Avoiding a Life of Allergy

Emerging Evidence and Implications for Practice

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Paediatrician
GenPaed Terrigal – 29 October 2022

Allergy in Australia

- Almost 20% of Australians have an allergic disease
- Allergy and immune diseases among ***fastest growing*** chronic conditions in Australia
- ***10% of infants*** now have a food allergy
- Hospital admissions with anaphylaxis have increased ***4-fold*** in 20 years
- Food-induced anaphylaxis has doubled in 10 years

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Allergy and Immune Diseases in Australia (AIDA) Report 2013

What can be done to prevent childhood allergy?

Your body is mostly microbes

Human gut microbiome

Sum of microbial life living in the human intestinal tract

- 100 trillion organisms – 10x number of adult human cells
- Bacterial mass 2-3kg (>combined mass of brain/lungs)
- Makes small molecules, neurotransmitters, hormones that modulate host immune/endocrine/genetic responses
- Poorly characterised (99% microbiome organisms anaerobic)
- Microbiome genome estimated >100x genes than human host

- Our biomes contain much more diversity than our genomes: individuals ~15% of 1000+ known species

Eckburg et al (2005) Science 308:1635-8

Microbiome and allergy

- Antigens present in microbiome exceed combined self and pathogen-derived antigens a person will encounter in lifetime[#]

Landscape in which body's immune responses are trained

- Factors that impact diversity and health of microbiome increasingly implicated in range of immune, endocrine and metabolic conditions

- Individual's microbiome – shaped in childhood – sets lifelong patterns of immune responses.. including allergy

[#]Gritz et al (2015) Front Pediatr 3(60)

Is our current practice unintentionally contributing to the allergy epidemic?

Maternal diet in pregnancy

- Excluding potentially allergic foods ***does not*** prevent allergy and is not recommended

- Omega-3 fatty acids (in fish) ***possibly*** associated with lower rates of infantile eczema
- Probiotics in pregnancy and while breastfeeding ***possibly*** associated with lower rates of infantile eczema but not yet recommended because optimal species and doses not known

- Eat healthy balanced diet rich in fibre, vegetables and fruit

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Cesarean Section and Chronic Immune Disorders

Astrid Sevelsted, Jakob Stokholm, Klaus Bønnelykke and Hans Bisgaard

Pediatrics originally published online December 1, 2014;

Does mode of birth effect rates of chronic immune disorders?

- Danish Medical Birth Registry/Danish National Patient Registry
- All births in 35-year period 1977-2012 (2.5 million children)
- Any hospital diagnosis of chronic immune disease/atopy
- Comparison by mode of birth: vaginal vs caesarian delivery
- Controlled for known confounders
- Exclusions for low birth weight/missing data → 1.9m analysed

TABLE 1 IRRs by Cesarean Delivery in the 35-Year Period 1977–2011 Following 1.9 Million Term Children in the Age Span 0 to 15 Years

	Cases	aIRR (95% Confidence Interval); *P*	PARF (Cases)
Asthma[a]	103 822	1.23 (1.21–1.25); $P < .0001$	3.07 (3187)
Asthma >5 y[b]	48 858	1.16 (1.13–1.19); $P < .0001$	2.19 (1070)
Systemic connective tissue disorders	7498	1.11 (1.04–1.19); $P = .0021$	1.53 (115)
Juvenile arthritis	6946	1.10 (1.02–1.18); $P = .0117$	1.34 (93)
Diabetes type 1	6136	1.01 (0.93–1.10); $P = .82$	—[d]
Inflammatory bowel diseases	2697	1.20 (1.06–1.36); $P = .004$	2.70 (73)
Immune deficiencies	2589	1.46 (1.32–1.62); $P < .0001$	6.09 (158)
Celiac disease	1944	0.99 (0.87–1.14); $P = .89$	—[d]
Leukemia	1631	1.17 (1.00–1.36); $P = .048$	2.31 (38)
Psoriasis	1306	0.98 (0.81–1.18); $P = .81$	—[d]
Arm fracture[a,c]	77 490	0.99 (0.96–1.01); $P = .19$	—[d]

Cases are defined by first in- or outpatient admission to a hospital in Denmark. IRRs are adjusted for age, calendar year, birth weight, parity, gender, season of birth, maternal age, and maternal illness. The PARF is calculated based on an overall prevalence of 14% cesarean deliveries for diseases with significant association to cesarean delivery.

