CHILD Study
HELP CHILDREN GROW UP HEALTHY

DEVOTION
Developmental Origins of Chronic Diseases in Children Network

University of Manitoba

the Children's Hospital Research Institute of Manitoba

Can Breastfeeding Protect Babies From Asthma?

New results and current research from the CHILD Study

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BABY FRIENDLY MANITOBA

Manitoba Breastfeeding Rounds – June 2017

Eur Respir J 2017; 49: 1602019

ORIGINAL ARTICLE
ASTHMA

Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study

Meghan B. Azad[1,2], Lorena Vehling[1,3], Zihang Lu[4], David Dai[5], Padmaja Subbarao[4], Allan B. Becker[1,2], Piushkumar J. Mandhane[6], Stuart E. Turvey[7], Diana L. Lefebvre[5] and Malcolm R. Sears[5,8] and the CHILD Study Investigators

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@ERSpublications
When mums with asthma #breastfeed longer, their babies are less likely to wheeze
http://ow.ly/KWEk3089ZEn

Cite this article as: Azad MB, Vehling L, Lu Z, *et al.* Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study. *Eur Respir J* 2017; 49: 1602019 [https://doi.org/10.1183/13993003.02019-2016].

EDITORIAL
ASTHMA

Formula one: best is no formula

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personalized medicine

"Human breastmilk is not only a perfectly adapted nutritional supply for the infant, but probably the most specific ***personalized medicine*** *that he or she is likely to receive, given at a time when gene expression is being* ***fine tuned for life****."*

Victora et al.
The Lancet Breastfeeding Series (2016)

gairdner

LES PRIX CANADA GAIRDNER AWARDS

CESAR VICTORA, WINNER OF THE JOHN DIRKS CANADA GAIRDNER GLOBAL HEALTH AWARD

In a Brazilian town, this researcher upended conventional wisdom on breastfeeding

by Stephanie Nolen

There is a joke in the city of Pelotas, in the far south of Brazil: the average family, they say, is comprised of a mother, a father, two children – and a public health researcher. Pelotas' population is often called the world's most examined, because of a study that began in 1982, when researchers set out to track every one of the 6,011 babies born there that year. New cohorts have been enrolled every 11 years – for a total of nearly 30,000 participants – but the first group, now well into their 30s, is still regularly being visited by a field worker toting questionnaires.

Objectives

- Review previous research on the association of **breastfeeding and asthma** development
- Understand how breastfeeding **mode, duration, and exclusivity** modify the health effects of breastfeeding
- Identify **bioactive components** of human milk and describe their potential role in asthma development.
- Discuss opportunities for **healthcare providers** to support breastfeeding

Developmental Origins of…

Allergies

1 in 4 Canadians have seasonal allergies

1 in 13 have food allergies

Canadian Allergy, Asthma and Immunology Foundation & 2013 SCAAALAR survey

Asthma

1 in 6 Canadian children have asthma

Public Health Agency of Canada (2007). Life and breath: Respiratory disease in Canada.

Obesity

1 in 3 Canadian children are overweight

Overweight and obesity in children and adolescents: Results from the 2009 to 2011 Canadian Health Measures Survey

RESEARCH LETTER

JAMA Pediatrics

Wheezing Patterns in Early Childhood and the Risk of Respiratory and Allergic Disease in Adolescence

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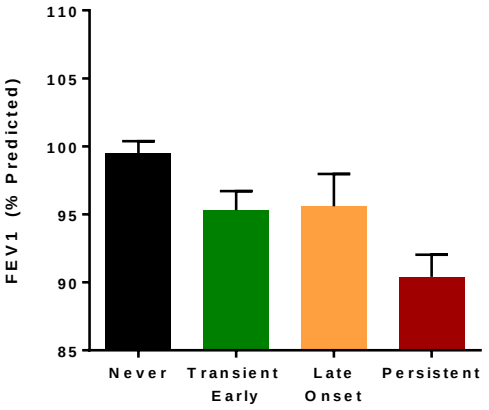
(Feb 2016)

Canadian Asthma Primary Prevention Study (CAPPS)

- 545 high-risk infants born in 1995 (Manitoba & BC)
- Prenatal randomization to multifaceted intervention
- Clinical follow up: 1, 2, 7, 15 years (N=326)



Wheezing Risk Factors

- **More** Wheeze:
  - Boys
  - Winnipeg
  - Early atopy
- **Less** Wheeze:
  - Intervention Group
  - **Exclusive breastfeeding >4m**

… HOW?

(Azad et al. JAMA Pediatrics 2016)

		Preschool Wheeze Phenotype (%)				
	N	Never	Transient Early	Late Onset	Persistent	p
Sex						
Girls	220	56.8	26.8	6.8	9.6	0.05
Boys	239	45.6	28.9	9.6	15.9	
City						
Vancouver	225	63.1	20.0	7.6	9.3	<0.001
Winnipeg	234	39.3	35.5	9.0	16.2	
Study Group						
Control	215	47.4	26.5	9.3	16.7	0.09
Intervention	244	54.1	29.1	7.4	9.4	
Maternal Atopy						
No	99	57.6	27.3	6.1	9.1	0.36
Yes	360	49.2	28.1	8.9	13.9	
Maternal Education						
< Postsecondary	103	38.8	35.0	10.7	15.5	0.05
≥ Postsecondary	356	54.5	25.8	7.6	12.1	
Household Pets						
No	301	51.2	29.6	8.0	11.3	0.45
Yes	158	50.6	24.7	8.9	15.8	
Household Smokers						
No	357	53.2	26.6	8.7	11.5	0.16
Yes	102	43.1	32.4	6.9	17.7	
Exclusive Breastfeeding						
< 4 months	289	46.4	29.8	8.3	15.6	0.03
≥ 4 months	169	59.2	24.3	8.3	8.3	
Atopy by 2 years						
No	333	54.4	29.1	7.2	9.3	0.002
Yes	116	43.1	24.1	11.2	21.6	

The Canadian Healthy Infant Longitudinal Development (CHILD) Study

*How do **genes** and the **environment** influence child health and development?*

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

AllerGen Allergy, Genes and Environment Network / le réseau des allergies, des gènes et de l'environnement

$30M	Invested
500,000	Samples: Blood, Urine, **Stool**, Nasal Swabs, Dust, **Breast Milk**
200,000	Questionnaires
3600	Families
40+	Researchers
20+	Disciplines
5(+)	Years Follow-Up
93%	Retention

www.canadianchildstudy.ca

CHILD Study

HELP CHILDREN GROW UP HEALTHY

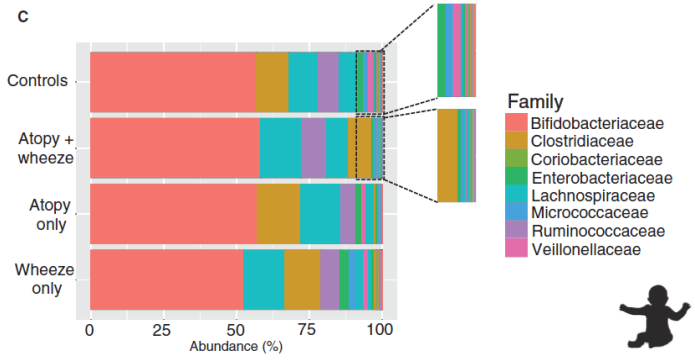
RESEARCH ARTICLE www.ScienceTranslationalMedicine.org 30 September 2015 Vol 7 Issue 307 307ra152

