsiveness or airway hyper-
	responsiveness or respiratory hyper responsiveness or respiratory hyper-responsiveness or
	wheez*).mp.
6	exp Hypersensitivity/ or exp Hypersensitivity Immediate/ or exp Hypersensitivity Delayed/ or
	(immediate hypersensitivit* or delayed hypersensitivit* or IgE-mediated hypersensitivit* or type I
	hypersensitivit* or type IV hypersensitivit* or atopic sensitization or atop* or allergic sensitization or
	allerg*).mp.
7	exp Dermatitis/ or exp Anaphylaxis/ or (atopic dermatitis or dermatitis or neurodermatiti* or besniers
	prurigo or besnier prurigo or atopic eczema or eczema or urticari* or anaphyla* or quinckes edema or
	quincke edema or angioneurotic edema or angioedema or hives).mp.
8	exp Food Hypersensitivity/ or (food hypersensitivit* or food allerg* or egg hypersensitivit* or egg
	allerg* or milk hypersensitivit* or milk allerg* or shellfish hypersensitivit* or shellfish allerg* or
	wheat hypersensitivit* or wheat allerg* or nut hypersensitivit* or nut allerg* or peanut
	hypersensitivit* or peanut allerg* or groundnut hypersensitivit* or groundnut allerg*).mp.

9	exp Rhinitis/ or exp Conjunctivitis/ or (allergic rhinoconjunctiviti* or rhinoconjunctiviti* or allergic
	rhiniti* or seasonal allergic rhiniti* or perennial allergic rhiniti* or rhiniti* or allergic conjunctiviti*
	or vernal keratoconjunctiviti* or vernal conjunctiviti* or giant papillary conjunctiviti* or hay fever or
	hayfever or pollinosis or nasal catarrh*).mp.
10	or/5-9
11	4 and 10
Full c	luery
((birth	order* or birth rank* or multiple birth* or parity).mp. or exp Family Characteristics/ or (family characteristic* or
family	size* or family structure* or family demograph* or family composition or household size* or household
demog	raph* or household composition).mp. or exp Sibling Relations/ or (sibling* or sister* or brother* or sibship size*
or sibs	hip*).mp.) and (exp Asthma/ or (bronchial asthma* or exercise-induced asthma* or exercise-induced
bronch	ospasm* or asthma* or respiratory hypersensitivit* or airway hyper responsiveness or airway hyper-
respon	siveness or respiratory hyper responsiveness or respiratory hyper-responsiveness or wheez*).mp. or exp
Hyper	sensitivity/ or exp Hypersensitivity Immediate/ or exp Hypersensitivity Delayed/ or (immediate hypersensitivit*
or dela	yed hypersensitivit* or IgE-mediated hypersensitivit* or type I hypersensitivit* or type IV hypersensitivit* or
atopic	sensitization or atop* or allergic sensitization or allerg*).mp. or exp Dermatitis/ or exp Anaphylaxis/ or (atopic
derma	itis or dermatitis or neurodermatiti* or besniers prurigo or besnier prurigo or atopic eczema or eczema or urticari*
or ana	phyla* or quinckes edema or quincke edema or angioneurotic edema or angioedema or hives).mp. or exp Food
Hyper	sensitivity/ or (food hypersensitivit* or food allerg* or egg hypersensitivit* or egg allerg* or milk hypersensitivit*
or mill	callerg* or shellfish hypersensitivit* or shellfish allerg* or wheat hypersensitivit* or wheat allerg* or nut
hypers	ensitivit* or nut allerg* or peanut hypersensitivit* or peanut allerg* or groundnut hypersensitivit* or groundnut
allerg*).mp. or exp Rhinitis/ or exp Conjunctivitis/ or (allergic rhinoconjunctiviti* or rhinoconjunctiviti* or allergic
rhiniti ³	* or seasonal allergic rhiniti* or perennial allergic rhiniti* or rhiniti* or allergic conjunctiviti* or vernal
kerato	conjunctiviti* or vernal conjunctiviti* or giant papillary conjunctiviti* or hay fever or hayfever or pollinosis or
i	

nasal catarrh*).mp.)

exp = include all narrower subject headings; mp= abstract, heading words, title

CABI; OAIster; Open Access Theses and Dissertations; Open Grey; ProQuest Dissertations & Theses Global; SciELO; WHO Global Index Medicus

#	Search term(s)
1	"birth order" OR "multiple births" OR "birth rank" OR "parity"
2	"family characteristics" OR "family size" OR "family structure" OR "family demography" OR
	"family composition" OR "household size" OR "household demography" OR "household
	composition"
3	"siblings" OR "sibling relations" OR "sister" OR "brother" OR "sibship"
4	"exercise-induced bronchospasm" OR "asthma" OR "airway hyper-responsiveness" OR "respiratory
	hyper-responsiveness" OR "wheeze" OR "wheezing"
5	"hypersensitivity" OR "atopic sensitization" OR "atopy" OR "allergic sensitization" OR "allergic
	disease" OR "allergic condition" OR "allergy" OR "allergies"

6	"dermatitis" OR "eczema" OR "neurodermatitis" OR "besnier's prurigo" OR "urticaria" OR	
	"anaphylaxis" OR "anaphylactic shock" OR "quincke's edema" OR "angionuerotic edema" OR	
	"angioedema" OR "hives"	
8	"rhinoconjunctivitis" OR "rhinitis" OR "allergic conjunctivitis" OR "vernal keratoconjunctivitis" OR	
	"vernal conjunctivitis" OR "giant papillary conjunctivitis" OR "hay fever" OR "pollinosis" OR	
	"pollenosis" OR "nasal catarrh"	
9	1 OR 2 OR 3	
10	4 OR 5 OR 6 OR 7 OR 8	
11	9 AND 10	
Full query		

("birth order" OR "multiple births" OR "birth rank" OR "parity" OR "family characteristics" OR "family size" OR "family structure" OR "family demography" OR "family composition" OR "household size" OR "household demography" OR "household composition" OR "siblings" OR "sibling relations" OR "sister" OR "brother" OR "sibship") AND ("exercise-induced bronchospasm" OR "asthma" OR "airway hyper-responsiveness" OR "respiratory hyper-responsiveness" OR "wheeze" OR "wheezing" OR "hypersensitivity" OR "atopic sensitization" OR "atopy" OR "allergic sensitization" OR "allergic disease" OR "allergic condition" OR "allergy" OR "allergies" OR "dermatitis" OR "eczema" OR "neurodermatitis" OR "besnier's prurigo" OR "urticaria" OR "anaphylaxis" OR "anaphylactic shock" OR "quincke's edema" OR "angionuerotic edema" OR "angioedema" OR "hives" OR "rhinoconjunctivitis" OR "rhinitis" OR "allergic conjunctivitis" OR "vernal keratoconjunctivitis" OR "vernal conjunctivitis" OR "giant papillary conjunctivitis" OR "hay fever" OR "pollinosis" OR "nosal catarrh")