[a] Attained age and calendar year included in 1-y categories.

[b] Attained calendar year included in 3-y and age in 6-y categories.

[c] Not adjusted for maternal disease.

[d] PARF is not calculated for insignificant associations.

IRR: incidence rate ratio
PARF: population attributable risk fraction

Cesarean Section and Chronic Immune Disorders
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JAMA Pediatrics | Original Investigation

Association Between Cesarean Birth and Risk of Obesity in Offspring in Childhood, Adolescence, and Early Adulthood

Changzheng Yuan, ScD; Audrey J. Gaskins, ScD; Arianna I. Blaine, ScM; Cuilin Zhang, MD, PhD; Matthew W. Gillman, MD, SM; Stacey A. Missmer, ScD; Alison E. Field, ScD; Jorge E. Chavarro, MD, ScD

IMPORTANCE Cesarean birth has been associated with higher risk of obesity in offspring, but previous studies have focused primarily on childhood obesity and have been hampered by limited control for confounders.

OBJECTIVE To investigate the association between cesarean birth and risk of obesity in offspring.

DESIGN, SETTING, AND PARTICIPANTS A prospective cohort study was conducted from September 1, 1996, to December 31, 2012, among participants of the Growing Up Today Study, including 22 068 offspring born to 15 271 women, followed up via questionnaire from ages 9 to 14 through ages 20 to 28 years. Data analysis was conducted from October 10, 2015, to June 14, 2016.

EXPOSURE Birth by cesarean delivery.

MAIN OUTCOMES AND MEASURES Risk of obesity based on International Obesity Task Force or World Health Organization body mass index cutoffs, depending on age. Secondary outcomes included risks of obesity associated with changes in mode of delivery and differences in risk between siblings whose modes of birth were discordant.

RESULTS Of the 22 068 offspring (20 950 white; 9359 male and 12 709 female), 4921 individuals (22.3%) were born by cesarean delivery. The cumulative risk of obesity through the end of follow-up was 13% among all participants. The adjusted risk ratio for obesity among offspring delivered via cesarean birth vs those delivered via vaginal birth was 1.15 (95% CI, 1.06-1.26; $P = .002$). This association was stronger among women without known indications for cesarean delivery (adjusted risk ratio, 1.30; 95% CI, 1.09-1.54; $P = .004$). Offspring delivered via vaginal birth among women who had undergone a previous cesarean delivery had a 31% (95% CI, 17%-47%) lower risk of obesity compared with those born to women with repeated cesarean deliveries. In within-family analysis, individuals born by cesarean delivery had 64% (8%-148%) higher odds of obesity than did their siblings born via vaginal delivery.

CONCLUSIONS AND RELEVANCE Cesarean birth was associated with offspring obesity after accounting for major confounding factors. Although additional research is needed to clarify the mechanisms underlying this association, clinicians and patients should weigh this risk when considering cesarean delivery in the absence of a clear indication.

Supplemental content

JAMA Pediatr. 2016;170(11):e162385. doi:10.1001/jamapediatrics.2016.2385
Published online September 6, 2016.

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Breastfeeding

- Breastfeeding recommended for its many health benefits
- ***Not*** consistent evidence showing that breastfeeding is effective in the prevention of allergic disease
- If breastfeeding is not possible, a standard cow-milk based formula can be given
- ***No*** convincing evidence for a protective role for partially/extensively-hydrolysed formulas, goat- or soy- based formulas in the ***prevention*** of eczema, food allergy, asthma or allergic rhinitis – not recommended

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Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial