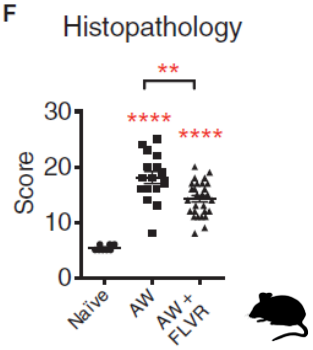
ASTHMA

Early infancy microbial and metabolic alterations affect risk of childhood asthma

Marie-Claire Arrieta,[1,2]* Leah T. Stiemsma,[2,3]* Pedro A. Dimitriu,[2] Lisa Thorson,[1] Shannon Russell,[1,2] Sophie Yurist-Doutsch,[1,2] Boris Kuzeljevic,[3] Matthew J. Gold,[4] Heidi M. Britton,[1] Diana L. Lefebvre,[5] Padmaja Subbarao,[6,7] Piush Mandhane,[8,9] Allan Becker,[10] Kelly M. McNagny,[4] Malcolm R. Sears,[5] Tobias Kollmann,[3,11] the CHILD Study Investigators,† William W. Mohn,[2] Stuart E. Turvey,[3,11‡§] B. Brett Finlay[1,2,12‡§]

"Infants at risk of asthma exhibited transient gut microbial dysbiosis during the **first 100 days of life."**



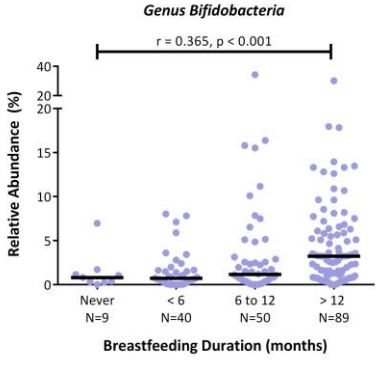


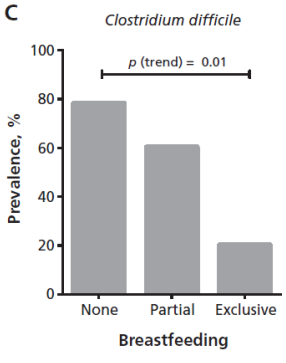
DOI: 10.1111/1471-0528.13601
www.bjog.org
BJOG An International Journal of Obstetrics and Gynaecology

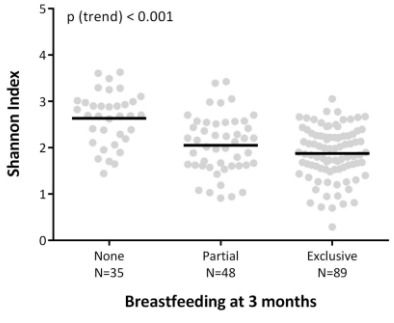
Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study

MB Azad,[a,b] T Konya,[c] RR Persaud,[d] DS Guttman,[e] RS Chari,[f] CJ Field,[g] MR Sears,[h] PJ Mandhane,[a] SE Turvey,[i] P Subbarao,[j] AB Becker,[b] JA Scott,[c] AL Kozyrskyj,[a] the CHILD Study Investigators†

Breastfeeding favours:
↑ *Bifidobacteria*, ↓ *Clostridium difficile*, ↓↑ Diversity…







Developmental Origins of CHILD HEALTH & Disease

Meghan Azad, PhD

Breastfeeding

Mechanisms
- Gut Microbiota
- Epigenetics
- Metabolism
- Lung Function
- Immunity

Allergies, Asthma, Obesity, Diabetes, Cognitive Development…

Milk Composition
- Microbiota
- Oligosaccharides
- Immune Factors
- Nutrients
- Hormones
- Toxins

Interventions

Maternal Factors

Modifiable: Obesity, Nutrition, Self-Efficacy, Smoking, Birth Mode, Pro/Antibiotics… **Fixed:** Age, Ethnicity, Genetics, Parity, Asthma…

DEVOTION

UNIVERSITY OF MANITOBA

Research Questions

1) DOES breastfeeding protect against asthma?
- *Optimal dose, duration…?*

2) HOW does breastfeeding protect against disease?
- *Milk bioactives? Epigenetics? Self regulation? Physical exercise? Psychosocial effects?*

3) Why do effects **VARY** between mothers? studies?
- *Variation in milk? Feeding modes? Definitions? Analyses?*

4) How can we **SUPPORT** mothers to achieve their breastfeeding goals?

Breastfeeding & Asthma

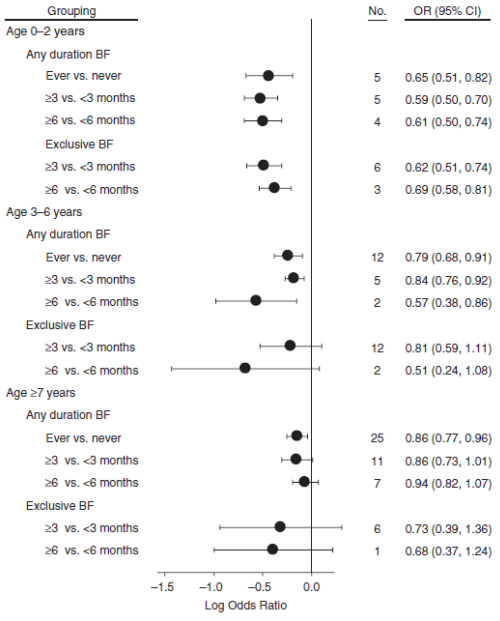
~30% reduced risk of "asthma" before 6 years