CINAHL

#	Search term(s)
1	(MH 'Birth Order+') OR (MH 'Parity+') OR 'birth order*' OR 'birth rank*' OR 'multiple birth*'
	OR 'parity'
2	(MH 'Family Characteristics+') OR (MH 'Family Health+') OR 'family charactersitic*' OR 'family
	size*' OR 'family structure*' OR 'family demograph*' OR 'family composition' OR 'household
	size*' OR 'household demograph*' OR 'household composition'
3	(MH 'Siblings+') OR (MH 'Sibling Relations+') OR 'sibling*' OR 'sister*' OR 'brother*' OR
	'sibship size*' OR 'sibship*'
4	(MH 'Asthma+') OR (MH 'Respiratory Hypersensitivity+') OR 'bronchial asthma*' OR 'exercise-
	induced asthma' OR 'asthma*' OR 'exercise-induced bronchospasm' OR 'respiratory
	hypersensitivit*' OR 'airway hyper responsiveness' OR 'airway hyper-responsiveness' OR
	'respiratory hyper responsiveness' OR 'respiratory hyper-responsiveness' OR 'wheez*'
5	(MH 'Hypersensitivity+') OR (MH 'Hypersensitivity, Immediate+') OR (MH 'Hypersensitivity,
	Delayed+') OR (MH 'Allergy and Immunology+') OR 'immedate hypersensitivit*' OR 'delayed
	hypersensitivit*' OR 'IgE-mediated hypersensitivit*' OR 'type I hypersensitivit*' OR 'type IV
	hypersensitivit*' OR 'hypersensitivit*' OR 'atopic sensitiziation' OR 'atop*' OR 'allergic
	sensitization' OR 'allergic disease* OR 'allerg*'

6	(MH 'Dermatitis, Atopic+') OR (MH 'Eczema+') OR (MH 'Angioedema+') OR (MH		
	'Anaphylaxis+') OR (MH 'Urticaria+') OR 'atopic dermatitis' OR 'dermatitis' OR 'atopic eczema'		
	OR 'eczema' OR 'nerudoarmatiti*' OR "besnier's prurigo" OR 'besniers prurigo' OR 'besnier		
	prurigo' OR 'urticari*' OR 'hives' OR 'anaphyla*' OR "quincke's edema" OR 'quinckes edema' OR		
	'quincke edema' OR 'angioneurotic edema' OR 'angioedema'		
7	(MH 'Food Hypersensitivity+') OR 'food hypersensitivit*' OR 'food allerg*' OR 'egg		
	hypersensitivit*' OR 'egg allerg*' OR 'milk hypersensitivit*' OR 'milk allerg*' OR 'shellfish		
	hypersensitivit*' OR 'shellfish allerg*' OR 'wheat hypersensitivit*' OR 'wheat allerg*' OR 'nut		
	hypersensitivit*' OR 'nut allerg*' OR 'peanut hypersensitivit*' OR 'peanut allerg*' OR 'groundnut		
	hypersensitivit*' OR 'groundnut allerg*'		
8	(MH 'Rhinitis, Allergic+') OR (MH 'Rhinitis, Allergic, Seasonal+') OR (MH 'Rhinitis, Allergic,		
	Perennial+') OR (MH 'Rhinitis+') OR (MH 'Conjunctivitis, Allergic+') OR (MH 'Conjunctivitis+')		
	OR 'allergic rhinoconjunctiviti*' OR 'rhinoconjunctiviti*' OR 'allergic rhiniti*' OR 'seasonal		
	allergic rhiniti*' OR 'perennial allergic rhiniti*' OR 'rhiniti*' OR 'allergic conjunctiviti*' OR		
	'vernal keratoconjunctiviti*' OR 'vernal conjunctiviti*' OR 'giant papillary conjunctiviti*' OR 'hay		
	fever' OR 'hayfever' OR 'pollinosis' OR 'pollenosis' OR 'nasal catarrh'		
9	1 OR 2 OR 3		
10	4 OR 5 OR 6 OR 7 OR 8		
11	9 AND 10		
Full o	Juery		
((MH	"Birth Order+") OR (MH "Parity+") OR "birth order*" OR "birth rank*" OR "multiple birth*" OR "parity" OR		
(MH "Family Characteristics+") OR (MH "Family Health+") OR "family characteristics" OR "family size*" OR			
"famil	y structure*" OR "family demograph*" OR "family composition" OR "household size*" OR "household		
demog	raph*" OR "household composition" OR (MH "Siblings+") OR (MH "Sibling Relations+") OR "sibling*" OR		
"sister	*" OR "brother*" OR "sibship size*" OR "sibship*") AND ((MH "Asthma+") OR (MH "Respiratory		
Hyper	sensitivity+") OR "bronchial asthma*" OR "exercise-induced asthma" OR "asthma*" OR "exercise-induced		
bronch	nospasm" OR "respiratory hypersensitivit*" OR 'airway hyper responsiveness" OR "airway hyper-responsiveness"		
OR "r	espiratory hyper responsiveness" OR "respiratory hyper-responsiveness" OR "wheez*" OR (MH		
"Нуре	rsensitivity+") OR (MH "Hypersensitivity, Immediate+") OR (MH "Hypersensitivity, Delayed+") OR (MH		
"Allergy and Immunology+") OR "immedate hypersensitivit*" OR "delayed hypersensitivit*" OR "IgE-mediated			
hypersensitivit*" OR "type I hypersensitivit*" OR "type IV hypersensitivit*" OR "hypersensitivit*" OR "atopic			
sensitiziation" OR "atop*" OR "allergic sensitization" OR "allergic disease* OR "allerg*" OR (MH "Dermatitis,			
Atopic+") OR (MH "Eczema+") OR (MH 'Angioedema+") OR (MH 'Anaphylaxis+") OR (MH "Urticaria+") OR			
OR "besniers prurigo" OR "besnier prurigo" OR "urticari*" OR "bives" OR "anaphyla*" OR "quincke's edema" OR			
"auinckes edema" OR "auincke edema" OR "angioneurotic edema" OR "angioedema" OR (MH "Food			
Hypersensitivity+") OR "food hypersensitivit*" OR "food allerg*" OR "egg hypersensitivit*" OR "egg allerg*" OR			
"milk hypersensitivit*" OR "milk allerg*" OR "shellfish hypersensitivit*" OR "shellfish allerg*" OR "wheat			
hypersensitivit*" OR "wheat allerg*" OR "nut hypersensitivit*" OR "nut allerg*" OR "peanut hypersensitivit*" OR			
"peanut allerg*" OR "groundnut hypersensitivit*" OR "groundnut allerg*" OR (MH "Rhinitis, Allergic+") OR (MH			
"Rhini	"Rhinitis, Allergic, Seasonal+") OR (MH "Rhinitis, Allergic, Perennial+") OR (MH "Rhinitis+") OR (MH		
"Conji	"Conjunctivitis, Allergic+") OR (MH "Conjunctivitis+") OR "allergic rhinoconjunctiviti*" OR "rhinoconjunctiviti*" OR		

"allergic rhiniti*" OR "seasonal allergic rhiniti*" OR "perennial allergic rhiniti*" OR "rhiniti*" OR "allergic
conjunctiviti*" OR "vernal keratoconjunctiviti*" OR "vernal conjunctiviti*" OR "giant papillary conjunctiviti*" OR
"hay fever" OR "hayfever" OR "pollinosis" OR "pollenosis" OR "nasal catarrh"))

