Early life exposure to antibiotics and laxatives in relation to infantile atopic eczema

Sarah El-Heis[1], Sarah Crozier R[1], Nicholas Harvey C[1], Eugene Healy[2], and Keith Godfrey[1]

[1]University of Southampton MRC Lifecourse Epidemiology Centre
[2]University of Southampton

February 22, 2023

Early life exposure to antibiotics and laxatives in relation to infantile atopic eczema

Sarah El-Heis [1] DM

Sarah R Crozier[1,2] PhD

Nicholas C Harvey[1,3] PhD

Eugene Healy[4] PhD

Keith M Godfrey[1,3,5] FMedSci

[1] Medical Research Council Lifecourse Epidemiology Centre, University of Southampton,

Southampton, UK

[2] NIHR Applied Research Collaboration Wessex, Southampton Science Park, Innovation Centre, Southampton, UK

[3] NIHR Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

[4] Dermatopharmacology, Faculty of Medicine, University of Southampton, Southampton, UK

[5] Developmental Sciences, University of Southampton, Southampton, UK

Correspondence to:

Professor Keith Godfrey

Medical Research Council Lifecourse Epidemiology Centre (University of Southampton)

Southampton General Hospital, Mail point 95

Southampton SO16 6YD

United Kingdom.

Tel: 44 (0)23 80777624

Fax: +44 (0)23 80704021

Email: kmg@mrc.soton.ac.uk

Conflict of interest

KMG has received reimbursement for speaking at conferences sponsored by companies selling nutritional products. KMG is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec and Danone. CC reports personal fees from ABBH, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier and Takeda, outside the submitted work. NCH reports personal fees, consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, Radius Health, UCB, Consilient Healthcare and Internis Pharma, outside the submitted work. The other authors have no competing interests.

Funding

This work was supported by grants from the Medical Research Council, British Heart Foundation, Food Standards Agency, Arthritis Research UK, National Osteoporosis Society, International Osteoporosis Foundation, Cohen Trust, European Union's Seventh Framework (FP7/2007-2013), projects EarlyNutrition and ODIN under grant agreement numbers 289346 and 613977, NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, NIHR Musculoskeletal Biomedical Research Unit, University of Oxford and British Lung Foundation.

Key words : Atopic eczema, antibiotics, laxatives, microbiome

Abbreviations: UK Working Party Criteria for the Definition of Atopic Dermatitis (UK WPDC), Directed Acyclic Graph (DAG), Odds Ratio (OR)

Word count: 1026

Figures: Figure 1. Directed Acyclic Graph (DAG) demonstrating the relationship between laxative and antibiotic exposure (exposure), infant atopic eczema (outcome) and variables. Confounders identified are: maternal BMI, parity, breastfeeding duration and infant sex.

Tables: Table 1. Atopic eczema at age 12 months in relation to exposure to maternal antibiotic use, maternal laxative use and infant antibiotic use.

The risk of developing atopic eczema is influenced by various events pre-conception, during pregnancy and throughout the neonatal period.[1, 2] Recent reports have suggested that early life exposure to microbiome altering medications, such as antibiotics and laxatives, could impact the risk of atopic eczema in infancy and childhood. For example, in this Journal, Lin et al., 2022 reported an increased risk of allergic disease in offspring whose mother used laxatives in pregnancy independent of laxative exposure in the offspring but no associations were found for maternal antibiotic use.[3]

As the evidence on this topic is sparse, in this study we aimed to further examine whether maternal gestational exposure to antibiotics or laxatives were associated with the risk of atopic eczema in infancy. We also examined the link between offspring antibiotic exposure in the first 12 months of life and risk of infantile atopic eczema.

Within the UK Southampton Women's Survey, a prospective mother-offspring cohort, maternal antibiotic and laxative exposure during pregnancy were contemporaneously recorded by research nurses during in-person interviews in early (median 11.8 weeks' gestation) and late (median 34.5 weeks' gestation) pregnancy; n=248 and n=304 reported antibiotic exposure, and n=67 and n=72 laxative exposure in early and late pregnancy, respectively. At age 12 months, offspring antibiotic exposure was recorded (n=1433 exposed); of these, 10.1% were exposed to maternal antibiotic use in early pregnancy 12.3% to maternal antibiotic use in late pregnancy, 2.5% to maternal laxative use in early pregnancy and 3.4% to maternal laxative use in late pregnancy. Atopic eczema was ascertained using the UK Working Party Criteria (UK WPDC) for the Definition of Atopic Dermatitis[4] at ages 6 and 12 months (cohort n= 2907 and 2870, respectively (n= 262 and 270, with eczema)).