Håvard Ove Skjerven, Eva Maria Rehbinder, Riyas Vettukattil, Marissa LeBlanc, Berit Granum, Guttorm Haugen, Gunilla Hedlin, Linn Landrø, Benjamin J Marsland, Knut Rudi, Kathrine Dønvold Sjøborg, Cilla Söderhäll, Anne Cathrine Staff, Kai-Håkon Carlsen, Anna Asarnoj, Karen Eline Stensby Bains, Oda C Lødrup Carlsen, Kim M Advocaat Endre, Peder Annæus Granlund, Johanne Uthus Hermansen, Hrefna Katrín Gudmundsdóttir, Katarina Hilde, Geir Håland, Ina Kreyberg, Inge Christoffer Olsen, Caroline-Aleksi Olsson Mägi, Live Solveig Nordhagen, Carina Madelen Saunders, Ingebjørg Skrindo, Sandra G Tedner, Magdalena R Værnesbranden, Johanna Wiik, Christine Monceyron Jonassen, Björn Nordlund, Karin C Lødrup Carlsen

Summary

Background Skin emollients applied during early infancy could prevent atopic dermatitis, and early complementary food introduction might reduce food allergy in high-risk infants. The study aimed to determine if either regular skin emollients applied from 2 weeks of age, or early complementary feeding introduced between 12 and 16 weeks of age, reduced development of atopic dermatitis by age 12 months in the general infant population.

Lancet 2020; 395: 951–61

Emollients/feeding for eczema

Do emollients/early solids for infants prevent eczema?

- 2697 pregnant women in Norway/Sweden recruited 2014-2016
- Randomised at mid-trimester scan to:
    1. no intervention (standard infant skin care/feeding advice)
    2. skin emollients (bath additives/face cream from 2 weeks)
    3. early solids (peanut, milk, wheat, egg from 12-16 weeks)
    4. combined early skin care/early feeding

- Blinded clinical review at 3, 6, 9, 12 months
- Primary outcome: atopic dermatitis at 12 months