117 Studies

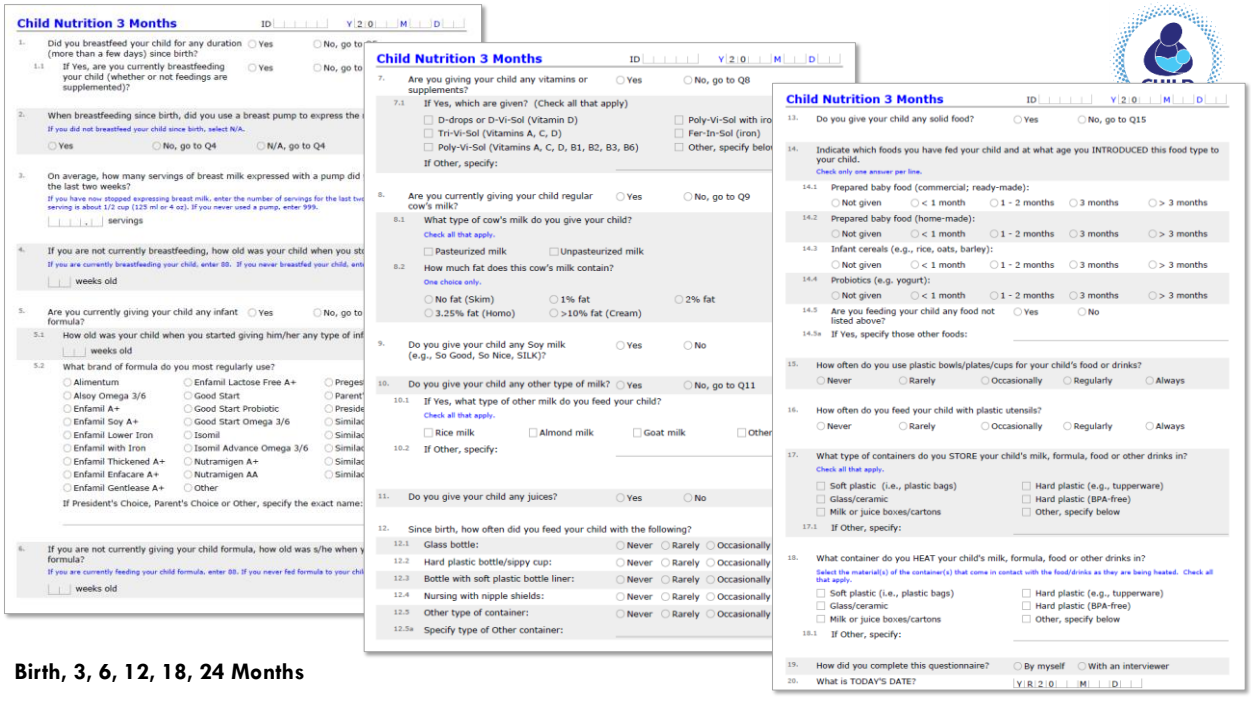
Inconsistent Evidence

Limitations of previous studies:

- Defining breastfeeding
- Defining asthma
- High drop out rates
- Short follow up
- Confounding factors

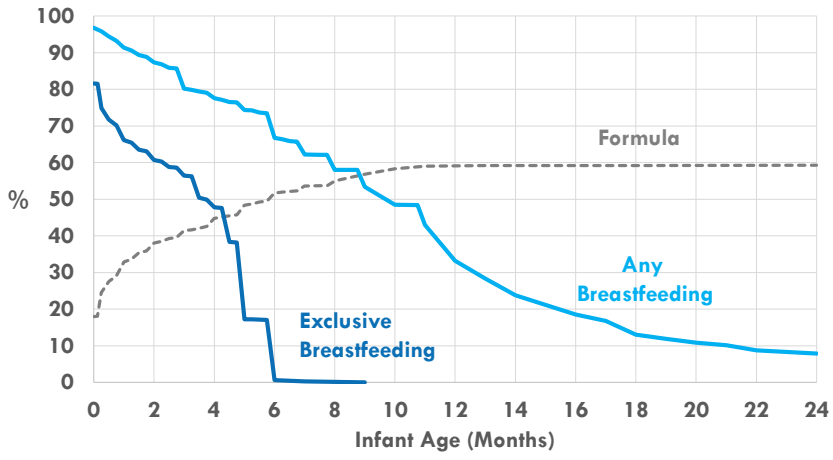


(Dogaru et al. *AJE* 2013)



Birth, 3, 6, 12, 18, 24 Months

Breastfeeding in the CHILD Study



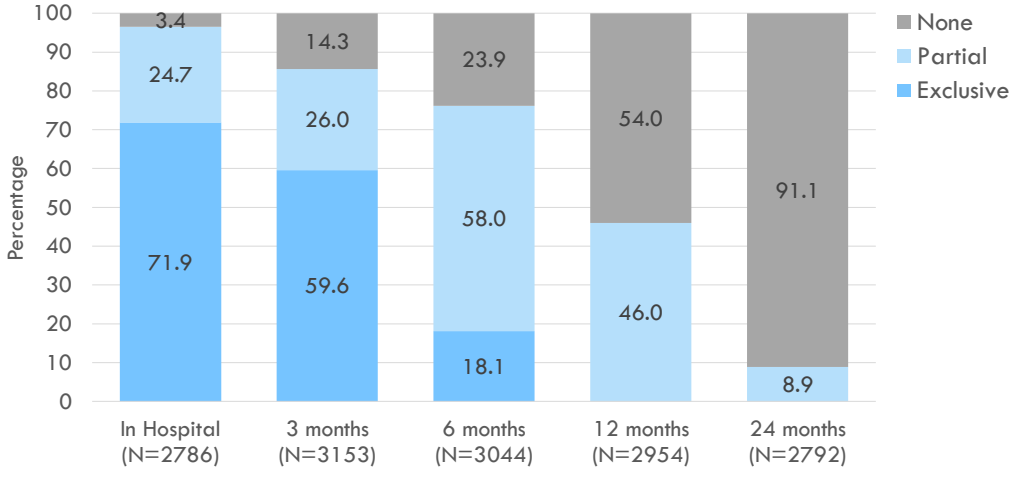
World Health Organization

Recommends:
Exclusive BF to **6 mos**
Continued BF to **2 yrs+**

N=3139 (Formula), 3159 (Any BF), 3057 (Exclusive BF)

(Vehling, Azad et al. Unpublished)

Breastfeeding in the CHILD Study



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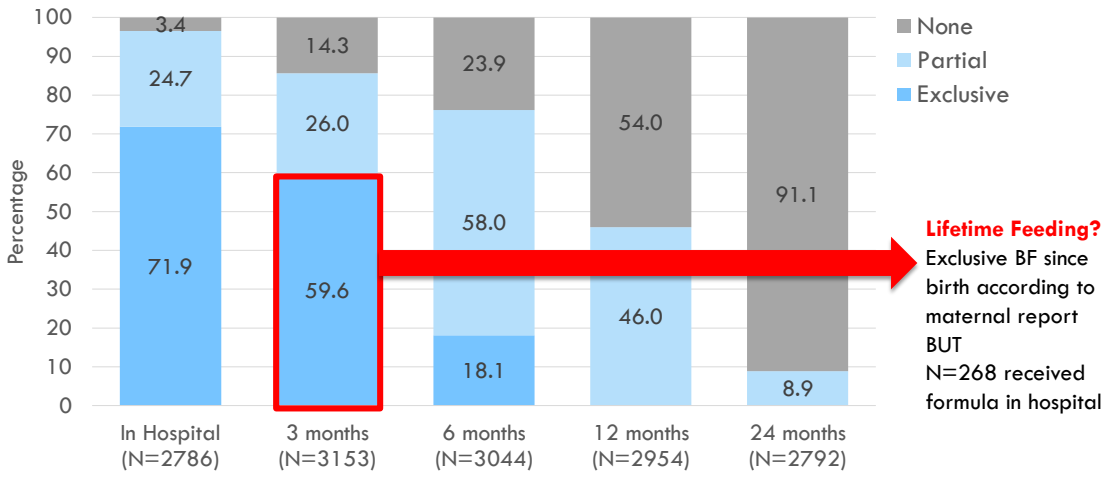
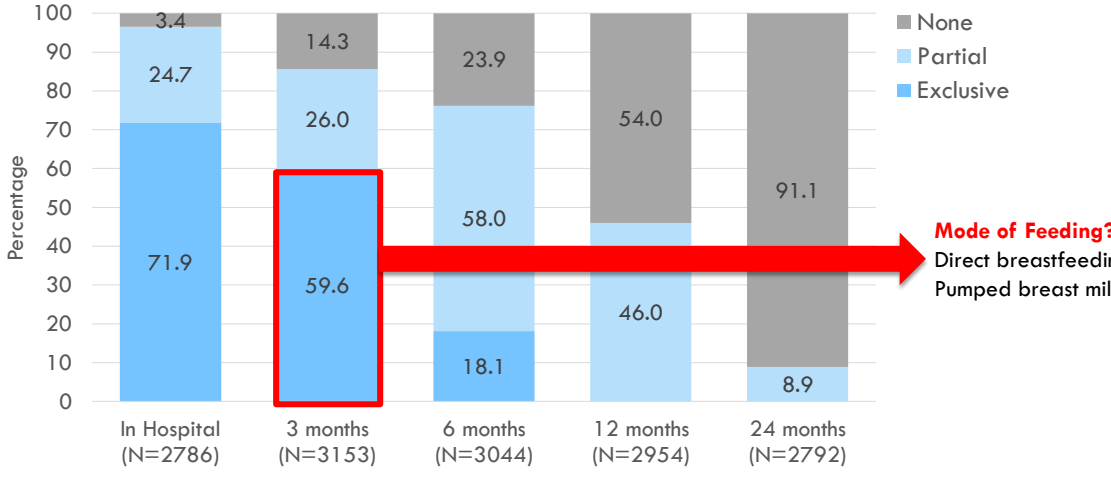


