thebmj.com Respiratory medicine updates from *The BMJ* are at www.bmj.com/specialties/respiratory-medicine

Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis

Anne K Örtqvist,[1] Cecilia Lundholm,[1] Helle Kieler,[2] Jonas F Ludvigsson,[1 3] Tove Fall,[4] Weimin Ye,[1] Catarina Almqvist[1 5]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, PO Box 281, 17177 Stockholm, Sweden
[2]Centre for Pharmacoepidemiology T2, Department of Medicine, Karolinska University Hospital, 17176 Stockholm, Sweden
[3]Department of Paediatrics, Örebro University Hospital, 70185 Örebro, Sweden
[4]Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Dag Hammarskjöldsväg 14B, Uppsala Science Park, Uppsala, Sweden
[5]Astrid Lindgren Children's Hospital, Lung and Allergy Unit, Karolinska University Hospital, 17176 Stockholm, Sweden
Correspondence to: A K Örtqvist
Anne.ortqvist@ki.se

Cite this as: *BMJ* 2014;349:g6979
doi: 10.1136/bmj.g6979

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g6979

STUDY QUESTION

Is the hypothesised association between exposure to antibiotics in fetal life and early childhood and subsequent asthma causal or can it be attributed to confounding factors?

SUMMARY ANSWER

The association between antibiotics and asthma is attributable to genetic and environmental factors shared within families, in addition to confounding by indication or reverse causation because of respiratory infections.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Numerous studies have reported conflicting results regarding the association between exposure to antibiotics as a fetus and during childhood and subsequent childhood asthma. By using sibling control analyses to further assess causality this study shows that previously reported positive associations were probably affected by confounding by familial factors in addition to confounding by respiratory infections.

Participants and setting

Swedish children born to women pregnant between July 2005 and December 2010, identified from population based demographic and health registers.

Design, size, and duration

In this nationwide prospective register based cohort study with a sibling control design, we investigated the association between exposure to antibiotics from start of pregnancy (fetal exposure to antibiotics given to the mother during pregnancy) up to school age and subsequent childhood asthma. Antibiotics were divided into three groups (any, airway, or urinary tract and skin) and asthma defined as both a doctor's diagnosis of asthma and prescribed asthma drugs. Firstly, we used Cox proportional hazard regression to investigate the association between antibiotic exposure in fetal life or early childhood and asthma in the whole cohort (n=493 785). Secondly, we used a stratified Cox proportional hazard model conditional on sibling group to adjust for factors shared within families, such as genetic predisposition to respiratory infections and asthma, consultation patterns, or other lifestyle and home environmental factors. In total, 180 894 were eligible for the sibling control analyses. A sibling case was defined as a child with asthma. For the controls we used all full siblings who did not have asthma yet and who were still in the study at the age when their sibling had the outcome. We assessed confounding by respiratory infections by investigating whether the specific groups of antibiotics were associated with asthma.

Hazard ratios (95% confidence interval) for asthma in relation to exposure to antibiotics in fetal and early life in full cohort of children and for children with siblings

	Full cohort	Children with siblings
Antibiotic exposure in fetal life		
Any antibiotic	1.28 (1.25 to 1.32)	0.99 (0.92 to 1.07)
Airway antibiotics	1.31 (1.27 to 1.35)	0.98 (0.90 to 1.07)
Urinary tract/skin antibiotics	1.23 (1.18 to 1.28)	0.98 (0.88 to 1.10)
Antibiotic exposure in early life (0-0.5 years)		
Any antibiotic	3.71 (3.41 to 4.03)	2.11 (1.61 to 2.76)
Airway antibiotics	4.12 (3.78 to 4.50)	2.36 (1.78 to 3.13)
Urinary tract/skin antibiotics	1.54 (1.24 to 1.92)	0.85 (0.47 to 1.55)

Main results and the role of chance

Exposure to all groups of antibiotics in fetal life was associated with an increased risk of asthma in cohort analyses but not in sibling analyses, indicating confounding by factors shared within families. In cohort analyses, antibiotics used to treat respiratory infections in childhood were associated with a more pronounced increased risk of asthma (hazard ratio 4.12, 95% confidence interval 3.78 to 4.50, for the youngest children) than antibiotics used for urinary tract and skin infections (1.54, 1.24 to 1.92). In sibling analyses, the excess risks after exposure to antibiotics for respiratory infections clearly decreased (2.36, 1.78 to 3.13) and disappeared for urinary tract and skin antibiotics (0.85, 0.47 to 1.55). These results imply confounding by familial factors and by indication or reverse causation.

Bias, confounding, and other reasons for caution

The study included a limited age range because of restricted availability of information on the exposure. Furthermore, exposure to antibiotics was defined as a prescription for antibiotics being filled, which is not equivalent to adherence to treatment.

