THE UNIVERSITY OF ARIZONA
College of Medicine
Tucson

Developmental Origins of Asthma

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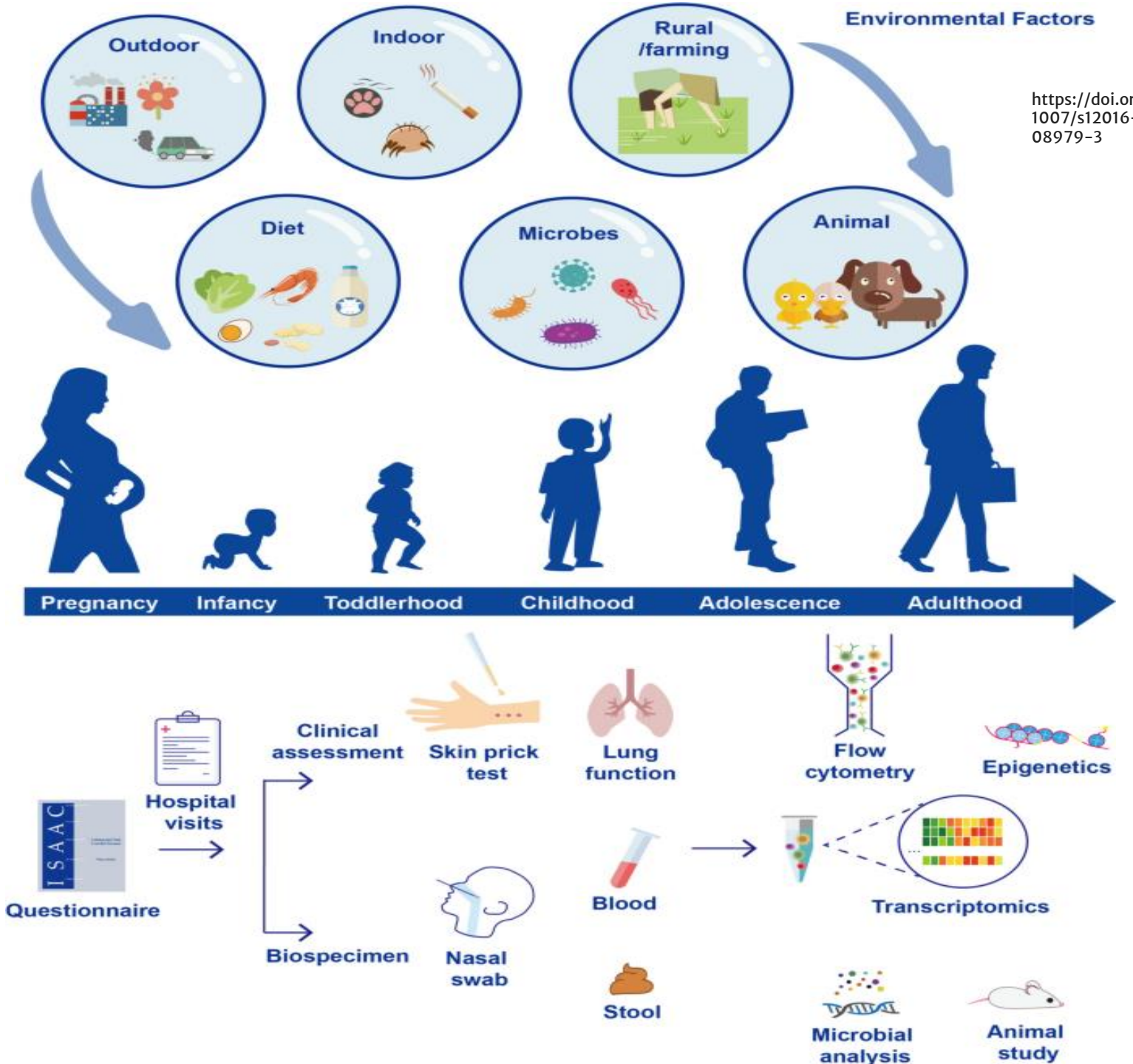
Disclosures