MH = *subject heading*

Embase

#	Search term(s)
1	sibship.mp.
2	birth order.mp. or exp birth order/
3	birth rank.mp.
4	multiple birth.mp.
5	parity.mp. or exp parity/
6	family characteristic.mp. or exp family size/
7	family structure.mp.
8	family demograph.mp.
9	family demograph*.mp.
10	family composition.mp.
11	household size.mp.
12	household demograph*.mp.
13	household composition.mp.
14	exp sibling relation/ or sibling.mp. or sibling/
15	exp sister/ or sister.mp.
16	siblings.mp.
17	sisters.mp.
18	brother.mp. or exp brother/
19	brothers.mp.
20	or/1-19
21	exp Asthma/ or (bronchial asthma* or exercise-induced asthma* or exercise-induced bronchospasm*
	or asthma* or respiratory hypersensitivit* or airway hyper responsiveness or airway hyper-
	responsiveness or respiratory hyper responsiveness or respiratory hyper-responsiveness or
	wheez*).mp.
22	exp Hypersensitivity/ or exp Hypersensitivity Immediate/ or exp Hypersensitivity Delayed/ or
	(immediate hypersensitivit* or delayed hypersensitivit* or IgE-mediated hypersensitivit* or type I
	hypersensitivit* or type IV hypersensitivit* or atopic sensitization or atop* or allergic sensitization or
	allerg*).mp.
23	exp Dermatitis/ or exp Anaphylaxis/ or (atopic dermatitis or dermatitis or neurodermatiti* or besnier
	prurigo or besniers prurigo or besnier prurigo or atopic eczema or eczema or urticari* or anaphyla*
	or quincke edema or quinckes edema or quincke edema or angioneurotic edema or angioedema or
	hives).mp.

24	exp Food Hypersensitivity/ or (food hypersensitivit* or food allerg* or egg hypersensitivit* or egg allerg* or milk hypersensitivit* or milk allerg* or shellfish hypersensitivit* or shellfish allerg* or wheat hypersensitivit* or wheat allerg* or nut hypersensitivit* or nut allerg* or peanut hypersensitivit* or peanut allerg* or groundnut hypersensitivit* or groundnut allerg*).mp.
25	exp Rhinitis/ or exp Conjunctivitis/ or (allergic rhinoconjunctiviti* or rhinoconjunctiviti* or allergi rhiniti* or seasonal allergic rhiniti* or perennial allergic rhiniti* or rhiniti* or allergic conjunctiviti* or vernal keratoconjunctiviti* or vernal conjunctiviti* or giant papillary conjunctiviti* or hay fever or hayfever or pollinosis or pollinosis or nasal catarrh*).mp.
26	or/21-25
27	20 and 26

Google Scholar

#	Search term(s)
1	"family size" OR "family structure" OR "household size"
2	"sibling" OR "sibship"
3	"asthma" OR "wheezing"
4	"atopy" OR "allergy"
5	"eczema" OR "urticaria" OR "angioedema" OR "anaphylaxis"
6	"rhinitis" OR "allergic conjunctivitis" OR "hay fever"
7	1 OR 2
8	3 OR 4 OR 5 OR 6
9	7 AND 8
Full query	
("family size" OR "family structure" OR "household size" OR "sibling" OR "sibship") AND ("asthma" OR "wheezing"	
OR "a	topy" OR "allergy" OR "anaphylaxis" OR "eczema" OR "urticaria" OR "angioedema" OR "rhinitis" OR "allergic

PsycINFO

conjunctivitis" OR "hay fever")

#	Search term(s)
1	SU.EXACT.EXPLODE("Birth Order") OR TI,AB("birth order*") OR TI,AB("multiple birth*") OR
	TI,AB("birth rank*") OR TI,AB("parity")
2	SU.EXACT.EXPLODE("Family Structure") OR SU.EXACT.EXPLODE("Family Size") OR
	TI,AB("family characteristic*") OR TI,AB("family size*") OR TI,AB("family structure*") OR
	TI,AB("family demograph*") OR TI,AB("family composition") OR TI,AB("household size*") OR
	TI,AB("household demograph*") OR TI,AB("household composition")
3	SU.EXACT.EXPLODE("Siblings") OR SU.EXACT.EXPLODE("Sibling Relations") OR
	TI,AB("sibling*") OR TI,AB("sister*") OR TI,AB("brother*") OR TI,AB("sibship size*") OR
	TI,AB("sibship size*") OR TI,AB("sibship*")

4	SU.EXACT.EXPLODE("Asthma") OR TI,AB("bronchial asthma*") OR TI,AB("exercise-induced		
	asthma*") OR TI,AB("asthma*") OR TI,AB("exercise-induced bronchospasm*") OR		
	TI,AB("respiratory hypersensitivit*") OR TI,AB("airway hyper responsiveness") OR		
	TI,AB("airway hyper-responsiveness") OR TI,AB("respiratory hyper responsiveness") OR		
	TI,AB("respiratory hyper-responsiveness") OR TI,AB("wheez*")		
5	SU.EXACT.EXPLODE("Allergic Disorders") OR TI,AB("immediate hypersensitivit*") OR		
	TI,AB("delayed hypersensitivit*") OR TI,AB("hypersensitivit*") OR TI,AB("IgE-mediated		
	hypersensitivit*") OR TI,AB("type I hypersensitivit*") OR TI,AB("type IV hypersensitivit*") OR		
	TI,AB("atopic sensitization") OR TI,AB("atop*") OR TI,AB("allergic sensitization") OR		
	TI,AB("allergic disease*") OR TI,AB("allerg*")		
6	SU.EXACT.EXPLODE("Allergic Skin Disorders") OR SU.EXACT.EXPLODE("Neurodermatitis")		
	OR SU.EXACT.EXPLODE("Dermatitis") OR SU.EXACT.EXPLODE("Eczema") OR		
	SU.EXACT.EXPLODE("Anaphylactic Shock") OR TI,AB("atopic dermatitis") OR		
	TI,AB("dermatitis") OR TI,AB("atopic eczema") OR TI,AB("eczema") OR		
	TI,AB("neurodermatiti*") OR TI,AB("besnier's prurigo") OR TI,AB("besniers prurigo") OR		
	TI,AB("besnier prurigo") OR TI,AB("urticari*") OR TI,AB("hives") OR TI,AB("anaphyla*") OR		
	TI,AB("quincke's edema") OR TI,AB("quinckes edema") OR TI,AB("quincke edema") OR		
	TI,AB("angioneurotic edema") OR TI,AB("angioedema")		
7	SU.EXACT.EXPLODE("Food Allergies") OR TI,AB("food hypersensitivit*") OR TI,AB("food		
	allerg*") OR TI,AB("egg hypersensitivit*") OR TI,AB("egg allerg*") OR TI,AB("milk		
	hypersensitivit*") OR TI,AB("milk allerg*") OR TI,AB("shellfish hypersensitivit*") OR		
	TI,AB("shellfish allerg*") OR TI,AB("wheat hypersensitivit*") OR TI,AB("wheat allerg*") OR		
	TI,AB("nut hypersensitivit*") OR TI,AB("nut allerg*") OR TI,AB("peanut hypersensitivit*") OR		
	TI,AB("peanut allerg*") OR TI,AB("groundnut hypersensitivit*") OR TI,AB("groundnut allerg*")		
8	TI,AB("allergic rhinoconjunctiviti*") OR TI,AB("rhinoconjunctiviti*") OR TI,AB("allergic		
	rhiniti*") OR TI,AB("rhiniti*") OR TI,AB("seasonal allergic rhiniti*") OR TI,AB("perennial		
	allergic rhiniti*") OR TI,AB("allergic conjunctiviti*") OR TI,AB("vernal keratoconjunctiviti*") OR		
	TI,AB("vernal conjunctiviti*") OR TI,AB("giant papillary conjunctiviti*") OR TI,AB("hay fever")		
	OR TI,AB("hayfever") OR TI,AB("pollinosis") OR TI,AB("pollenosis") OR TI,AB("nasal		
	catarrh*")		
9	1 OR 2 OR 3		
10	4 OR 5 OR 6 OR 7 OR 8		
11	9 AND 10		
Full o	query		
(SU.E	XACT.EXPLODE("Birth Order") OR TI,AB("birth order*") OR TI,AB("multiple birth*") OR TI,AB("birth		
rank*") OR TI,AB("parity") OR SU.EXACT.EXPLODE("Family Structure") OR SU.EXACT.EXPLODE("Family			
Size") OR TI,AB("family characteristic*") OR TI,AB("family size*") OR TI,AB("family structure*") OR			
TI,AB("family demograph*") OR TI,AB("family composition") OR TI,AB("household size*") OR TI,AB("household			
SUEXACT.EXPLODE("Sibling Relations") OR TI AB("sibling*") OR TI AB("sister*") OR TI AB("brother*") OR			
SULTACT.EATLODE(SIDING RELATIONS) OK 11, AD(SIDING*) OK 11, AB(SISTE*) OK 11, AB("DFOTTOPF*") OK			