FINDINGS: no difference

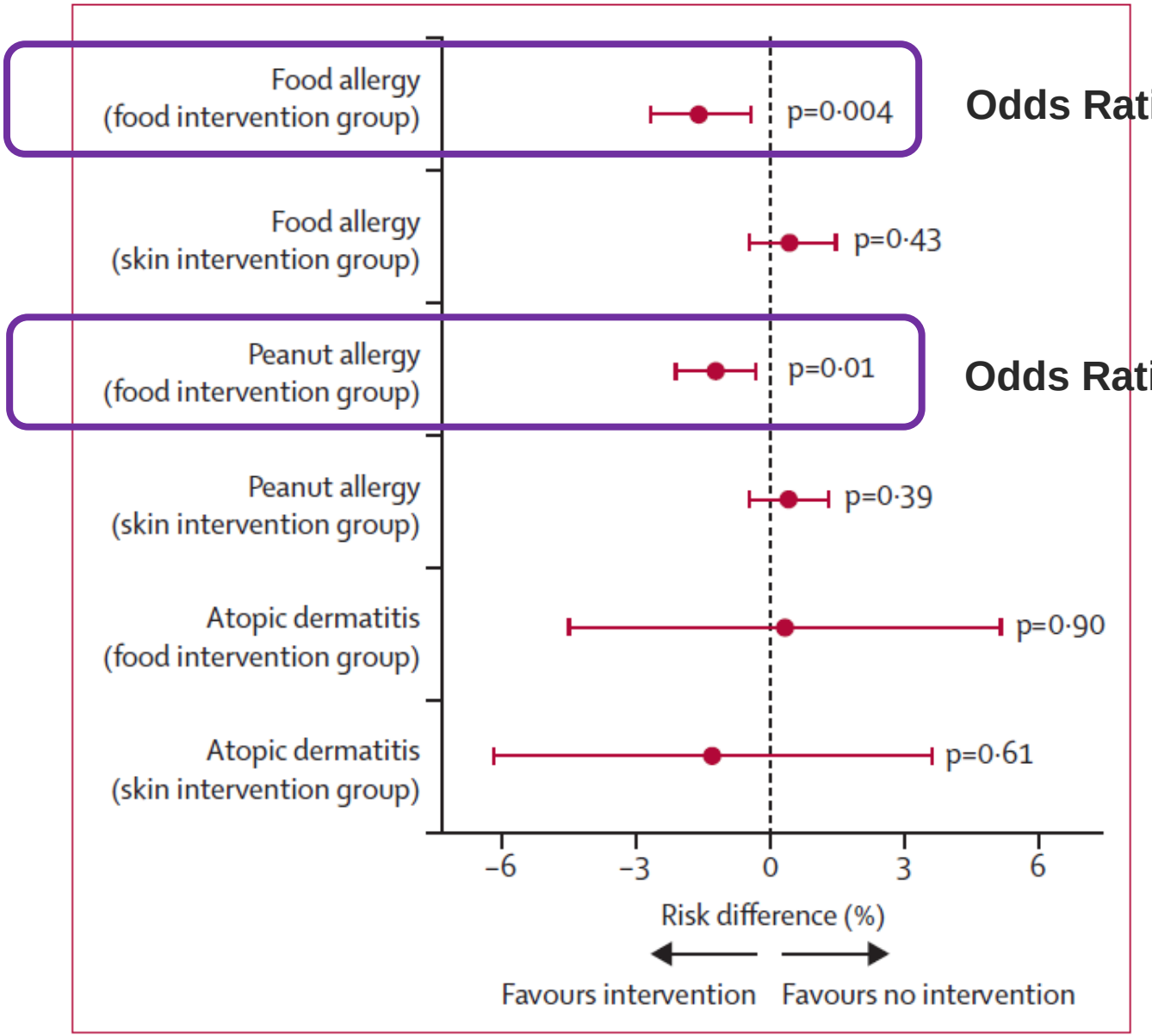
Lancet 2020; 395: 951–61

Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial

Håvard Ove Skjerven, Anine Lie, Riyas Vettukattil*, Eva Maria Rehbinder, Marissa LeBlanc, Anna Asarnoj, Kai-Håkon Carlsen†, Åshild Wik Despriee, Martin Färdig, Sabina Wärnberg Gerdin, Berit Granum, Hrefna Katrín Gudmundsdóttir, Guttorm Haugen, Gunilla Hedlin, Geir Håland, Christine Monceyron Jonassen, Linn Landrø, Caroline-Aleksi Olsson Mägi, Inge Christoffer Olsen, Knut Rudi, Carina Madelen Saunders, Marius Kurås Skram, Anne Cathrine Staff, Cilla Söderhäll, Sandra G Tedner, Sigve Aadalen, Hilde Aaneland, Björn Nordlund, Karin C Lødrup Carlsen*

Lancet 2022; 399; 2398–411

What about prevention of food allergy?



Odds Ratio 0.4 (CI 0.2-0.8)

Odds Ratio 0.4 (CI 0.2-0.8)

***Figure 3*: Risk reduction of food allergy for each primary prevention strategy**
Error bars show 95% CIs. Food allergies are presented as main effects, whereas atopic dermatitis is presented as a marginal estimate.

Lancet 2022; 399; 2398–411

Emollients/feeding for food allergy

- Overall lower rates of food allergy in study cohort than reported in in Australian cohorts (~3% vs ~10%)
- 95% breastfed at 3 months

Early solids (from 3-4 months) helps reduce food allergy

Aggressive eczema treatment with emollients does not

Lancet 2022; 399; 2398–411

The NEW ENGLAND JOURNAL of MEDICINE

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Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

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ABSTRACT

BACKGROUND

The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and peanut allergy is becoming apparent in Africa and Asia. We evaluated strategies of peanut consumption and avoidance to determine which strategy is most effective in preventing the development of peanut allergy in infants at high risk for the allergy.