I have nothing to disclose as a conflict of interest

Goals

1. Be familiar with what birth cohort studies have taught us about asthma's origins
2. Know what the asthma predictive index is and how to use it
3. Understand the genetics of asthma development
4. Know what the clean hygiene hypothesis is and how microbes play a role in asthma development

Birth cohorts

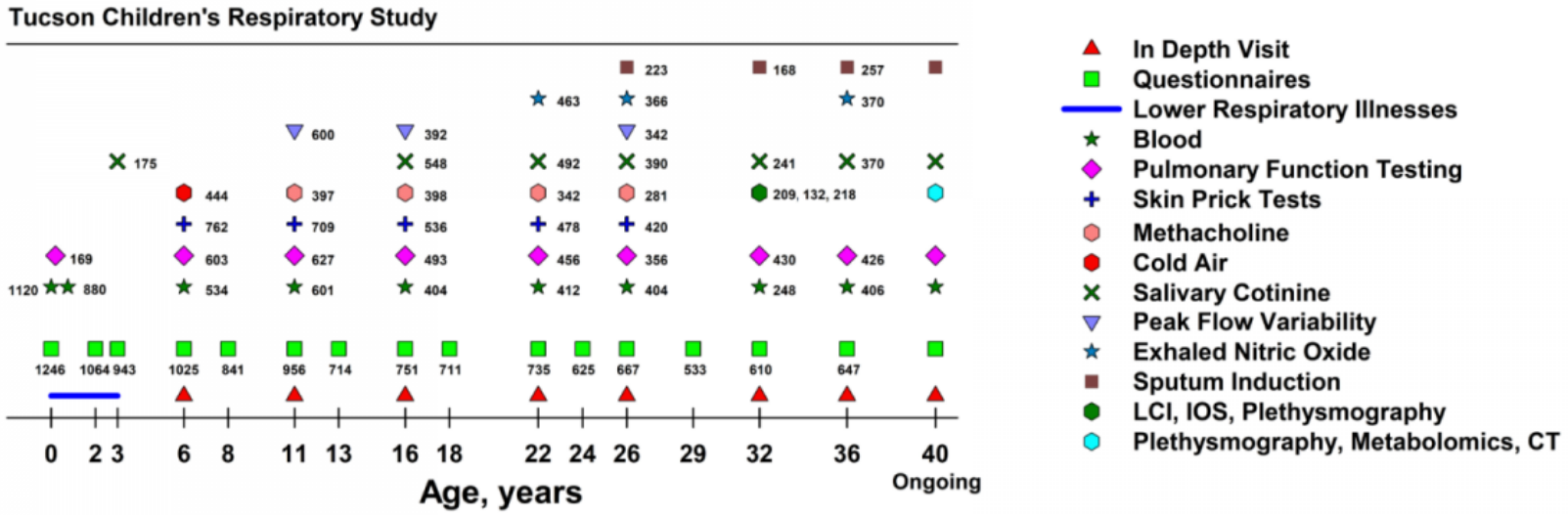


https://doi.org/10.1007/s12016-024-08979-3

Tucson Childrens Respiratory Study

- enrolled 1246 healthy newborns between 1980 to 1984, and followed these children from birth till now and these adults are now in their 4th decade of life
- to delineate the complex interrelationships between a large number of potential risk factors, acute lower respiratory tract illnesses, and chronic lung disorders later in childhood and early adult life, especially asthma.
- Nine hundred seventy-four (78%) of the original subjects are still being followed

Longitudinal data collection and numbers of participants with each data type.