Lifetime Feeding?
Exclusive BF since birth according to maternal report
BUT
N=268 received formula in hospital

(Vehling, Azad et al. Unpublished)

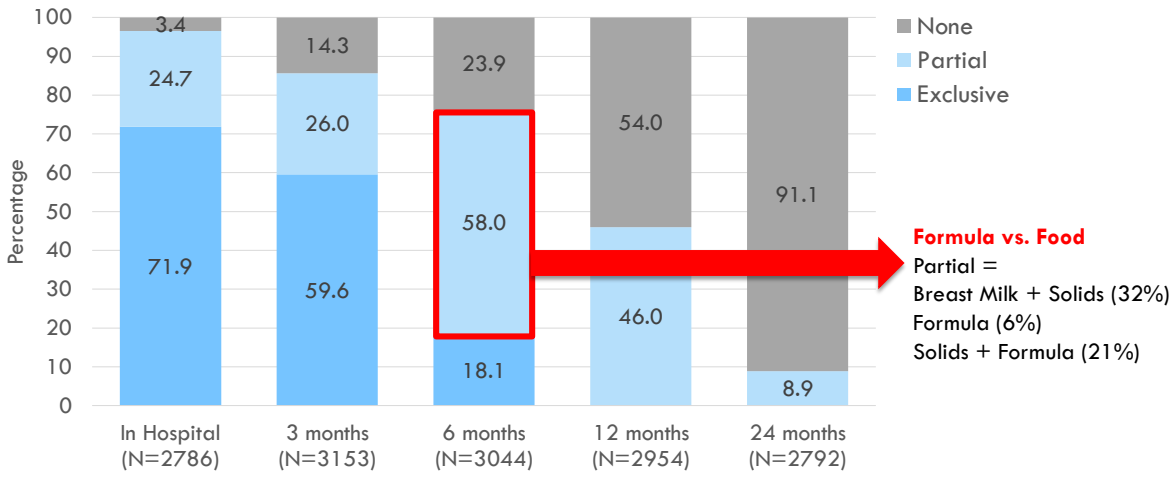
Breastfeeding in the CHILD Study



Mode of Feeding?
Direct breastfeeding?
Pumped breast milk?

(Vehling, Azad et al. Unpublished)

Breastfeeding in the CHILD Study



(Vehling, Azad et al. Unpublished)

Eur Respir J 2017; 49: 1602019

Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study

Meghan B. Azad[1,2], Lorena Vehling[1,3], Zihang Lu[4], David Dai[5], Padmaja Subbarao[4], Allan B. Becker[1,2], Piushkumar J. Mandhane[6], Stuart E. Turvey[7], Diana L. Lefebvre[5] and Malcolm R. Sears[5,8] and the CHILD Study Investigators

N=2773 Canadian infants from the CHILD Study

- **21%** of mothers had asthma
- **46%** breastfed >12 months
- **21%** of infants wheezed in 1st year

Less Breastfeeding & More Infant Wheezing:

- Smokers (mother or others in household)
- Lower maternal education
- Young mothers (<25 years)
- Lower gestational age (<37 weeks)

→ Analysis controlled for these confounders

Eur Respir J 2017; 49: 1602019

Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study

Meghan B. Azad[1,2], Lorena Vehling[1,3], Zihang Lu[4], David Dai[5], Padmaja Subbarao[4], Allan B. Becker[1,2], Piushkumar J. Mandhane[6], Stuart E. Turvey[7], Diana L. Lefebvre[5] and Malcolm R. Sears[5,8] and the CHILD Study Investigators

Among infants born to mothers with asthma, breastfeeding associated with **significantly reduced risk of infant wheezing**, after controlling for maternal smoking, education, age, etc.

DOSE EFFECTS: stronger association with **longer** / more **exclusive** breastfeeding:
- **62%** reduced risk with 6 months exclusive BF
- **37%** with partial BF (without formula)

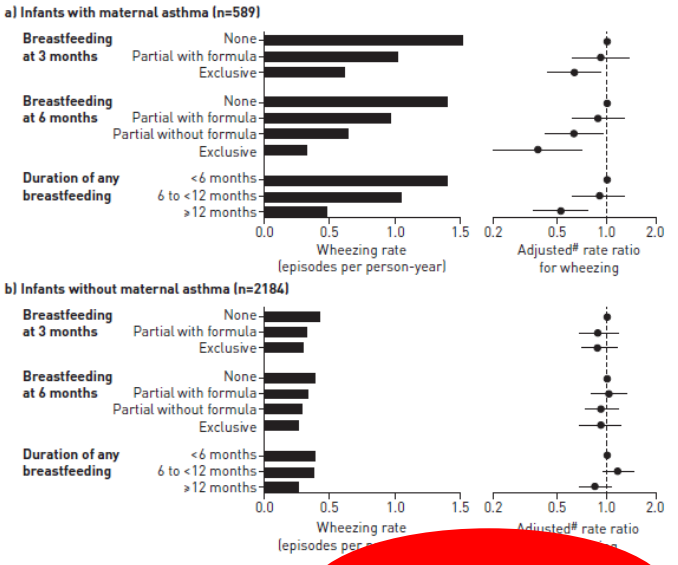


FIGURE 1 Breastfeeding and wheezing rates [illegible] Longitudinal Development (CHILD) Study, for [illegible] maternal asthma (n=2184). Among infants born [illegible] lower with increasing breastfeeding exclusivity [illegible] maternal age, postsecondary education, ethnicity, smoki[illegible] site; [illegible] age.

Asthma?
Ages 3 & 5 years

Eur Respir J 2017; 49: 1700105

EDITORIAL ASTHMA

Formula one: best is no formula

Andrew Bush[1,2] and Adnan Custovic[2]

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"We are facing an **Armageddon** of COPD death…"

"The **public health implications** are stark.

The extent of use of formula feeds described in this study is nothing short of a **disgrace.**

Although it is clear that there are some women who cannot breast feed for the best of medical reasons… there is **no reason at all** why more than half these mothers did not breast feed for more than a year.

Women with asthma need to **understand the benefits to their child of avoiding formula.**

Would it be too radical to suggest formula milk should be made **prescription only** for children of asthmatic mothers? Perhaps, but something needs to be done; and that effectively and soon."