We used a Directed Acyclic Graph (DAG) to identify potential confounders and competing exposures that should be included in our statistical models[5]; these were maternal BMI, parity, breastfeeding duration and infant sex (Figure 1). Standard univariable and multivariable logistic regression analyses were carried

out adjusting for potential confounders as identified by the DAG to relate maternal use of antibiotics and laxatives in pregnancy, and infant antibiotic exposure to infantile atopic eczema at ages 6 and 12 months (Stata version 14.1, Statacorp LP, TX). Antibiotic exposure captured at age 12 months was not used to predict infant eczema at 6 months.

We found no associations between maternal antibiotic use in pregnancy and infantile atopic eczema (Table 1). Similarly, maternal laxative use had no associations with infantile atopic eczema at ages 6 or 12 months. Findings were unaltered taking into account potential confounders. The use of antibiotics in infancy, however, was associated with an increased risk of atopic eczema at 12 months and remained significant in multivariable analyses (OR (95% CI) 1.57 (1.21-2.05), p=0.001) (Table 1). The risks of atopic eczema at age 12 months were similar in those who had antibiotics in the first 6 months and those who had antibiotics during age 6-12 months compared to those who did not have antibiotics. Exposure to antibiotics once only (n=794), 2-3 times (n=458) and more than three times (n=164) in the first year of life were associated with similarly increased risks of atopic eczema (1.50 (1.10-2.03), p=0.01, 1.60 (1.12-2.28), p=0.009 and 1.59 (0.94-2.68), p=0.085, for once only, 2-3 times and more than three times, respectively).

The findings support evidence that postnatal antibiotic exposure is associated with the infant's risk of developing atopic eczema. Further work is needed to disentangle whether the postnatal antibiotic exposure plays a causal role in infantile eczema, or whether the antibiotic exposure occurs as a consequence of the eczema. Our data provides limited information on the condition for which antibiotics were prescribed and the sample size for documented individual infections is too small to draw conclusions (e.g. pneumonia 4%, bronchitis 15%), but the similar relationships for early and late infancy antibiotic exposure provide weak evidence against the antibiotics simply being prescribed as a consequence of the eczema

Wohl et al reported an increased risk of atopic eczema at the age of 2 years in infants whose mothers took antibiotics during pregnancy.[6] In our study maternal gestational antibiotic or laxative exposure, however, were not related to infant atopic eczema. A systematic review of prenatal and infant antibiotic exposure and childhood allergic disease reported that prenatal antibiotics had an overall effect on eczema but the findings for infant antibiotic exposure were less consistent.[7] Variation in definition of eczema or in study methodology may have contributed to this. In our study, atopic eczema was defined by UK WPDC which are recognized diagnostic criteria used in clinical and research settings and involved a standardized questionnaire and an examination undertaken by trained research nurses. Data on infant exposure to laxatives was not available in this cohort. We also used a DAG which is a robust method for identifying cofounders in large observational epidemiological studies.[5]

Gut microbiome regulates the gut environment but it also influences the regulation of the microbiome of barrier sites such as the skin and the lungs. The timing of dysbiosis that is likely to impact the offspring's developing immune system is not known but it has been suggested that the first 6 months after birth should be considered a time of susceptibility as the microbiome develops rapidly and may induce long-term immunological changes.[7, 8] Supportive evidence from animal studies has shown that antibiotic exposure in neonatal mice was associated with shifts in the gut microbiome and subsequent signs of allergic asthma. These changes were not seen in exposed adult mice.[9] Nonetheless, alterations in the microbiome may be related to atopic eczema and not a direct effect of antibiotics.

Maternal enteric dysbiosis may result from medications, which in turn may cause enteric dysbiosis of the fetus via the translocation of microbes through the bloodstream, and increase their predisposition to developing allergic disease. While we did not demonstrate evidence for this, we did identify that antibiotic use in infancy was associated with development of atopic eczema during the first 12 months of life. Based on our data and the results of recent studies, we recommend further research to examine the impact of early life antibiotic and laxative exposure on the microbiome-immune-atopy axis.