Generalisability to other populations

Our study population was identified from national registers and included almost all children born in 2006-10; thus our population based design has generalisable findings.

Study funding/potential competing interests

Financial support was provided by the Swedish Research Council, grants provided by the Stockholm County Council (ALF project), the strategic research programme in epidemiology at Karolinska Institutet, and the Swedish Heart Lung Foundation. HK has received institutional fees from various pharmaceutical companies (see thebmj.com for details) for studies not relevant to the submitted work.

Innovative research methods for studying treatments for rare diseases: methodological review

Joshua J Gagne, Lauren Thompson, Kelly O'Keefe, Aaron S Kesselheim

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
Correspondence to: J J Gagne
jgagne1@partners.org

Cite this as: *BMJ* 2014;349:g6802
doi: 10.1136/bmj.g6802

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g6802

thebmj.com
See related infographic at http://www.bmj.com/infographics

STUDY QUESTION

What innovative approaches to research have been, or can be, applied to overcome the methodological challenges in the study of rare diseases?

SUMMARY ANSWER

Though numerous studies apply unique clinical trial designs and considerations to assess patient health outcomes in rare diseases, less attention has been paid to innovative methods for studying rare diseases using observational data.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Because rare diseases are clinically dissimilar, clinicians, scientists, and other stakeholders working in one medical specialty may not be familiar with methods being applied in other disciplines. Several promising strategies that may contribute substantial advances to the study of health outcomes in patients with rare diseases have been proposed, particularly for randomized trials, but greater attention to innovative methods for using observational data to study health outcomes in rare diseases is needed.

Selection criteria for studies

We conducted a methodological review of existing literature by searching PubMed, Embase, and Academic Search Premier. We included articles describing innovative approaches to randomized trial design and analysis methods and methods for conducting observational research in patients with rare diseases.

Primary outcomes

We assessed information related to the proposed methods, the specific rare disease being studied, and outcomes from the application of the methods. We summarized methods with respect to their advantages in studying health outcomes in rare disease and provide examples of their application.

Main results and role of chance

Several methods were identified, especially for randomized trials. Most proposed methods aim at minimizing the number of required participants or maximizing the number who receive treatment.

Bias, confounding, and other reasons for caution

The literature search was focused on articles that mentioned "rare disease" in a searchable field. Because of the large number of unique rare diseases, we were not able to search for applications of innovative methods related to each specific disease. Also, the review was intended to provide a general overview of non-traditional methods that have been proposed or applied to studying rare diseases; other, more technical reviews, exist.

Study funding/potential competing interests

This project was funded under contract No 290 2010 00006l TO #4 from the Agency for Healthcare Research and Quality, US Department of Health and Human Services as part of the Developing Evidence to Inform decisions about Effectiveness (DEcIDE) program. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the US Department of Health and Human Services.

Summary of research strategies for studying rare diseases and their advantages

	Address small Nos of patients and outcomes				Promote recruitment and retention	
Strategy	Minimize No of required participants	Make use of conventionally underpowered studies	Maximize outcome information among participants	Facilitate confounding adjustment with sparse data	Maximize No of participants who receive treatment	Expand access to studies and participants
Study design options						
Factorial designs	X	—	—	—	—	—
Response-adaptive randomization	X	—	—	—	X	—
Sequential designs	X	—	—	—	—	—
Crossover, n-of-1, alternating designs	X	—	—	X	X	—
Use continuous outcome	—	—	X	—	—	—
Use surrogate outcome	—	—	X	—	—	—
Use composite outcome	—	—	X	—	—	—
Use repeated measure outcome	—	—	X	—	—	—
Increase duration of follow-up	—	—	X	—	—	—
Case-control sampling	—	—	—	—	—	—
Recruitment and enrollment strategies:						
Focus on high risk patients	—	—	X	—	—	—
Trial networks and distributed data networks	—	—	—	—	—	X
Statistical options:						
Increase α	—	X	—	—	—	—
Propensity scores	—	—	—	X	—	—
Incorporation into larger evidence context:						
Conduct study as part of prospectively planned meta-analysis	—	X	—	—	—	—
Incorporate study into bayesian framework	—	X	—	—	—	—

The association between exaggeration in health related science news and academic press releases: retrospective observational study

Petroc Sumner,[1 2] Solveiga Vivian-Griffiths,[1 2] Jacky Boivin,[2] Andy Williams,[3] Christos A Venetis,[4] Aimée Davies,[2] Jack Ogden,[2] Leanne Whelan,[2] Bethan Hughes,[2] Bethan Dalton,[2] Fred Boy,[5] Christopher D Chambers[1 2]