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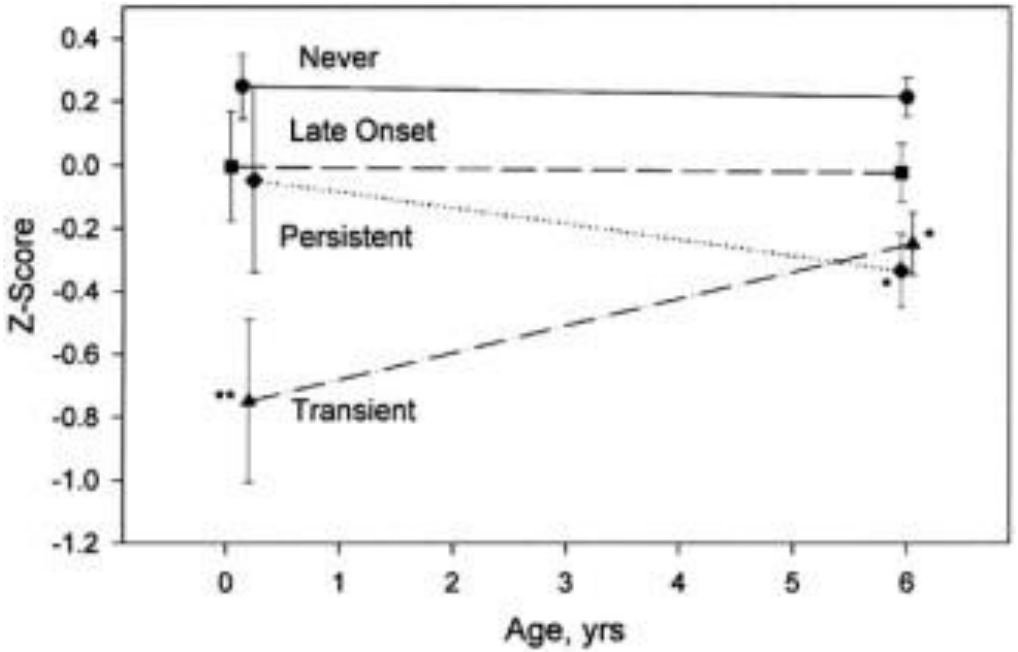
TCRS

- described various wheezing disorders (transient, nonatopic, atopic) and their characteristics
- evaluated many risk factors for acute respiratory tract illnesses during the first 3 years of life
- Identified sensitization to *Alternaria* and wheezing illnesses related to respiratory syncytial virus (RSV) as major risk factors for asthma
- loss of lung function already occurred in the first 6 years of life in those children who were persistent wheezers
- developed an Asthma Predictive Index



Modified Asthma Predictive Index (mAPI)