Research Questions

1) **DOES** breastfeeding protect against asthma?
   - *Optimal dose, duration…?*

2) **HOW** does breastfeeding protect against disease?
   - ***Milk bioactives?*** *Epigenetics? Self regulation?* ***Physical exercise****? Psychosocial effects?*

3) Why do effects **VARY** between mothers? studies?
   - *Variation in milk? Feeding modes? Definitions? Analyses?*

4) How can we **SUPPORT** mothers to achieve their breastfeeding goals?

Physical Exercise: Breast vs. Bottle

- ↓ Rate of swallowing, interruption of breathing
- ↑ Negative pressure (98 mmHg; 3x higher)
- ↑ Sucking exercise (8 min; 2x longer)
- ↑ Ventilator efforts
- ↑ Lung capacity

Mizuno et al. *Pediatr Res* 2006
Miller et al. *Pediatr Res* 1995
Goldfield et al. *Pediatr Res* 2006
Koenig et al. *J Appl Physiol* 1990
Ogbuanau et al. *Paediatrics* 2009

Nature's first functional food

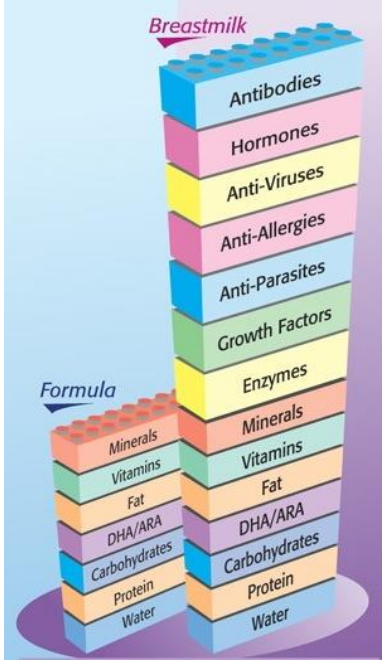
Breast milk feeds helpful microbes, fights harmful ones, provides immunity, and jump-starts a newborn's life

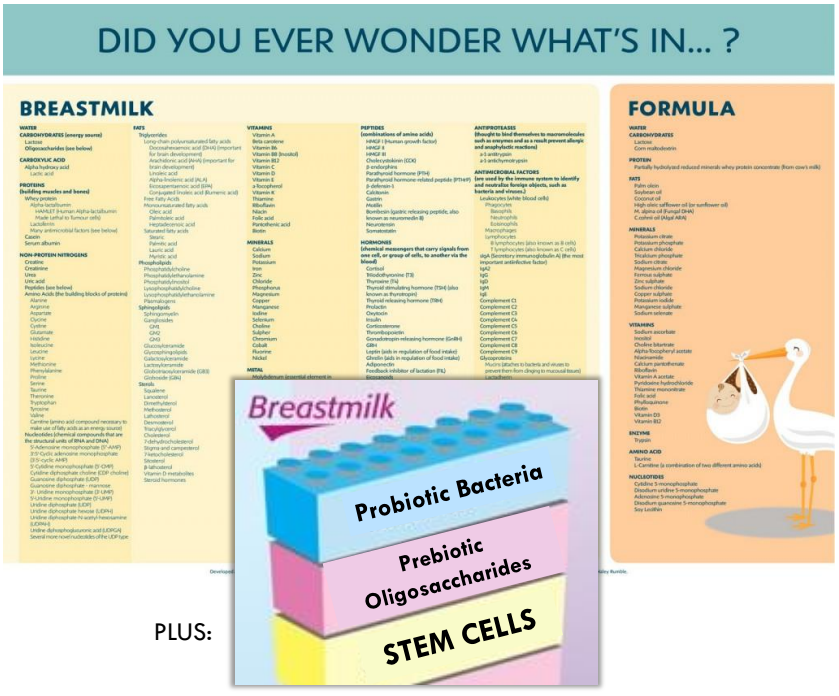
ing explored once again. Sor
have focused on making bet
microbiome fostered by milk
have documented how bre
more than feed a newborn
bacteria. Mother's milk als

SCIENCE 15 AUGUST 2014 • VOL 345 ISSUE 6198

"Milk is really a genius fluid that was outrageously understudied. If we can identify components of human breast milk that are important, then we can understand the wisdom of milk–and take advantage of them."

David Mills, UC Davis



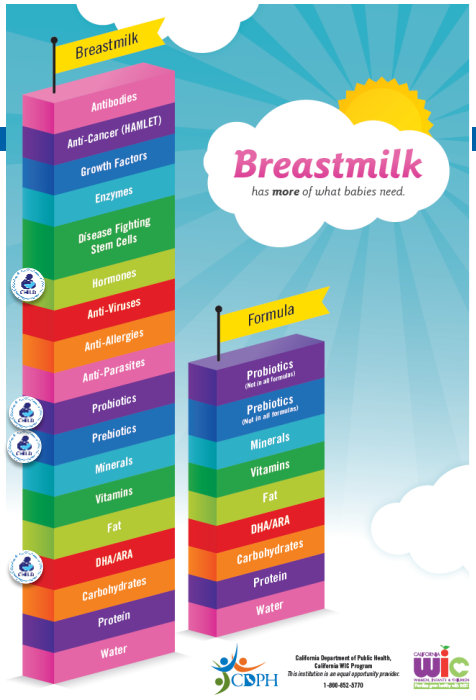


Milk Bioactives

CHILD Breast Milk (N~2800):
- 1 sample per mother
- Mix of fore + hind milk, multiple feeds
- Median lactation = 16 weeks (IQR 14-19)

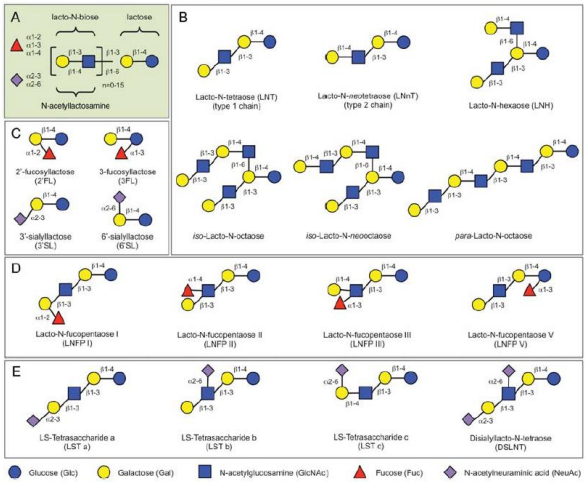
Representative Subset (N=430):

- **Fatty Acids** (C. Field, U. Alberta)
- **Endocrine Hormones** (C. Field, U. Alberta)
- **Microbiota** (E. Khafipour, U. Manitoba)
- **Oligosaccharides** (L. Bode, UC San Diego)
- **Wish list**: Toxins/Chemicals, Food antigens, Artificial Sweeteners, Cytokines…