References

1. Hui-Beckman J, Kim BE, Leung DY. Origin of Allergy From In Utero Exposures to the Postnatal Environment. Allergy Asthma Immunol Res. 2022;14(1):8-20.

2. El-Heis S, Crozier SR, Robinson SM, Harvey NC, Cooper C, Inskip HM, et al. Higher maternal serum concentrations of nicotinamide and related metabolites in late pregnancy are associated with a lower risk of offspring atopic eczema at age 12 months. Clin Exp Allergy. 2016;46(10):1337-43.

3. Lin TL, Wu CY, Fan YH, Chang YL, Ho HJ, Chen YJ. Association between early life laxative exposure and risk of allergic diseases A nationwide matched cohort study. Ann Allergy Asthma Immunol. 2022;128(3):291-8.e3.

4. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. Br J Dermatol. 1994;131(3):406-16.

5. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37-48.

6. Wohl DL, Curry WJ, Mauger D, Miller J, Tyrie K. Intrapartum antibiotics and childhood atopic dermatitis. J Am Board Fam Med. 2015;28(1):82-9.

7. Baron R, Taye M, der Vaart IB, Ujčič-Voortman J, Szajewska H, Seidell JC, et al. The relationship of prenatal antibiotic exposure and infant antibiotic administration with childhood allergies: a systematic review. BMC Pediatr. 2020;20(1):312.

8. van der Velden VH, Laan MP, Baert MR, de Waal Malefyt R, Neijens HJ, Savelkoul HF. Selective development of a strong Th2 cytokine profile in high-risk children who develop atopy: risk factors and regulatory role of IFN-gamma, IL-4 and IL-10. Clin Exp Allergy. 2001;31(7):997-1006.

9. Russell SL, Gold MJ, Hartmann M, Willing BP, Thorson L, Wlodarska M, et al. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. EMBO Rep. 2012;13(5):440-7.

Figure 1. Directed Acyclic Graph (DAG) demonstrating the relationship between laxative and antibiotic exposure (exposure), infant atopic eczema (outcome) and variables. Confounders identified are: maternal BMI, parity, breastfeeding duration and infant sex.

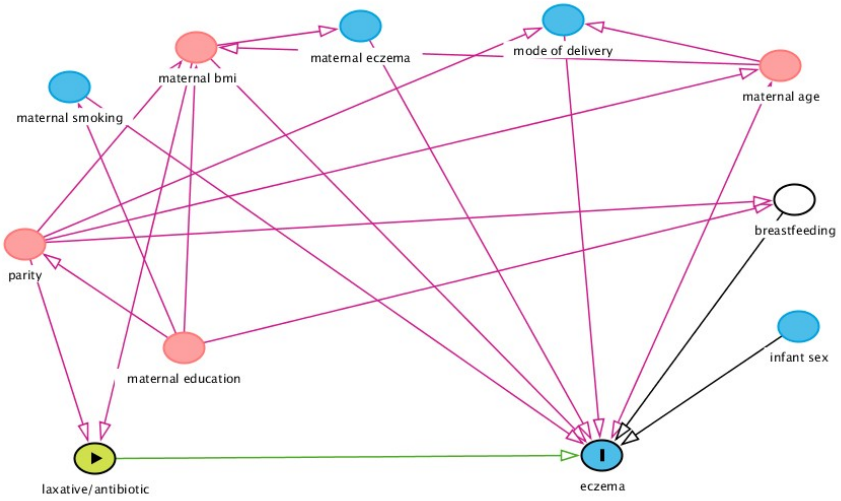

Table 1. Atopic eczema at age 12 months in relation to exposure to maternal antibiotic use, maternal laxative use and infant antibiotic use.*

	n	OR	95% CI	P value
Maternal antibiotic use Early pregnancy Late pregnancy	2467 2336	0.97 1.10	0.80-1.18 0.93-1.30	0.79 0.27
Maternal laxative use Early pregnancy Late pregnancy	2467 2336	0.99 1.25	0.42-2.33 0.59-2.66	0.98 0.56
Infant antibiotic use (in the first 12 months of life)	2730	1.57	1.21-2.05	0.001

*Multivariable logistic regression analyses adjusting for maternal BMI, parity, breastfeeding duration and infant sex.