≥4 Wheezing Illnesses *and*

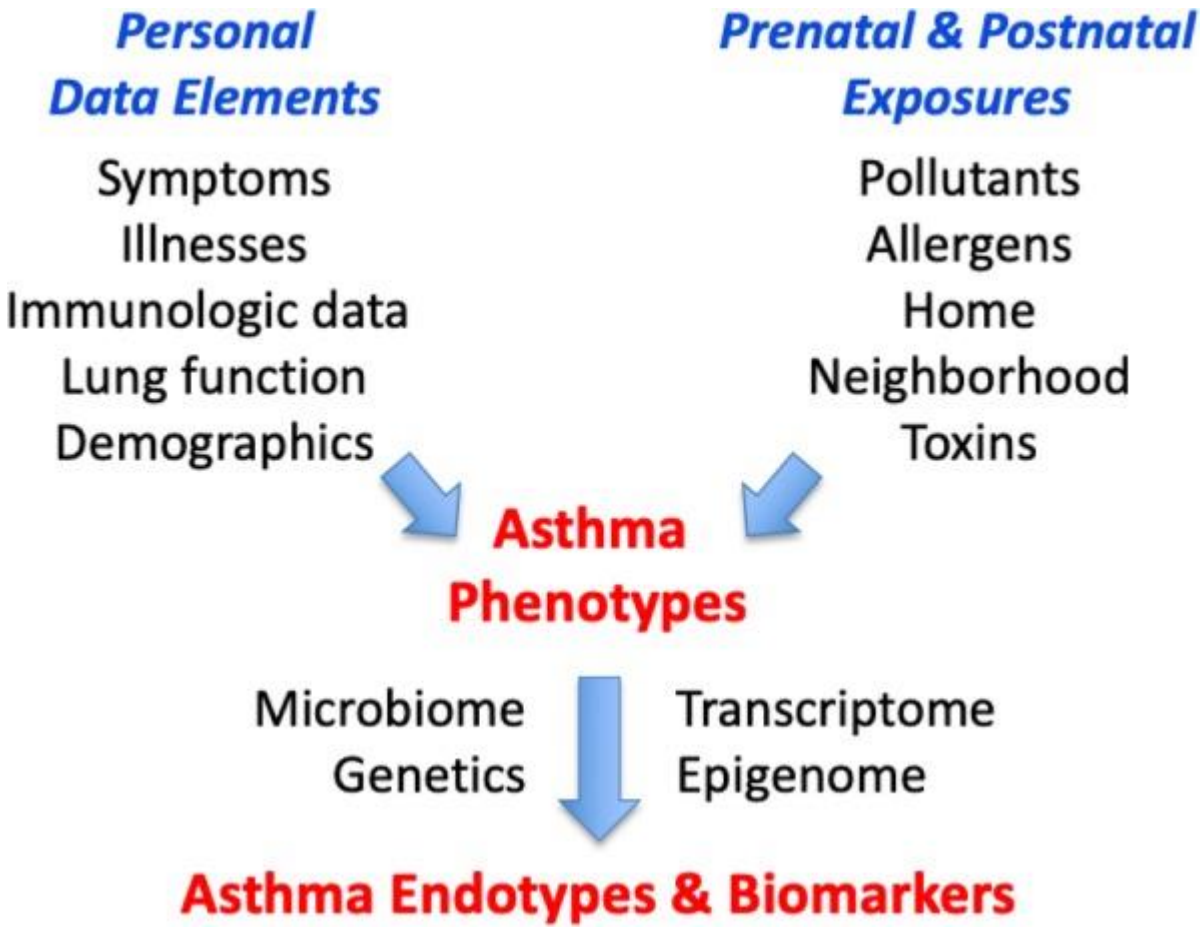
≥1 Major criteria		≥2 Minor criteria
-Parental asthma		-Food sensitization
-Atopic dermatitis (MD diagnosed)	*OR*	-Peripheral blood eosinophils ≥4%
-Aeroallergen sensitization		-Wheezing apart from colds

Birth Cohorts

- SAGE: Study of Asthma, Genes and the Environment
- INSPIRE: Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure
- COAST: Childhood Origins of Asthma
- COPSAC: Copenhagen Prospective Studies on Asthma
- MAAS: Manchester Asthma and Allergy study
  ALSPAC: Avon Longitudinal Study of Parents and Children
- CAS: Childhood Asthma Study
- COAST: Childhood Origins of Asthma
- COCOA: Cohort for Childhood Origin of Asthma and allergic diseases
- DCHS,: Drakenstein Child Health Study
- GUSTO: Growing Up in Singapore Towards healthy Outcomes
- JECS: Japan Environment and Children's Study, Japan
- MARC-30/35/43, the 30th/35th/43rd Multicenter Airway Research Collaboration
- PACAAS: Perth Childhood Acute Asthma Study
- PASTURE: Protection against Allergy—Study in Rural Environments
- URECA: Urban Environment and Childhood Asthma, Boston
- WHEALS: Wayne County Health, Environment, Allergy and Asthma Longitudinal Study

CREW (Childrens Respiratory and Environmental Work group)

12 individual cohorts and three additional scientific center



Difficulties with Cohort studies

- There is no gold standard set of diagnostic criteria nor an objective test for asthma
  - A comprehensive review of birth cohort asthma definitions found 60 different asthma definitions among 122 studies
- Difficult to apply to clinical practice
- Many look at single-level risk factors but these do not address the complex interplay between exposures at multiple levels (e.g., environmental exposures, host genome, transcriptome, metabolome, and microbiome)
- Difficulty with generalizability