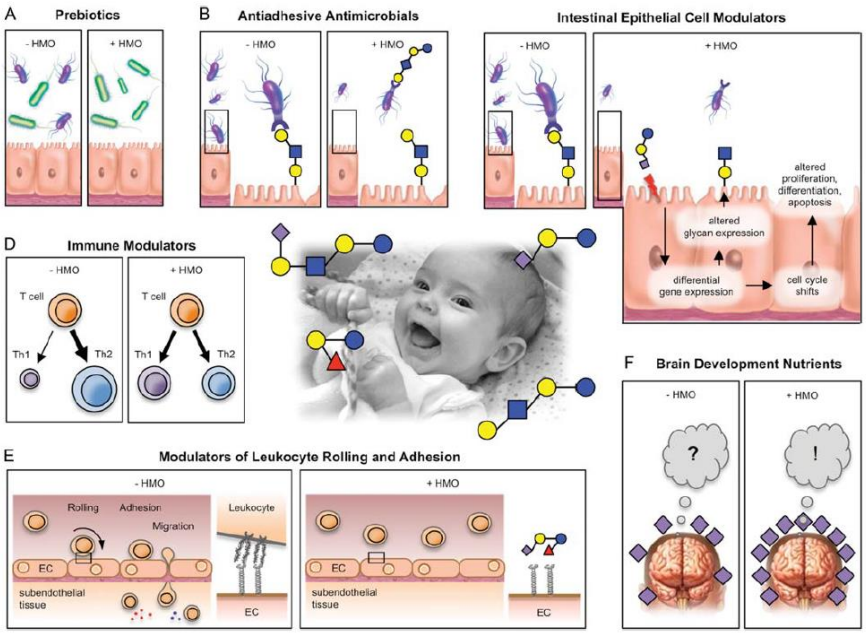


Human Milk Oligosaccharides (HMOs)

- Non-digestible carbohydrates
- Structurally diverse
  Cows: ~40 vs. Humans: >100
- Highly variable between mothers
- Small studies (N<50):
  - Possible associations with HIV transmission, allergy, infant adiposity
  - Maternal determinants (besides genetics) **unknown**



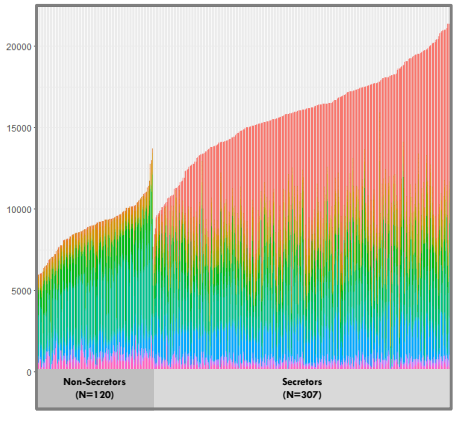
(Bode Glycobiology 2012 –"Every baby needs a sugar mama")



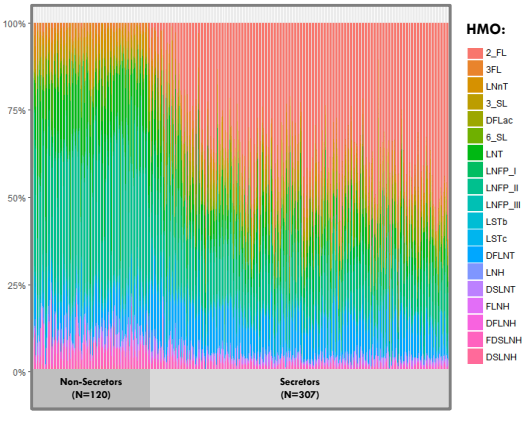
(Bode Glycobiology 2012 –"Every baby needs a sugar mama")

HMOs in the CHILD Cohort

Absolute HMO Concentration (nmol/mL)

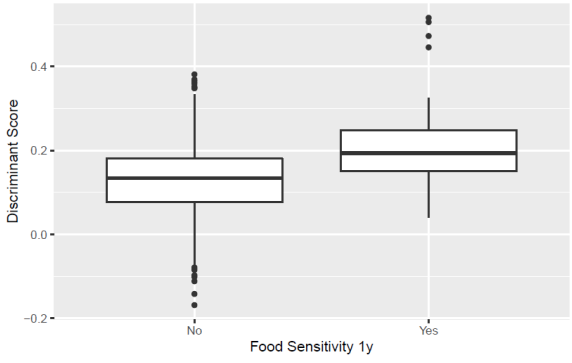


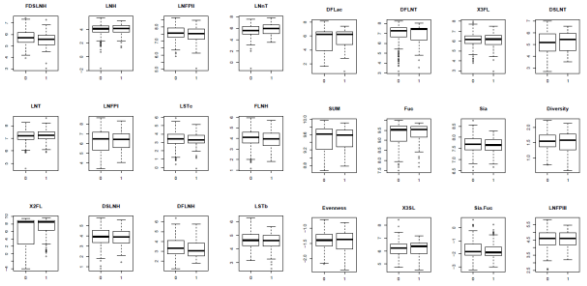
Relative HMO Composition (%)



(Azad, Bode, Robertson, et al. Unpublished)

HMOs & Allergy?





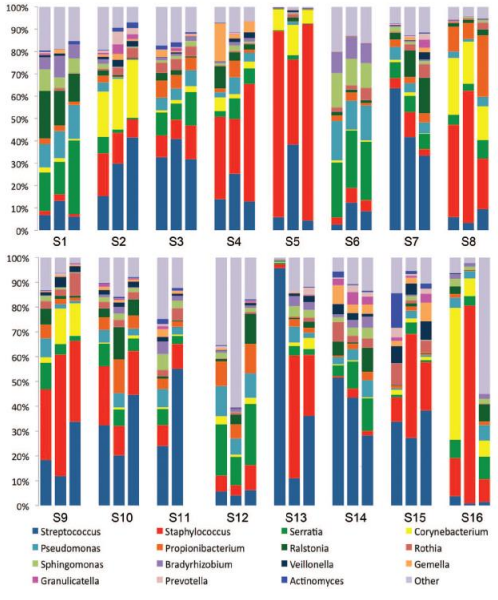
While no <u>single</u> HMO predicts food sensitization, the **<u>overall HMO profile</u>** is significantly associated with food sensitization.

N=430 dyads; 19 HMOs
Partial Least Squares Discriminant Analysis (PLS-DA) **P<0.001**
(robust to leave-one-out cross validation)

(Azad, Sharma, Bode et al. Unpublished)

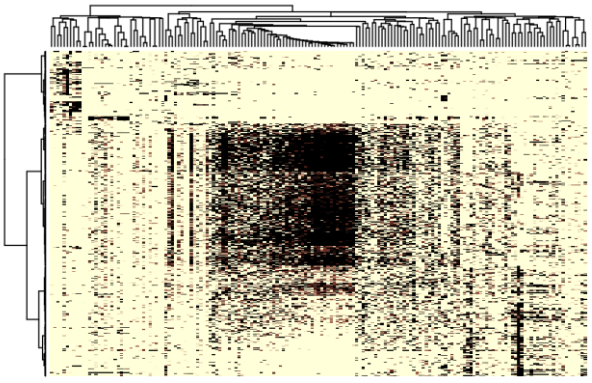
Milk Microbiota

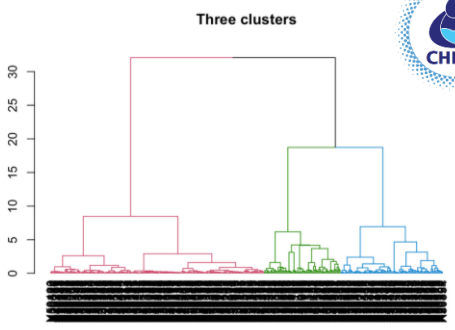
- Human milk is not sterile!
  - Breastfed infants consume 10^5–10^7 bacteria daily.
- Source of gut microbiota
  - Many health effects…
- A few small studies (N < 30):
  - Variation by birth mode, obesity, time postpartum, gestational age, genetics, country… **???**
  - **None** examined infant health

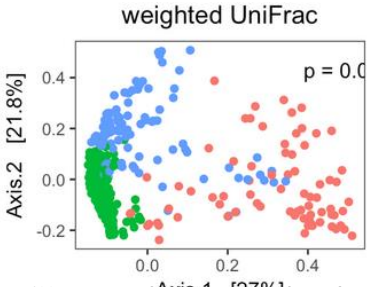


(Hunt et al. PLOS One 2011)

Milk Microbiota Clusters?