METHODS

We randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age. Participants, who were at least 4 months but younger than 11 months of age at randomization, were assigned to separate study cohorts on the basis of preexisting sensitivity to peanut extract, which was determined with the use of a skin-prick test — one consisting of participants with no

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LEAP study (2015): peanut allergy

- Followed observation of much less peanut allergy in children of jewish ancestory in Israel vs UK.
- Compared early introduction of peanuts (4-11 months) against peanut avoidance (>3 years) in UK children at risk of peanut allergy (severe eczema +/- egg allergy).
- ***Peanut allergy reduced by 86%*** in early peanut exposure (1.9%) vs avoidance (13.7%) group.
- Prompted worldwide shift in infant feeding advice towards earlier introduction of solids, reduced allergen avoidance

Infant Solids

Conflicting recommendations:

- “Infants can eat pureed, mashed and semi-solid foods **beginning at 6 months”**
- “..infants exclusively breastfed until ***around 6 months”***
- “..introducing solids ***around 6 months***. There are no benefits to introducing solid foods before this time.”
- Previously “4-6 months”, since 2020 “..around 6 months (not before 4 months)”

Pediatr Allergy Immunol. 2013 Dec; 24(8): 762–771. PMCID: PMC3995010
Published online 2013 Dec 2. doi: 10.1111/pai.12153

Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: A dose-dependent relationship

Lauren Hoskin-Parr,[1] Alison Teyhan,[2] Ariel Blocker,[1] and A J W Henderson[2]

Is antibiotic use in early childhood associated with asthma?

- 4952 children UK longitudinal study new mothers (ALSPAC)
- Retrospective analysis of questionnaires completed at regular intervals from birth
- Compared antibiotic use age 0-2y and incidence of asthma, allergic rhinitis, hayfever, eczema (maternally reported)
- Atopy diagnosed as positive skin prick test (>2mm) to dust mite, grass mix or cat allergen aged 7.5y
- Headache used as control

Pediatr Allergy Immunol. 2013 Dec; 24(8): 762–771. PMCID: PMC3995010
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Antibiotic exposure in the first two years of life and development of asthma and other allergic diseases by 7.5 yr: A dose-dependent relationship

Lauren Hoskin-Parr,[1] Alison Teyhan,[2] Ariel Blocker,[1] and A J W Henderson[2]

RESULTS:

- Antibiotics in infancy were associated with asthma @ age 7.5y
- Overall odds ratio **OR 1.75** (95% CI 1.40-2.17)

- Asthma risk correlated strongly with *number* antibiotic courses:
  - 1 course: OR 1.11 (95% CI 0.84-1.48)
  - 2 courses: OR 1.5 (95% CI 1.14-1.98)
  - 3 courses: OR 1.79 (95% CI 1.34-2.40)
  - 4+ courses: **OR 2.82** (95% CI 2.19-3.63) → **~3x greater likelihood!!**

- No association with reported incidence of childhood headache

ORIGINAL ARTICLE

Antibiotic and acid-suppression medications during early childhood are associated with obesity

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2017-314971).

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ABSTRACT

Objective Gut microbiota alterations are associated with obesity. Early exposure to medications, including acid suppressants and antibiotics, can alter gut biota and may increase the likelihood of developing obesity. We investigated the association of antibiotic, histamine-2 receptor antagonist (H2RA) and proton pump inhibitor (PPI) prescriptions during early childhood with a diagnosis of obesity.

Design We performed a cohort study of US Department of Defense TRICARE beneficiaries born from October 2006 to September 2013. Exposures were defined as having any dispensed prescription for antibiotic, H2RA or PPI medications in the first 2 years of life. A single event analysis of obesity was performed using Cox proportional hazards regression.

Results 333 353 children met inclusion criteria, with 241 502 (72.4%) children prescribed an antibiotic, 39 488 (11.8%) an H2RA and 11 089 (3.3%) a PPI. Antibiotic prescriptions were associated with obesity (HR 1.26; 95% CI 1.23 to 1.28). This association persisted regardless of antibiotic class and strengthened with each additional class of antibiotic prescribed. H2RA and PPI prescriptions were also associated with obesity, with a stronger association for each 30-day supply prescribed. The HR increased commensurately with exposure to each additional medication group prescribed.

Conclusions Antibiotics, acid suppressants and the combination of multiple medications in the first 2 years of life are associated with a diagnosis of childhood obesity. Microbiota-altering medications administered in early childhood may influence weight gain.