TI,AB("sibship size*") OR TI,AB("sibship size*") OR TI,AB("sibship*")) AND (SU.EXACT.EXPLODE("Asthma") OR TI,AB("bronchial asthma*") OR TI,AB("exercise-induced asthma*") OR TI,AB("asthma*") OR TI,AB("exercise-induced asthma*") OR TI,AB("exercise-induced asthma*" induced bronchospasm*") OR TI,AB("respiratory hypersensitivit*") OR TI,AB("airway hyper responsiveness") OR TI,AB("airway hyper-responsiveness") OR TI,AB("respiratory hyper responsiveness") OR TI,AB("respiratory hyperresponsiveness") OR TI,AB("wheez*") OR SU.EXACT.EXPLODE("Allergic Disorders") OR TI,AB("immediate hypersensitivit*") OR TI,AB("delayed hypersensitivit*") OR TI,AB("hypersensitivit*") OR TI,AB("IgE-mediated hypersensitivit*") OR TI,AB("type I hypersensitivit*") OR TI,AB("type IV hypersensitivit") OR TI,AB("atopic sensitization") OR TI,AB("atop*") OR TI,AB("allergic sensitization") OR TI,AB("allergic disease*") OR TI,AB("allerg*") OR SU.EXACT.EXPLODE("Allergic Skin Disorders") OR SU.EXACT.EXPLODE("Neurodermatitis") OR SU.EXACT.EXPLODE("Dermatitis") OR SU.EXACT.EXPLODE("Eczema") OR SU.EXACT.EXPLODE("Anaphylactic Shock") OR TI,AB("atopic dermatitis") OR TI,AB("dermatitis") OR TI,AB("atopic eczema") OR TI,AB("eczema") OR TI,AB("neurodermatitis") OR TI,AB("besnier's prurigo") OR TI,AB("besniers prurigo") OR TI,AB("besnier prurigo") OR TI,AB("urticari*") OR TI,AB("hives") OR TI,AB("anaphyla*") OR TI,AB("quincke's edema") OR TI,AB("quinckes edema") OR TI,AB("quincke edema") OR TI,AB("angioneurotic edema") OR TI,AB("angioedema") OR SU.EXACT.EXPLODE("Food Allergies") OR TI,AB("food hypersensitivit*") OR TI,AB("food allerg*") OR TI,AB("egg hypersensitivit*") OR TI,AB("egg allerg*") OR TI,AB("milk hypersensitivit*") OR TI,AB("milk allerg*") OR TI,AB("shellfish hypersensitivit*") OR TI,AB("shellfish allerg*") OR TI,AB("wheat hypersensitivit*") OR TI,AB("wheat allerg*") OR TI,AB("nut hypersensitivit*") OR TI,AB("nut allerg*") OR TI,AB("peanut hypersensitivit*") OR TI,AB("peanut allerg*") OR TI,AB("groundnut hypersensitivit*") OR TI,AB("groundnut allerg*") OR TI,AB("allergic rhinoconjunctiviti*") OR TI,AB("rhinoconjunctiviti*") OR TI,AB("allergic rhiniti*") OR TI,AB("rhiniti*") OR TI,AB("seasonal allergic rhiniti*") OR TI,AB("perennial allergic rhiniti*") OR TI,AB("allergic conjunctiviti*") OR TI,AB("vernal keratoconjunctiviti*") OR TI,AB("vernal conjunctiviti*") OR TI,AB("giant papillary conjunctiviti*") OR TI,AB("hay fever") OR TI,AB("hayfever") OR TI,AB("pollinosis") OR TI,AB("pollenosis") OR TI,AB("nasal catarrh*"))

SU = all subjects and indexing; TI,AB = title, abstract

PubMed

#	Search term(s)
1	Birth Order[mh] OR Parity[mh] OR birth order*[tiab] OR multiple birth*[tiab] OR birth rank*[tiab]
	OR parity[tiab]
2	Family Characteristics[mh] OR Family Health[mh] OR family characteristic*[tiab] OR family
	size*[tiab] OR family structure*[tiab] OR family demograph*[tiab] OR family composition[tiab] OR
	household size*[tiab] OR household demograph*[tiab] OR household composition[tiab]
3	Siblings[mh] OR Sibling Relations[mh] OR sibling*[tiab] OR sister*[tiab] OR brother*[tiab] OR
	sibship size*[tiab] OR sibship*[tiab]
4	Asthma[mh] OR Asthma, Exercise-Induced[mh] OR Respiratory Hypersensitivity[mh] OR bronchial
	asthma*[tiab] OR exercise-induced asthma*[tiab] OR exercise-induced bronchospasm*[tiab] OR
	asthma*[tiab] OR respiratory hypersensitivit*[tiab] OR airway hyper responsiveness[tiab] OR airway
	hyper-responsiveness[tiab] OR respiratory hyper responsiveness[tiab] OR respiratory hyper-
	responsiveness[tiab] OR wheez*[tiab]