Genetics of asthma

- Asthma runs in families but is polygenetic and multifactorial
- Asthma susceptibility genes fall mainly into three categories
  - functioning of the immune system
  - mucosal biology and function
  - lung function and disease expression
- Genome wide association studies and candidate gene associations studies have identified hundreds of candidate genes
- ADAM33
- Filaggrin

EGR-1	Early growth response protein 1	1p34	49
PTGER3	Prostaglandin E receptor 3	1p31	49
CLCA1	Chloride channel calcium activated family member	1p22-31	49,51,52
V-CAM 1	Vascular cell adhesion protein 1 precursor	1p21	49
GSTM1	Glutatione-S-transferase	1p13.3	49
A3AR	Adenosine A3 receptor	1p13	49
CHIA	An effector response for IL-13	1q13.1	53
LELP1	Late cornified envelope like proline-rich1	1q21	54
FLG	Filaggrin	1q21.3	50,55
IL-10	IL-10 gene	1q31	56
A1	Adenosine A1 receptor	1q32	49
CHI3L1	Chitinase 3-like 1 (Cartilage glycoprotein-39)	1q32	57
TGF-β2	Transforming growth factor beta 2 precursor	1q41	49
IL-1R1	Interleukin-1 receptor	2q11	49
INPP4A	Inositol polyphosphate 4 phosphatase type I	2q11.2	58
IL-1RN	Interleukin-1 receptor antagonist protein precursor	2q13	49
IL-1 (α, β)	Interleukin-1 alpha and beta precursors	2q21	6,49
CTLA4	Cytytoxic T-lymphocyte antigen 4	2q33	50
IL-8RA	High affinity interleukin-8 receptor A	2q35	49
DPP10	Dipeptidylpeptidase 10 isoform 1	2q14	49,50,59,52
CCR1	C-C chemokine receptor type 1	3p21	49
IL-8	Interleukin-8 precursor	4q13	49
APA	Aminopeptidase A	4q25	49
IL-21	IL-21 gene	4q26	60
IL-3,4,5,9,10,12,13	Interleukin-3,4,5,9,10,12,13 precursors	5q31	6,46,50,55
CD14	Monocyte differentiation antigen CD14 precursor	5q31	49,50
SPINK5	Serine protease inhibitor Kazal-type 5 precursor	5q32	49,50
ADRB2	Beta-2 adrenergic receptor	5q31-32	47,48
UGRP1	Uteroglobin related protein1	5q32	61,62
GPX3	Plasma glutathione peroxidase precursor	5q33	49
CYFIP2	Cytoplasmic FMR1 interacting protein 2	5q33	57
HAVCR1	Hepatitis A virus cellular receptor 1	5q33.2	50
SLP-2 LCP2	SH2 domain-containing leucocyte protein	5q35	49
SLP-76	Lymphocyte cytosolic protein 2	5q35	49
LTC4S	Leukotriene C4 synthase	5q35	50
TCRβV	T cell Receptor V β	6p	6
IL-17	Interleukin-17 precursor	6p	51
HLA-DRB1	Major histocompatibility complex – class II – DR beta 1	6p21	4,6,49,50
TNF-α	Tumor necrosis factor precursor	6p21.3	6,49,50
PIM1	Pim-1 oncogene	6p21	49
PAF-2	Peroxisome assembly factor-2	6p21	49
ARG1	Arginase I	6p23	49
TGFβ1	Transforming growth factor BETA 1	6q11	63
SOD2	Superoxide dismutase 2 mitochondrial	6q25	49
IL-6	Interleukin-6	7p15	49
GPRA	G-protein-coupled receptor for asthma susceptibility	7p14	49,50,64,52
TCRG	T cell receptor gamma	7p14	49
EGFR	Epidermal growth factor receptor precursor	7p11	49