Significance of this study

What is already known on this subject?

- Obesity has been linked to variations in the native gut microbiota.
- Several commonly prescribed paediatric medications are known to cause alterations in the native gut microbiota.
- There is conflicting evidence about the role of exposure to microbiota-altering medications and the development of childhood obesity.

What are the new findings?

- Prescriptions for antibiotics and acid-suppressing medications are associated with the development of obesity, with a stronger association noted after prolonged courses or with prescriptions to multiple antibiotic classes.
- Combinations of multiple microbiota-altering medication groups are associated with a commensurate increase in obesity.

How might it impact on clinical practice in the foreseeable future?

- These results further quantify the potential long-term risk of obesity associated with early exposure to acid-suppressing medications and antibiotics.
- The findings offer a framework for prospective research on inpatient and outpatient medication exposures and the subsequent development of obesity in paediatric patients. The recognition of modifiable risk factors for obesity is an essential step towards reducing the incidence and burden of the disease.

Antibiotics/PPIs and obesity

Do meds that alter gut microbiota effect childhood obesity rates?

- US Department of Defence Tricare database; 2006-2013
- Dispensed prescriptions in first 2 years of ***antibiotics***, ***PPIs***, ***histamine receptor antagonists*** (ranitidine)
- Correlation to childhood obesity

- Results for 333,353 eligible children
  - 72% prescribed antibiotic
  - 11% prescribed H2RA
  - 3% prescribed PPI

Stark CM, *et al*. *Gut* 2019;**68**:62–69. doi:10.1136/gutjnl-2017-314971

Antibiotics/PPIs and obesity

RESULTS:

- Early antibiotics correlate with higher childhood obesity (HR 1.26)

- Association strengthens with each additional antibiotic course
- Association strengthens with each additional antibiotic class
- Association strengthens with each additional medication type

- Highly statistically significant results

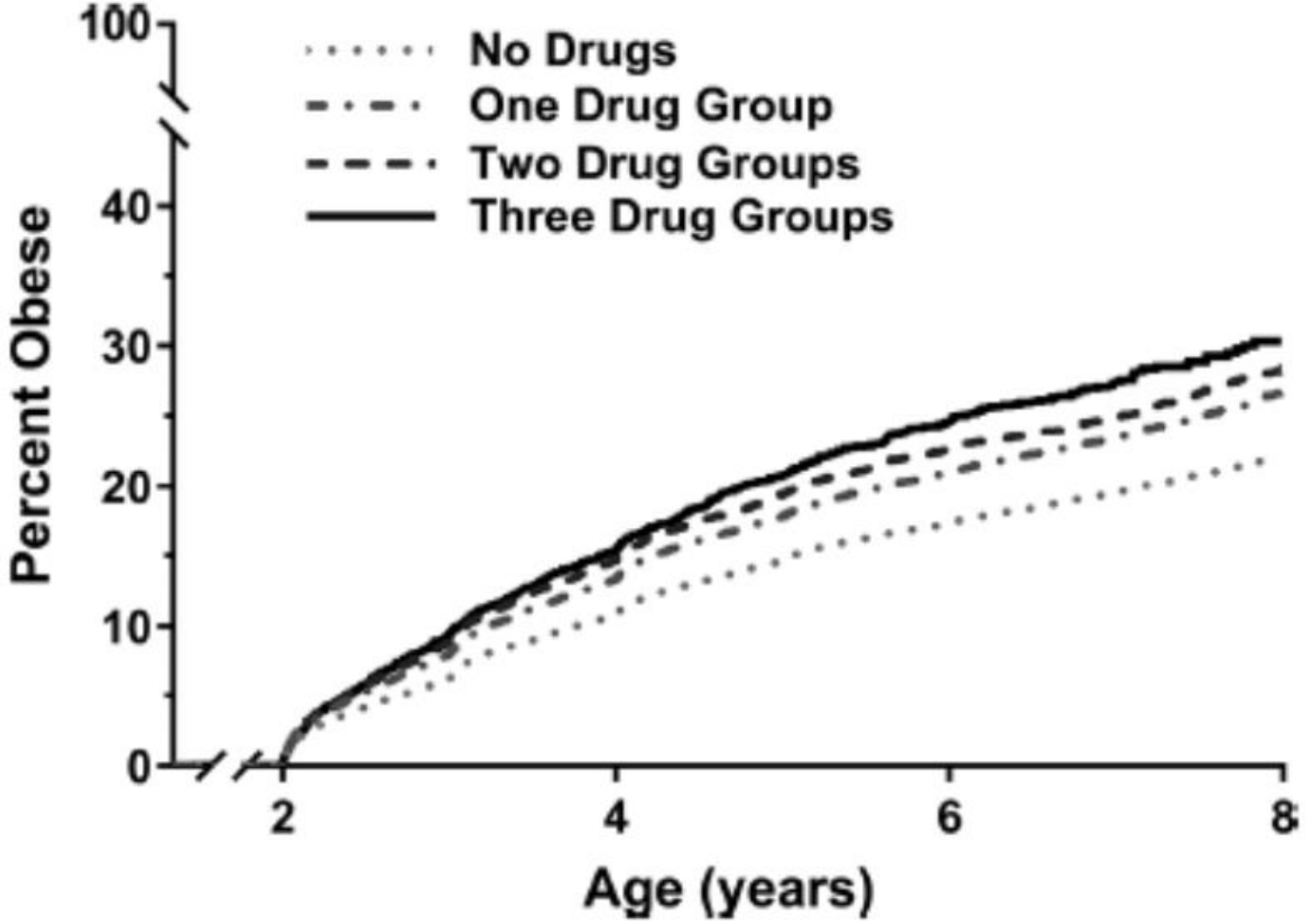
Stark CM, *et al*. *Gut* 2019;**68**:62–69. doi:10.1136/gutjnl-2017-314971