5	Hypersensitivity[mh] OR Hypersensitivity, Immediate[mh] OR Hypersensitivity, Delayed[mh] OR		
	Allergy and Immunology[mh] OR Allergens / Immunology[mh] OR immediate hypersensitivit*[tiab]		
	OR delayed hypersensitivit*[tiab] OR hypersensitivit*[tiab] OR IgE-mediated hypersensitivit*[tiab]		
	OR type I hypersensitivit*[tiab] OR type IV hypersensitivit*[tiab] OR atopic sensitization[tiab] OR		
	atop*[tiab] OR allergic sensitization[tiab] OR allergic disease*[tiab] OR allerg*[tiab]		
6	Dermatitis, Atopic[mh] OR Eczema[mh] OR Angioedema[mh] OR Anaphylaxis[mh] OR		
	Urticaria[mh] OR atopic dermatitis[tiab] OR dermatitis[tiab] OR atopic eczema[tiab] OR		
	eczema[tiab] OR neurodermatiti*[tiab] OR besnier's prurigo[tiab] OR besniers prurigo[tiab] OR		
	besnier prurigo[tiab] OR urticari*[tiab] OR anaphyla*[tiab] OR quincke edema[tiab] OR quinckes		
	edema[tiab] OR quincke's edema[tiab] OR angioneurotic edema[tiab] OR angioedema[tiab] OR		
	hives[tiab]		
7	Food Hypersensitivity[mh] OR food hypersensitivit*[tiab] OR food allerg*[tiab] OR egg		
	allerg*[tiab] OR egg hypersensitivit*[tiab] OR milk allerg*[tiab] OR milk hypersensitivit*[tiab] OR		
	shellfish allerg*[tiab] OR shellfish hypersensitivit*[tiab] OR wheat allerg*[tiab] OR wheat		
	hypersensitivit*[tiab] OR nut allerg*[tiab] OR nut hypersensitivit*[tiab] OR peanut allerg*[tiab] OR		
	peanut hypersensitivit*[tiab] OR groundnut hypersensitivit*[tiab]		
8	Pollen / Immunology[mh] OR Rhinitis, Allergic[mh] OR Rhinitis, Allergic, Seasonal[mh] OR		
	Rhinitis, Allergic, Perennial[mh] OR Rhinitis[mh] OR Conjunctivitis, Allergic[mh] OR		
	Conjunctivitis / Immunology[mh] OR Conjunctivitis / Epidemiology[mh] OR Conjunctivitis /		
	Etiology[mh] OR allergic rhinoconjunctiviti*[tiab] OR rhinoconjunctiviti*[tiab] OR allergic		
	rhiniti*[tiab] OR rhiniti*[tiab] OR seasonal allergic rhiniti*[tiab] OR perennial allergic rhiniti*[tiab]		
	OR allergic conjunctiviti*[tiab] OR vernal keratoconjunctiviti*[tiab] OR vernal conjunctiviti*[tiab]		
	OR giant papillary conjunctiviti*[tiab] OR hay fever[tiab] OR hayfever[tiab] OR pollinosis[tiab] OR		
	pollenosis[tiab] OR nasal catarrh*[tiab]		
9	1 OR 2 OR 3		
10	4 OR 5 OR 6 OR 7 OR 8		
11	9 AND 10		
Full o	query		
(Birth	Order[mh] OR Parity[mh] OR birth order*[tiab] OR multiple birth*[tiab] OR birth rank*[tiab] OR parity[tiab] OR Family		
Characteristics[mh] OR Family Health[mh] OR family characteristic*[tiab] OR family size*[tiab] OR family structure*[tiab] OR			
family demograph*[tiab] OR family composition[tiab] OR household size*[tiab] OR household demograph*[tiab] OR household			

Characteristics[mh] OR Family Health[mh] OR family characteristic*[tiab] OR family size*[tiab] OR family structure*[tiab] OR family structure*[tiab] OR family structure*[tiab] OR family demograph*[tiab] OR family composition[tiab] OR household size*[tiab] OR household demograph*[tiab] OR household composition[tiab] OR Sibling Relations[mh] OR sibling*[tiab] OR sister*[tiab] OR bother*[tiab] OR sibship size*[tiab] OR Siblings[mh] OR Sibling Relations[mh] OR asthma, Exercise-Induced[mh] OR Respiratory Hypersensitivity[mh] OR bronchial asthma*[tiab] OR exercise-induced asthma*[tiab] OR exercise-induced bronchospasm*[tiab] OR asthma*[tiab] OR respiratory hyper responsiveness[tiab] OR areway hyper responsiveness[tiab] OR areway hyper-responsiveness[tiab] OR Hypersensitivity[mh] OR Hypersensitivity, Immediate[mh] OR Hypersensitivity, Delayed[mh] OR Allergy and Immunology[mh] OR Allergens / Immunology[mh] OR immediate hypersensitivit*[tiab] OR type I hypersensitivit*[tiab] OR type I N hypersensitivit*[tiab] OR atopic sensitization[tiab] OR atopic sensitization[tiab] OR angioedema[mh] OR Angipylaxis[mh] OR urticaria[mh] OR atopic dermatitis[tiab] OR dermatitis[tiab] OR atopic eczema[tiab] OR eczema[tiab] OR neurodermatiti*[tiab]OR urticari*[tiab] OR angioedema[tiab] OR quincke edema[tiab] OR quincke's edema[tiab] OR angioneurotic edema[tiab] OR angioedema[tiab] OR hives[tiab]

OR Food Hypersensitivity[mh] OR food hypersensitivit*[tiab] OR food allerg*[tiab] OR egg allerg*[tiab] OR egg hypersensitivit*[tiab] OR milk allerg*[tiab] OR milk hypersensitivit*[tiab] OR shellfish allerg*[tiab] OR shellfish hypersensitivit*[tiab] OR wheat allerg*[tiab] OR wheat hypersensitivit*[tiab] OR nut allerg*[tiab] OR nut hypersensitivit*[tiab] OR peanut allerg*[tiab] OR peanut hypersensitivit*[tiab] OR groundnut hypersensitivit*[tiab] OR Pollen / Immunology[mh] OR Rhinitis, Allergic[mh] OR Rhinitis, Allergic, Seasonal[mh] OR Rhinitis, Allergic, Perennial[mh] OR Rhinitis[mh] OR Conjunctivitis, Allergic[mh] OR Conjunctivitis / Immunology[mh] OR Conjunctivitis / Epidemiology[mh] OR Conjunctivitis, Allergic rhinoconjunctiviti*[tiab] OR rhinoconjunctiviti*[tiab] OR allergic rhiniti*[tiab] OR rhiniti*[tiab] OR seasonal allergic rhiniti*[tiab] OR perennial allergic rhiniti*[tiab] OR allergic conjunctiviti*[tiab] OR vernal keratoconjunctivitis*[tiab] OR vernal conjunctiviti*[tiab] OR giant papillary conjunctiviti*[tiab] OR hay fever[tiab] OR hayfever[tiab] OR pollinosis[tiab] OR pollenosis[tiab] OR nasal catarrh*[tiab])