(Moossavi, Khamposun, Azad et al. Unpublished)

Research Questions

1) DOES breastfeeding protect against allergy, asthma, obesity…?

- *Optimal dose, duration…?*

2) HOW does breastfeeding protect against disease?

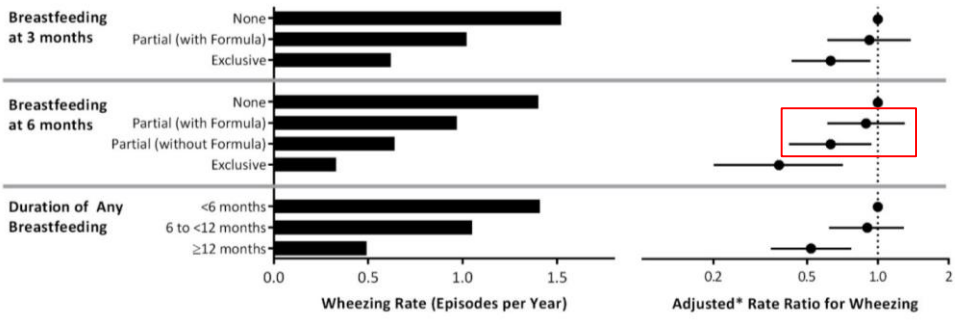
- *Milk bioactives? Epigenetics? Self regulation? Psychosocial effects?*

3) Why do effects **VARY** between mothers? studies?

- *Variation in Milk Composition? Feeding Modes? Definitions? Analyses?*

4) How can we **SUPPORT** mothers to achieve their breastfeeding goals?

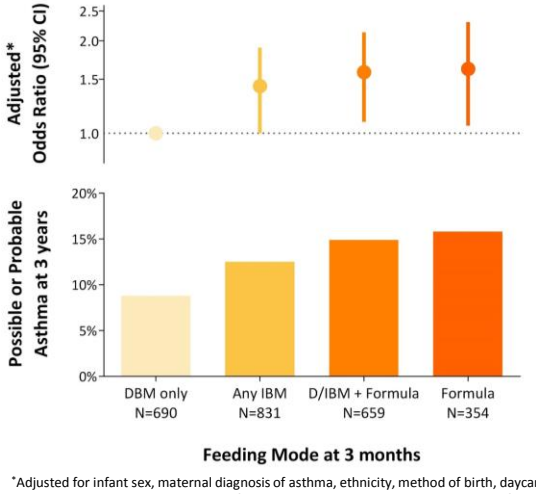
Variation in "Breastfeeding" Definitions



*Adjusted for maternal age, ethnicity, asthma, smoking during pregnancy, postsecondary education; and gestational age.

(Azad et al. *European Respiratory Journal*, 2017)

Variation in Mode of Breastmilk Feeding



*Adjusted for infant sex, maternal diagnosis of asthma, ethnicity, method of birth, daycare attendance, gestational age and solid food introduction; with multiple imputation of missing data.

DBM = Direct Breast Milk
IBM = Indirect (pumped) Breast Milk

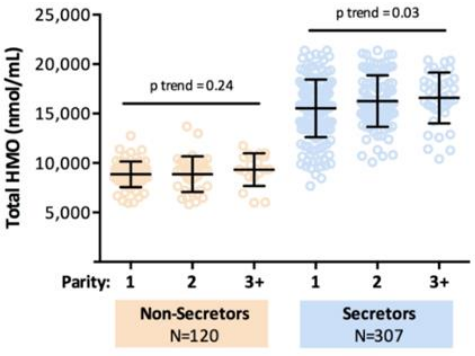
Compared to direct breastfeeding, **<u>any other mode of infant feeding</u>** was associated with an **<u>increased risk</u>** of possible or probable asthma by 3 years of age.

- Bioactivity of milk?
- Physical lung exercise?
- Skin-to-skin contact?
- Infant→Mother signalling?
- Toxins from plastic bottles?

(Klopp et al. submitted)

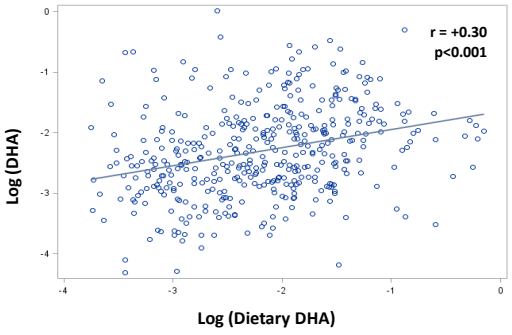
Variation in Milk Oligosaccharides, Fatty Acids…

Total HMOs & Parity



(Azad, Robertson, Bode et al. Unpublished)

Maternal DHA Intake & Milk DHA



(Azad, Sinnock et al. Unpublished)

Research Questions

1) DOES breastfeeding protect against asthma…?

- *Optimal dose, duration…?*

2) HOW does breastfeeding protect against disease?

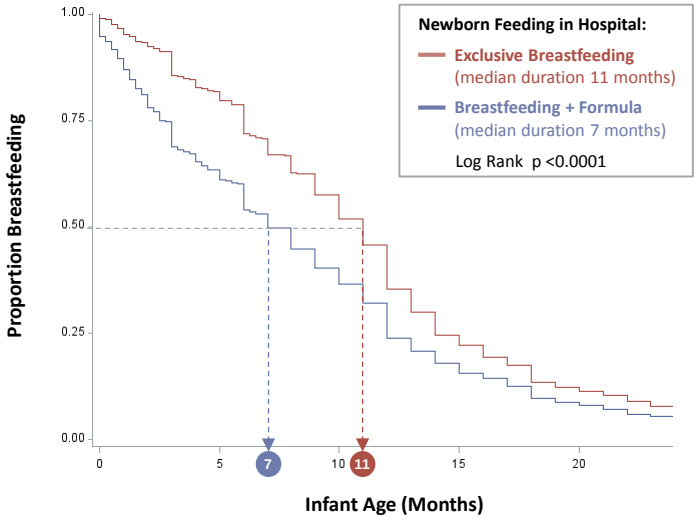
- *Milk bioactives? Epigenetics? Self regulation? Physical exercise? Psychosocial effects?*

3) Why do effects **VARY** between mothers? studies?

- *Variation in Milk Composition? Feeding Modes? Definitions? Analyses?*

4) How can we **SUPPORT** mothers to achieve their breastfeeding goals?

