Author’s response to reviews

Title: Early antibiotic exposure and development of asthma and allergic rhinitis in childhood

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Author’s Response to Reviewers

In reply to Dr. Kiwako Yamamoto-Hanada, MD, PhD (Reviewer 1): This study reported the association between antibiotic exposure and allergic diseases such as asthma and eczema.

Introduction

It seems to be strange that the authors evaluate allergic outcomes and obesity in the same study. These outcomes have different background.

Response: Obesity as an outcome was removed from our analysis as a primary disease outcome due to inability to control for confounding variables in our limited dataset and different background from our other primary diseases. References were adjusted accordingly.

Methods

The authors mentioned target population was children, however they did not set the limit of age including in this study.
Response: Age limit of our study population was addressed in study design section of the methods.

Oral antibiotics and venous antibiotics are difference exposure levels. The authors should distinguish between these different exposure routes.

Response: This step in data extraction was not performed and was a limitation to our study. Route of antibiotic administration was addressed in study exposure section of the methods.

Please specify a designated time frame.

Response: Time frame of our study is addressed in the study design section of the methods.

Eczema definition is not appropriate. Eczema of ICD-9 included contact dermatitis mainly, but eczema of ICD-10 did not include contact dermatitis. The list of ICD-9 and 10 should include atopic dermatitis. The definition of eczema was not appropriate for evaluating eczema. Usually, eczema means atopic dermatitis. Atopic dermatitis is different from contact dermatitis, and these mechanisms also differ. Eczema definition need to have major revision. Please contact at dermatologist.

Response: This was an error in our data collection methods. Thus, eczema as an outcome was excluded from our analysis as a primary disease outcome due to insufficient ICD diagnostic coding. References were adjusted accordingly.

I think some children had eczema before antibiotic exposure. All outcomes came after antibiotic exposures?

Response: Eczema was excluded from our data analysis for reasons listed above.

The authors mentioned that prematurity and birth weight as covariates. Did they check multicollinearity, evaluating VIF?

Response: In terms of multicollinearity, the results from our analysis did not indicate multicollinearity because our estimates did not vary from model to model

Results

"Children younger than one year of age at the time of our study were excluded…" This sentence should be written in the method section.
Response: this sentence was moved to the method section as suggested.

"similarly, children younger than….were excluded " this sentence should be written in the method section."

Response: this sentence was moved to the method section as suggested.

"our disease prevalence rates were comparable…however, fewer children…..data" should be written in the discussion section.

Response: this sentence was moved to the discussion section as suggested.

Table 2: poverty status might be changed to living area with poverty

Response: Poverty status was changed to living in an area with poverty as suggested.

The authors mentioned that 44.2% of children were exposed to antibiotics within the first year of life. They could obtain the information of the visiting timing. How did they obtain all antibiotics information? Children usually obtain antibiotics in primary care clinic. This study was done in the large academic center. I believe it was impossible to obtain all past history about antibiotic exposure.

Response: Additional antibiotic exposure outside of the data collection method was unable to be obtained by our data extraction methods, and was addressed in limitations section of discussion.

The authors did not show details of exposure status. They should add another table showing background information of each antibiotic exposure status.

Response: antibiotic exposure status was not distinguished in our dataset as we had coded antibiotic exposure as a binary outcome. This was a weakness to our study and was addressed in our limitations section of discussion.

Discussion

This study could not actual causal relationship between antibiotic exposure and future likelihood to have allergic diseases.

Response: the inability to determine causality is addressed in our limitations section of the discussion.
The authors should review past reports about the relationship between allergic disease and antibiotic exposure.

Response: Additional references regarding antibiotic exposure and allergic diseases were obtained (references 21-26).

In response to Reviewer 2 (Reviewer 2): PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?

Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?

Not sure - key details are missing from the manuscript

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?

Not sure - key details are missing from the manuscript

Statistics - Is the use of statistics in the manuscript appropriate?

Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?

No - there are minor issues

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?

Maybe - with major revisions

PEER REVIEWER COMMENTS:
GENERAL COMMENTS: Overall impression of the study: This is a well written report. The significance of the study should be discussed in more detail. Nevertheless, the study objectives are clear and the design is appropriate. The process of medical record review and any effort taken to address potential bias should be described.

Response: thank you for your review. Data extraction, medical record review and potential bias were addressed in the methods section as suggested and as detailed below.

REQUESTED REVISIONS:

The novelty of the study need to be better explained in the introductory section.

Response: we believe that the novelty of our study lies in the timepoints used for antibiotic exposure and in the study of the dose-response relationship between antibiotics and disease. This was further expanded upon in our introduction section.

The methodology section should provide further information on: (1) The setting; (2) Characteristics of the data source (the electronic medical record) in terms of accuracy and completion; (3) Data extraction process: Measures taken to assure that data extraction was consistent with the operational definitions adopted should be explained.

Response: These three points were addressed in the study design section of our methods as suggested. Figure 1 further details the completion of our data source in terms of missing data.

Method of handling missing data. Identification of people in-charge of coding the data.

Response: Handling of missing data was addressed in the study designed section of our methods.

If more than one person participated in the extraction and coding of the data, description of the measures taken to estimate intercoder agreement. Efforts taken to address potential bias.

Response: One person participated in the extraction and coding of the data, thus there was no significant need for measures to ensure intercoder agreement. Data extraction was addressed in the study design section of our methods.

With regard to the discussion: In p. 4, line 4-31, authors explain that (1) many environmental factors that were not controlled for in the study are likely to contribute to the development of obesity and (2) that obesity tends to manifest in older individuals. Thus, is it appropriate to include obesity among the study primary outcomes with the available data/ selected cohort of children? How?
Response: obesity was excluded from our primary disease outcomes due to different background from other diseases studied.