mh = MeSH; tiab = title, abstract

Scopus

#	Search term(s)	
1	TITLE-ABS-KEY("birth order*") OR TITLE-ABS-KEY("multiple birth*") OR TITLE-ABS-	
	KEY("birth rank*") OR TITLE-ABS-KEY("parity")	
2	TITLE-ABS-KEY("family characteristic*") OR TITLE-ABS-KEY("family size*") OR TITLE-	
	ABS-KEY("family structure*") OR TITLE-ABS-KEY("family demograph*") OR TITLE-ABS-	
	KEY("family composition") OR TITLE-ABS-KEY("household size*") OR TITLE-ABS-	
	KEY("household demograph*") OR TITLE-ABS-KEY("household composition*")	
3	TITLE-ABS-KEY("sibling relation*") OR TITLE-ABS-KEY("sibling*") OR TITLE-ABS-	
	KEY("brother*") OR TITLE-ABS-KEY("sister*") OR TITLE-ABS-KEY("sibship size*") OR	
	TITLE-ABS-KEY("sibship*")	
4	TITLE-ABS-KEY("bronchial asthma*") OR TITLE-ABS-KEY("exercise-induced asthma*") OR	
	TITLE-ABS-KEY("asthma*") OR TITLE-ABS-KEY("exercise-induced bronchospasm*") OR	
	TITLE-ABS-KEY("respiratory hypersensitivit*") OR TITLE-ABS-KEY("airway hyper	
	responsiveness") OR TITLE-ABS-KEY("airway hyper-responsiveness") OR TITLE-ABS-	
	KEY("respiratory hyper responsiveness") OR TITLE-ABS-KEY("respiratory hyper-	
	responsiveness") OR TITLE-ABS-KEY("wheez*")	
5	TITLE-ABS-KEY("immediate hypersensitivit*") OR TITLE-ABS-KEY("delayed hypersensitivit*")	
	OR TITLE-ABS-KEY("IgE-mediated hypersensitivit*") OR TITLE-ABS-KEY("type I	
	hypersensitivit*") OR TITLE-ABS-KEY("type IV hypersensitivit*") OR TITLE-ABS-KEY("atopic	
	sensitization") OR TITLE-ABS-KEY("atop*") OR TITLE-ABS-KEY("allergic sensitization") OR	
	TITLE-ABS-KEY("allergic disease") OR TITLE-ABS-KEY("allerg*")	
6	TITLE-ABS-KEY("atopic dermatitis") OR TITLE-ABS-KEY("dermatitis") OR TITLE-ABS-	
	KEY("atopic eczema") OR TITLE-ABS-KEY("eczema") OR TITLE-ABS-	
	KEY("neurodermatitis*") OR TITLE-ABS-KEY("besnier's prurigo") OR TITLE-ABS-	
	KEY("besniers prurigo") OR TITLE-ABS-KEY("besnier prurigo") OR TITLE-ABS-	
	KEY("quincke's edema") OR TITLE-ABS-KEY("quinckes edema") OR TITLE-ABS-	
	KEY("quincke edema") OR TITLE-ABS-KEY("angioneurotic edema") OR TITLE-ABS-	
	KEY("hives") OR TITLE-ABS-KEY("anaphyla*") OR TITLE-ABS-KEY("urticari*")	

7	TITLE-ABS-KEY("food hypersensitivit*") OR TITLE-ABS-KEY("food allerg*") OR TITLE-ABS-		
	KEY("egg allerg*") OR TITLE-ABS-KEY("egg hypersensitivit*") OR TITLE-ABS-KEY("milk		
	allerg*") OR TITLE-ABS-KEY("milk hypersensitivit*") OR TITLE-ABS-KEY("shellfish allerg*")		
	OR TITLE-ABS-KEY("shellfish hypersensitivit*") OR TITLE-ABS-KEY("wheat allerg*") OR		
	TITLE-ABS-KEY("wheat hypersensitivit*") OR TITLE-ABS-KEY("nut allerg*") OR TITLE-ABS-		
	KEY("nut hypersensitivit*") OR TITLE-ABS-KEY("peanut allerg*") OR TITLE-ABS-		
	KEY("peanut hypersensitivit*") OR TITLE-ABS-KEY("groundnut allerg*") OR TITLE-ABS-		
	KEY("groundnut hypersensitivit*")		
8	TITLE-ABS-KEY("allergic rhinoconjunctiviti*") OR TITLE-ABS-KEY("rhinoconjunctiviti*") OR		
	TITLE-ABS-KEY("seasonal allergic rhiniti*") OR TITLE-ABS-KEY("perennial allergic rhiniti*")		
	OR TITLE-ABS-KEY("allergic rhiniti*") OR TITLE-ABS-KEY("rhiniti*") OR TITLE-ABS-		
	KEY("allergic conjunctiviti*") OR TITLE-ABS-KEY("vernal keratoconjunctiviti*") OR TITLE-		
	ABS-KEY("vernal conjunctiviti*") OR TITLE-ABS-KEY("giant papillary conjunctiviti*") OR		
	TITLE-ABS-KEY("hay fever") OR TITLE-ABS-KEY("hayfever") OR TITLE-ABS-		
	KEY("pollinosis") OR TITLE-ABS-KEY("pollenosis") OR TITLE-ABS-KEY("nasal catarrh*")		
9	1 OR 2 OR 3		
10	4 OR 5 OR 6 OR 7 OR 8		
11	9 AND 10		

Full query

(TITLE-ABS-KEY("birth order*") OR TITLE-ABS-KEY("multiple birth*") OR TITLE-ABS-KEY("birth rank*") OR TITLE-ABS-KEY("parity") OR TITLE-ABS-KEY("family characteristic*") OR TITLE-ABS-KEY("family size*") OR TITLE-ABS-KEY("family structure*") OR TITLE-ABS-KEY("family demograph*") OR TITLE-ABS-KEY("family composition") OR TITLE-ABS-KEY("household size*") OR TITLE-ABS-KEY("household demograph*") OR TITLE-ABS-KEY("household composition*") OR TITLE-ABS-KEY("sibling relation*") OR TITLE-ABS-KEY("sibling*") OR TITLE-ABS-KEY("brother*") OR TITLE-ABS-KEY("sister*") OR TITLE-ABS-KEY("sibship size*") OR TITLE-ABS-KEY("sibship*")) AND (TITLE-ABS-KEY("bronchial asthma*") OR TITLE-ABS-KEY("exerciseinduced asthma*") OR TITLE-ABS-KEY("asthma*") OR TITLE-ABS-KEY("exercise-induced bronchospasm*") OR TITLE-ABS-KEY("respiratory hypersensitivit*") OR TITLE-ABS-KEY("airway hyper responsiveness") OR TITLE-ABS-KEY("airway hyper-responsiveness") OR TITLE-ABS-KEY("respiratory hyper responsiveness") OR TITLE-ABS-KEY("respiratory hyper-responsiveness") OR TITLE-ABS-KEY("wheez*") OR TITLE-ABS-KEY("immediate hypersensitivit*") OR TITLE-ABS-KEY("delayed hypersensitivit*") OR TITLE-ABS-KEY("IgE-mediated hypersensitivit*") OR TITLE-ABS-KEY("type I hypersensitivit*") OR TITLE-ABS-KEY("type IV hypersensitivit*") OR TITLE-ABS-KEY("atopic sensitization") OR TITLE-ABS-KEY("atop*") OR TITLE-ABS-KEY("allergic sensitization") OR TITLE-ABS-KEY("allergic disease") OR TITLE-ABS-KEY("allerg*") OR TITLE-ABS-KEY("atopic dermatitis") OR TITLE-ABS-KEY("dermatitis") OR TITLE-ABS-KEY("atopic eczema") OR TITLE-ABS-KEY("eczema") OR TITLE-ABS-KEY("neurodermatitis*") OR TITLE-ABS-KEY("besnier's prurigo") OR TITLE-ABS-KEY("besniers prurigo") OR TITLE-ABS-KEY("besnier prurigo") OR TITLE-ABS-KEY("quincke's edema") OR TITLE-ABS-KEY("quinckes edema") OR TITLE-ABS-KEY("quincke edema") OR TITLE-ABS-KEY("angioneurotic edema") OR TITLE-ABS-KEY("hives") OR TITLE-ABS-KEY("anaphyla*") OR TITLE-ABS-KEY("urticari*") OR TITLE-ABS-KEY("food hypersensitivit*") OR TITLE-ABS-KEY("food allerg*") OR TITLE-ABS-KEY("egg allerg*") OR TITLE-ABS-KEY("egg hypersensitivit*") OR TITLE-ABS-KEY("milk allerg*") OR TITLE-ABS-KEY("milk hypersensitivit*") OR TITLE-ABS-KEY("shellfish allerg*") OR TITLE-ABS-KEY("shellfish