Table 3 Adjusted HRs for those prescribed histamine-2 receptor antagonists (H2RA) and antibiotics stratified by sex

	Adjusted HR (95% CI)	
	Male	**Female**
H2RA prescription	1.02 (1.01 to 1.03)	1.00 (0.98 to1.01)
Antibiotic class prescriptions		
0	Ref	Ref
1	1.13 (1.09 to 1.17)	1.12 (1.07 to 1.16)
2	1.22 (1.18 to 1.27)	1.24 (1.19 to 1.29)
3	1.31 (1.26 to 1.36)	1.36 (1.30 to 1.42)
4+	1.36 (1.30 to 1.43)	1.50 (1.42 to 1.58)

4 or more courses of antibiotics before age 2 years associated with increased risk childhood obesity of 36%

Stark CM, *et al*. *Gut* 2019;**68**:62–69. doi:10.1136/gutjnl-2017-314971


No Drugs
One Drug Group
Two Drug Groups
Three Drug Groups
Percent Obese
100
40
30
20
10
0
2
4
6
8
Age (years)

Summary

- Infant microbiome likely contributes to allergy risk
- Food exclusions in pregnancy are unnecessary
- Vaginal birth appears protective against atopy
- Breastfeeding is good (but poor allergy evidence)
- Start solids early, especially allergenic foods
- Take care with early antibiotics (atopy+obesity)
- PPIs for “colic” rarely help and are likely harmful

- Tell your friends

HealthPathways Central Coast NSW

PRIMARY HEALTH NETWORK

phn HUNTER NEW ENGLAND AND CENTRAL COAST An Australian Government Initiative

NSW GOVERNMENT Health Central Coast Local Health District

Session 3 – Allergy Take 2
Relevant HealthPathways

- Central Coast HealthPathways website – https://centralcoast.communityhealthpathways.org/ Username: centralcoast Password: 1connect
- Unsettled Infant pathway
- Adverse Food Reactions in Children pathway
- Eczema (Atopic Dermatitis) in Children pathway
- Non-urgent Paediatric Assessment referral page
- Paediatric Medical Advice referral page
- Non-urgent Immunology and Allergy Assessment referral page