EDITORIAL by Goldacre

[1]Cardiff University Brain Research Imaging Centre, School of Psychology, Cardiff University, Cardiff CF10 3AT, UK
[2]School of Psychology, Cardiff University, UK
[3]School of Journalism, Media & Cultural Studies, Cardiff University, UK
[4]School of Women's and Children's Health, University of New South Wales, and Graduate School of Medicine, Faculty of Science, Medicine and Health, University of Wollongong, Australia
[5]Department of Psychology, Swansea University, UK
Correspondence to: P Sumner or C D Chambers
sumnerp@cardiff.ac.uk or **chambersc1@cardiff.ac.uk**

Cite this as: *BMJ* 2014;349:g7015
doi: 10.1136/bmj.g7015

This is a summary of a paper that was published on thebmj.com as *BMJ* 2014;349:g7015

thebmj.com
Access this article online to watch a video abstract of the paper's authors talking about their findings

STUDY QUESTION

To what extent does misreporting of health related science in the print media begin with exaggeration in university press releases?

SUMMARY ANSWER

When press releases contained exaggerated advice, claims about causal effects, or inference to humans, the odds that corresponding news stories also contained exaggeration were 6 to 56 times higher than when press releases were not exaggerated.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Health and science news stories can have a widespread influence on public health, and exaggerations are often blamed on media agendas or journalists' ignorance. We found that little exaggeration appears de novo in print news; most is already in the press releases issued by academic institutions and generally approved by scientists.

Rationale, design, data collection method

Press releases are a recognised influential link between academia and the media, and thus a potential source of exaggeration as well as information. We collected 462 press releases on biomedical and health related research in 2011 from the databases of 20 leading UK university press offices, alongside their associated peer reviewed research articles and news stories (n=668). We analysed these texts for levels of advice, causal claims from correlational (observational) data, and inference to humans from animal research, and whether these levels were increased in press releases and news compared with the journal article.

Participants and setting

Units of analysis were press releases, associated peer reviewed journal articles, and news stories.

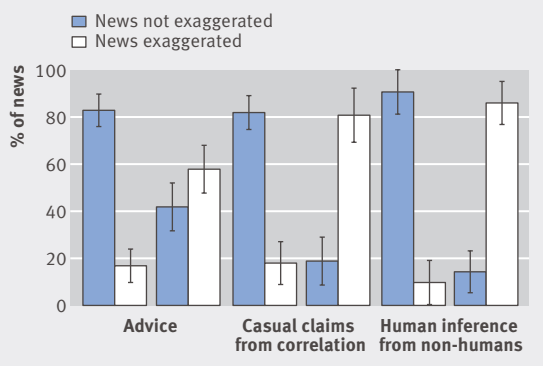
Recruitment/sampling strategy

From the entire population of press releases issued by UK Russell Group universities in 2011 (n=4093), we extracted those based on a peer reviewed research article with possible relevance for human health (biomedical and psychological sciences). For each relevant press release we sourced the associated journal article and associated print or online news stories from the UK national press.

Data analysis method

We first assessed exaggeration rates in press releases (using bootstrapping for 95% confidence intervals). Secondly, we calculated the association (odds ratios) between exaggeration in press releases and news stories using generalised estimating equations. Thirdly, we assessed whether exaggeration in press releases is associated with greater news coverage, and finally whether caveats and justifications had any association with exaggeration rates or news uptake.

Proportions of news with exaggerated advice, causal statements from correlational research, or human inference from non-human studies



Main findings

Press releases had high levels of exaggeration, and the odds of exaggeration in news were much higher when press releases contained exaggeration than when they did not: odds ratios 6.5 (95% confidence interval 3.5 to 12), 20 (7.6 to 51), and 56 (15 to 211) for exaggerations relating to advice, causal claims, and inference to humans from animal research, respectively. We found no evidence that exaggeration was associated with greater news coverage or that caveats were associated with reduced coverage.

Implications

Exaggeration in health news is strongly associated with exaggeration in the preceding academic press releases, but such exaggeration may not increase news coverage. Improving the accuracy of press releases could represent an opportunity for reducing the prevalence of misleading health related science reporting.

Bias, limitations, generalisability

As a retrospective correlational analysis, our results cannot show a causal association between exaggeration in press releases and news. Similarly, they cannot show that exaggeration does not increase news uptake if such exaggeration is also correlated with other factors (for example, news value of the original research article). We do not yet know whether these results can be generalised to other press releases important for health news.

Study funding/potential competing interests

The study was supported by grants from the British Psychological Society, Experimental Psychology Society, the Wellcome Trust, the Economic and Social Research Council, the Biotechnology and Biological Sciences Research Council, and Cardiff University. We have no competing interests except association with some of the universities studied.