hypersensitivit*") OR TITLE-ABS-KEY("wheat allerg*") OR TITLE-ABS-KEY("wheat hypersensitivit*") OR TITLE-ABS-KEY("nut allerg*") OR TITLE-ABS-KEY("peanut allerg*") OR TITLE-ABS-KEY("peanut allerg*") OR TITLE-ABS-KEY("peanut hypersensitivit*") OR TITLE-ABS-KEY("groundnut allerg*") OR TITLE-ABS-KEY("groundnut allerg*") OR TITLE-ABS-KEY("groundnut allerg*") OR TITLE-ABS-KEY("groundnut hypersensitivit*") OR TITLE-ABS-KEY("allergic rhinoconjunctiviti*") OR TITLE-ABS-KEY("perennial allergic rhiniti*") OR TITLE-ABS-KEY("allergic rhiniti*") OR TITLE-ABS-KEY("perennial allergic rhiniti*") OR TITLE-ABS-KEY("allergic rhiniti*") OR TITLE-ABS-KEY("rhiniti*") O

TITLE-ABS-KEY = title, abstract, keywords

Web of Science

#	Search term(s)
1	TS="birth order*" OR TS="multiple birth*" OR TS="birth rank*" OR TS="parity"
2	TS="family characteristic*" OR TS="family size*" OR TS="family structure*" OR TS="family
	demograph*" OR TS="family composition" OR TS="household size*" OR TS="household
	demograph*" OR TS="household composition"
3	TS="sibling*" OR TS="sister*" OR TS="brother*" OR TS="sibship size*" OR TS="sibship *"
4	TS="bronchial asthma*" OR TS="exercise-induced asthma*" OR TS="exercise-induced
	bronchospasm*" OR TS="asthma*" OR TS="respiratory hypersensitivit*" OR TS="respiratory
	hyper-responsiveness*" OR TS="airway hyper responsiveness*" OR TS="airway hyper-
	responsiveness*" OR TS=wheez*
5	TS="immediate hypersensitivit*" OR TS="delayed hypersensitivit*" OR TS="IgE-mediated
	hypersensitivit*" OR TS="type I hypersensitivit*" OR TS="type IV hypersensitivit*" OR
	TS="hypersensitivit*" OR TS="atopic sensitization" OR TS="atop*" OR TS="allergic sensitization"
	OR TS="allergic disease*" OR TS="allerg*"
6	TS="atopic dermatitis" OR TS="dermatitis" OR TS="atopic eczema" OR TS="eczema" OR
	TS="neurodermatiti*" OR TS="besnier's prurigo" OR TS="besniers prurigo" OR TS="besnier
	prurigo" OR TS="urticari*" OR TS="anaphyla*" OR TS="quincke's edema" OR TS="quinckes
	edema" OR TS="quincke edema" OR TS="angioneurotic edema" OR TS="angioedema" OR
	TS="hives"
7	TS="food hypersensitivit*" OR TS="food allerg*" OR TS="egg allerg*" OR TS="egg
	hypersensitivit*" OR TS="milk allerg*" OR TS="milk hypersensitivit*" OR TS="shellfish allerg*"
	OR TS="shellfish hypersensitivit*" OR TS="wheat allerg*" OR TS="wheat hypersensitivit*" OR
	TS="nut allerg*" OR TS="nut hypersensitivit*" OR TS="peanut allerg*" OR TS="peanut
	hypersensitivit*" OR TS="groundnut allerg*" OR TS="groundnut hypersensitivit*"
8	TS="pollen allerg*" OR TS="allergic rhinoconjunctiviti*" OR TS="rhinoconjunctiviti*" OR
	TS="seasonal allergic rhiniti*" OR TS="perennial allergic rhiniti*" OR TS="allergic rhiniti*" OR
	TS="rhiniti*" OR TS="allergic conjunctiviti*" OR TS="vernal keratoconjunctiviti*" OR

	TS="vernal conjunctiviti*" OR TS="giant papillary conjunctiviti*" OR TS="hay fever" OR	
	TS="hayfever" OR TS="pollinosis" OR TS="pollenosis" OR TS="nasal catarrh*"	
9	1 OR 2 OR 3	
10	4 OR 5 OR 6 OR 7 OR 8	
11	9 AND 10	
Full q	uery	
(TS="b	oirth order*" OR TS="multiple birth*" OR TS="birth rank*" OR TS="parity" OR TS="family characteristic*"	
OR TS	="family size*" OR TS="family structure*" OR TS="family demograph*" OR TS="family composition" OR	
TS="ho	ousehold size*" OR TS="household demograph*" OR TS="household composition" OR TS="sibling*" OR	
TS="sister*" OR TS="brother*" OR TS="sibship size*" OR TS="sibship*") AND (TS="bronchial asthma*" OR		
TS="exercise-induced asthma*" OR TS="exercise-induced bronchospasm*" OR TS="asthma*" OR TS="respiratory		
hyperse	ensitivit*" OR TS="respiratory hyper-responsiveness*" OR TS="airway hyper responsiveness*" OR TS="airway	
hyper-responsiveness*" OR TS=wheez* OR TS="immediate hypersensitivit*" OR TS="delayed hypersensitivit*" OR		
TS="Ig	E-mediated hypersensitivit*" OR TS="type I hypersensitivit*" OR TS="type IV hypersensitivit*" OR	
TS="hy	ypersensitivit*" OR TS="atopic sensitization" OR TS="atop*" OR TS="allergic sensitization" OR TS="allergic	
disease	*" OR TS="allerg*" OR TS="atopic dermatitis" OR TS="dermatitis" OR TS="atopic eczema" OR TS="eczema"	
OR TS	="neurodermatiti*" OR TS="besnier's prurigo" OR TS="besniers prurigo" OR TS="besnier prurigo" OR	
TS="u	rticari*" OR TS="anaphyla*" OR TS="quincke's edema" OR TS="quinckes edema" OR TS="quincke edema"	
OR TS	="angioneurotic edema" OR TS="angioedema" OR TS="hives" OR TS="food hypersensitivit*" OR TS="food	
allerg*" OR TS="egg allerg*" OR TS="egg hypersensitivit*" OR TS="milk allerg*" OR TS="milk hypersensitivit*"		
OR TS="shellfish allerg*" OR TS="shellfish hypersensitivit*" OR TS="wheat allerg*" OR TS="wheat hypersensitivit*"		
OR TS="nut allerg*" OR TS="nut hypersensitivit*" OR TS="peanut allerg*" OR TS="peanut hypersensitivit*" OR		
TS="groundnut allerg*" OR TS="groundnut hypersensitivit*" OR TS="pollen allerg*" OR TS="allergic		
rhinoco	rhinoconjunctiviti*" OR TS="rhinoconjunctiviti*" OR TS="seasonal allergic rhiniti*" OR TS="perennial allergic	
rhiniti*	rhiniti*" OR TS="allergic rhiniti*" OR TS="rhiniti*" OR TS="allergic conjunctiviti*" OR TS="vernal	
keratoc	keratoconjunctiviti*" OR TS="vernal conjunctiviti*" OR TS="giant papillary conjunctiviti*" OR TS="hay fever" OR	
TS="ha	ayfever" OR TS="pollinosis" OR TS="pollenosis" OR TS="nasal catarrh*")	