Supporting Breastfeeding



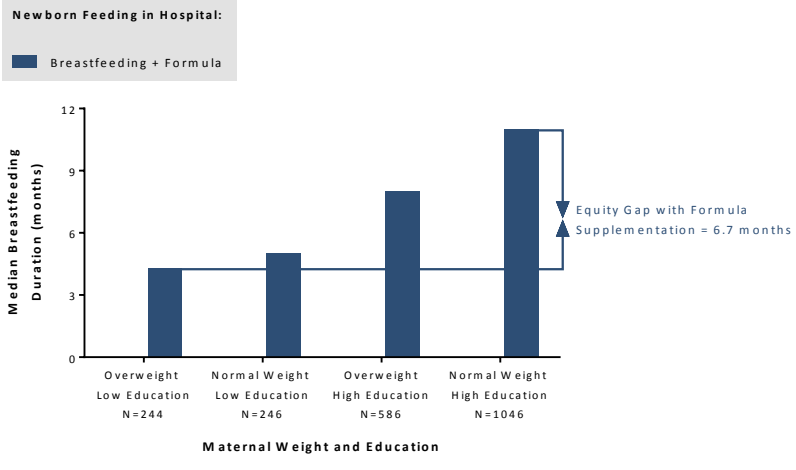
Compared to newborns who received formula supplementation, those who were exclusively breastfed in hospital had a **21% reduced risk** of breastfeeding cessation over time. (HR 0.79; 95%CI: 0.72-0.88)

Accredited as Baby Friendly by unicef

(Vehling et al. Submitted)

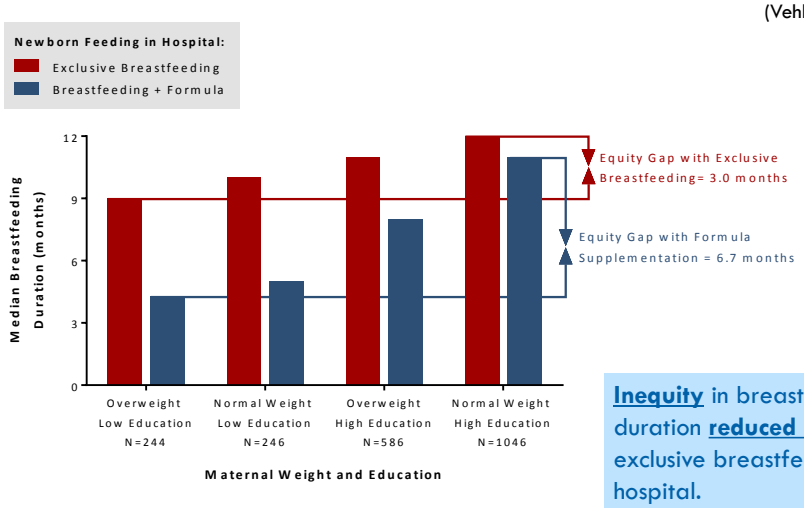
Newborn Feeding & Breastfeeding (in)Equity

(Vehling, Azad et al. Submitted)



Newborn Feeding & Breastfeeding (in)Equity

(Vehling, Azad et al. Submitted)

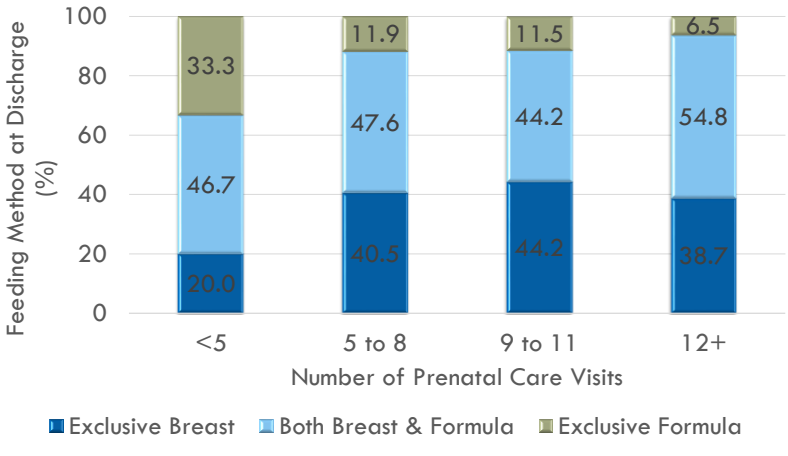


Inequity in breastfeeding duration **reduced by 55%** with exclusive breastfeeding in hospital.

Prenatal Care & Newborn Feeding

Chart review:
N=147 mother-infant dyads at HSC Winnipeg

Lower breastfeeding rates among women attending <5 prenatal care visits



Any Breastfeeding: P-trend = 0.036*
Any Formula Feeding: P-trend = 0.340

(Coneys, Azad et al. Unpublished)

Developmental Origins of CHILD HEALTH & Disease

Meghan Azad, PhD

DEVOTION

Developmental Origins of Chronic Diseases in Children Network

University of Manitoba

Breastfeeding

Mechanisms
- Gut Microbiota
- Epigenetics
- Metabolism
- Lung Function
- Immunity

Allergies, Asthma, Obesity, Diabetes, Cognitive Development…

Milk Composition
- Microbiota
- Oligosaccharides
- Immune Factors
- Nutrients
- Hormones
- Toxins

Interventions

Maternal Factors

Modifiable: Obesity, Nutrition, Self-Efficacy, Smoking, Birth Mode, Pro/Antibiotics… **Fixed:** Age, Ethnicity, Genetics, Parity, Asthma…

Objectives

- Review previous research on the association of **breastfeeding and asthma** development
  - *Protective. Limitations addressed by CHILD study.*
- Understand how breastfeeding **mode, duration, and exclusivity** modify the health effects of breastfeeding
  - *Dose effects. Mode matters. Formula (not food) diminishes benefits.*
- Identify **bioactive components** of human milk and describe their potential role in asthma development.
  - *Nutrients, microbiota, oligosaccharides... Highly variable. Fixed & modifiable factors.*
- Discuss opportunities for **healthcare providers** to support breastfeeding
  - *Prenatal (community) and early postpartum (hospital)*

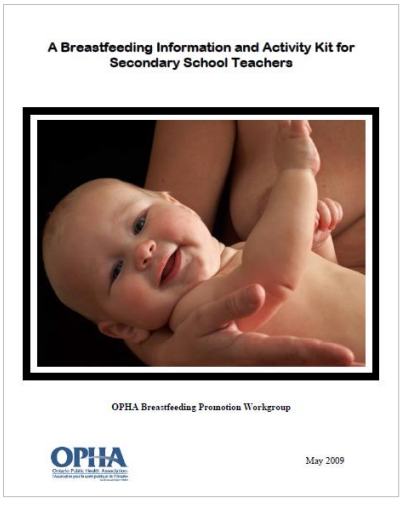
New Project!

"Breastfeeding is the responsibility of a **society**, not an individual woman."

– Cesar Victora, Gairdner Laureate

https://www.unicef.org.uk/babyfriendly/baby-friendly-resources/video/call-to-action-video/

Breastfeeding Education in Manitoba Schools



Ideas?

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National: Malcolm Sears, Diana Lefebvre (McMaster) & Team

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Catherine Field, Sue Goruck (U. Alberta)
Lars Bode, Bianca Robertson (U. California San Diego)
Nathan Nickel (Manitoba Centre for Health Policy / U. Manitoba)

Questions?