TS = title, abstract, author keywords, Keywords Plus

Appendix to

Sibship Size, Birth Order and Risk of Asthma and Allergy: Protocol for a Systematic

Review and Meta-Analysis

Daniil Lisik, Athina Ioannidou, Gregorio Paolo Milani, Sungkutu Nyassi, Saliha Selin Özuygur Ermis, Giulia Spolidoro, Emma Goksör, Göran Wennergren, Bright I Nwaru

Appendix 3: Data Extraction Form

Reviewer (initials)	
Date of data extraction (yyyy-mm-dd)	
General information	
Author (for first author: surname, given	
name(s))	
Title of article	
Year of publication	
Country of origin of study	
Contact information to author(s)	
Study characteristics	
Study design	
Study aims/objectives	
Exposure(s) (for each exposure: 1)	
method(s) of assessment; 2) objectivity	
of assessment (objective/subjective ¹); 3)	
validity (yes ² /no); 4) reliability	
(yes ³ /no))	
Outcome(s) (for each outcome: 1)	
method(s) of assessment; 2) objectivity	
(objective/subjective ⁴); 3) validity	
(yes ² /no); 4) reliability (yes ³ /no))	
Follow-up (method; length)	Method:
	Length:
	Or: not applicable
Study was conducted during (year(s))	
Participant selection	
Inclusion criteria	
Exclusion criteria	
Source(s) of subjects	
Population characteristics	
Participants recruited (n; details)	n:
	Details:

Participants eligible (n; % of	n:
"Participants recruited"; eligibility	% of "Participants recruited":
criteria)	Eligibility criteria:
Participants included (n; % of	n:
"Participants eligible")	% of "Participants eligible":
	Or:
Participants completing follow-up (n; %	n:
of "Participants included")	% of "Participants included":
	Or:
Participants lost (n; % of "Participants	n:
included"; details; how it was dealt	% of "Participants included":
with)	Details:
	How it was dealt with:
	Or:
Data lost (n; % of "Participants	n:
included"; details; how it was dealt	% of "Participants included":
with)	Details:
	How it was dealt with:
Participants characteristics (for each	
group: 1) n _{total} ; 2) age (mean (SD)); 3)	
gender distribution (n_{males} (% of n_{total}));	
4) ethnicity; 5) country; 6) economic	
classification of country by the World	
Bank; 7) setting; 8) co-morbidity)	
Results	
Outcomes (for each outcome for each	
exposure, stratified by group ⁵ if	
applicable: 1) n (% of n _{group}); 2) effect	
size (measure of effect) 95% CI; 3) p-	
value)	
Analysis	
Statistical analysis method	
Confounders (what confounders were	Confounders identified:
identified; how they were controlled for;	How they were controlled for:
% of confounders controlled for)	
	% of confounders controlled for:
Free-text interpretation of	
findings/conclusion	
Generalizability (is it likely that	
individuals selected for this study to be	
representative of the target population?)	
Miscellaneous	
Other comments/notes	

Quality assessment (based on the	
Effective Public Health Practice	
Project (EPHPP) quality assessment	
tool ⁶)	
(A) Selection bias	
(Q1) Is it likely that individuals selected	
for this study to be representative of the	
target population?	
(Q2) How many of eligible individuals	
agreed to participate in the study? (%)	
Section rating	
(B) Study design	
Indicate the design of the study	
Was the study setting randomized? If	
"No", go to (C)	
If "Yes", was the randomization method	
described?	
If "Yes", was the method referred to	
above appropriate?	
Section rating	
Rate longitudinal studies as "moderate",	
and cross-sectional studies as "weak"	
(C) Confounders	
(Q1) Did the groups have significant	
differences in relation to each other prior	
to the intervention?	
(Q2) If "Yes", indicate how many	
relevant confounders that were	
controlled for in any way (e.g. in study	
design through matching, stratification,	
or in analysis) (%)	
Section rating	
Rate studies without a control group as	
weak	
(D) Blinding	
(Q1) Did the outcome assessor(s) know	
about the exposure status of the	
(O2) Did the meeticine star of the study	
(Q2) Did the participants of the study	
know about the research question?	
Beta as "weak" if 01 is 1 and 02 is 2	
(E) Date collection motheds	
(E) Data collection methods	
(Q1) were the tools used for data collection shown to be valid?	
(O2) Were the tools used for data	
(Q2) were the tools used for data	
conection shown to be reflable?	

Section rating	
(F) Withdrawals and drop-outs	
(Q1) Did numbers and/or reasons for	
withdrawals and drop-outs per group get	
documented?	
(Q2) How many participants completed	
the study (if the value is different	
between groups, state the lowest)? (%)	
Section rating	
Global rating	
Did the two reviewers give different	
section ratings for A-F?	
If "Yes", what is the reason for the	
difference(s)?	
Final rating of both reviewers	

¹ Objective: medical records/official statistics. Subjective: self-report, observation.

² Yes: The assessment gives usable, meaningful information for the research question.

³ Yes: Results from assessment type are consistent and stable.

⁴ Objective: ICD code, verified diagnosis based on medical examination. Subjective: otherwise observed or selfreported symptoms/disease.

⁵ Applicable if specific stratification has been made in the analysis, e.g. significant differences and/or calculations based on gender of participants.

⁶ Modified version of EPHPP [1]. Original tool is available at: <u>https://www.ephpp.ca/quality-assessment-tool-for-quantitative-studies/</u>. The questions and answer alternatives are modified in phrasing for readability and the nature of relevant studies. Modifications of rating are clarified in green text above, based on the modifications of EPHPP done in a systematic review by Smith et al. in 2017 [2].

References

 Armijo-Olivo S, Stiles CR, Hagen NA, Biondo PD, Cummings GG. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. J Eval Clin Pract. 2012;18(1):12-18.
Smith M, Hosking J, Woodward A, Witten K, MacMillan A, Field A, et al. Systematic literature review of built environment effects on physical activity and active transport – an update and new findings on health equity. International Journal of Behavioral Nutrition and Physical Activity. 2017;14(1):158.