PAI-1	Plasminogen activator inhibitor-1 precursor	7q22	49
eNOS; NOS3	Nitric-oxide synthase – endothelial	7q36	49
NAT2	N-acetyltransferase 2	8p22	50
PAF-1	Peroxisome assembly factor-1	8q21	49
PTPRD	Protein-tyrosine phosphatase receptor-type delta	9p	65
PTGES	Prostaglandin E synthase	9q34	49
PTEN	Phosphatase and tensin homolog deleted	10q23.3	66
MUC2	Mucin 2	11p15	49
PTGDR	Prostaglandin D2 receptor DP	11q	49
FcRI β	High affinity Ig epsilon receptor beta-subunit	11q12.1	6,20,50,86
GSTP1	Glutatione-S-transferase	11q13	49,50
CC16	Clara cell secretory protein	11q13	50,67
IL-18	Interleukin-18 precursor	11q22.2	50
CD69	Early activation antigen CD69	12p13	49
AICDA	Activation-induced cytidine deaminase	12p13	68
VDR	Vitamin D3 receptor	12q13-23	49,103
STAT6	Signal transducer and activator of transcription 6	12q13	49
IRAK3	Interleukin-1 receptor-associated kinase 3	12q14	49
IL-22	Interleukin-22 precursor	12q15	49
IFNG	Interferon gamma precursor	12q15	6,20,49,69
KITLG	Kit ligand precursor	12q21	49
NF-YB#	Nuclear transcription factor Y subunit beta	12q23	49
nNOS; NOS1	Nitric-oxide synthase type I	12q14-24.2	49
SFRS8	Splicing factor, arginine /Serine rich 8	12q24	57
SETDB2	SET domain bifurcated 2	13q14	49,52
PHF11	PHD finger protein 11	13q14	59,70,52,71
RCC1	Regulator of chromosome condensation	13q14	49
CYSLTR2	Cysteinyl leukotriene receptor-2	13q14	51
CMA1	Mast cell chymase-1	14q11.2	51
PTGER2	Prostaglandin E receptor 2	14q22	49
ARG2	Arginase II	14q24	49
AACT	Alpha-1-antichymotrypsin precursor	14q32	49
ERK-3	Extracellular signal-regulated kinase 3	15q21	49
IL-4R	Interleukin-4 Receptor	16p12.1	6,72,68
CYBA	NADPH oxidase	16q24.3	73
ALOX15	Arachidonate 15-lipoxygenase	17p13	49
iNOS; NOS2	Nitric oxide synthase - inducible	17q11	49
CCL5	CC-chemokine ligand 5	17q11.2	50
CCL2; MCP-1	Small inducible cytokine A2 precursor	17q12	49
ORMDL3	Orosomucoid1 like3	17q21	50,55,57,74
STAT3	Signal transducer and activator of transcription 3	17q21	75
CCL11	CC-chemokine ligand 11	17q21.1	50
SCYA11	eotaxin gene	17q21.1	76
ACE	Angiotensin I converting enzyme	17q23.3	50
SCCA-1	SerpinB4 Squamous cell carcinoma antigen 1	18q21	49
TBXA2R	Thromboxane A2 receptor	19p13.3	49
Fc-ε-RII	Low affinity immunoglobulin epsilon Fc receptor	19p13	49
ICAM-1	Intercellular adhesion molecule-1 precursor	19p13	49
PTGER1	Prostaglandin E receptor 1	19q13	49
TGFβ1	Transforming growth factor beta 1 precursor	19q13	46,50
ADAM33	Disintegrin and metalloproteinase domain 33	20p13	50,77,78,52
CDH26	Cadherin- like 26	20q13	52
SOD1	Superoxide dismutase [Cu-Zn]	21q22	49
CBR1	Prostaglandin-E(2) 9-reductase	21q22	49
GSTT1	Glutatione-S-transferase	22q11.23	49,50
TIMP1	Tissue inhibitor of metalloproteinase 1	Xq11	49,55
CYSLTR1	Cysteinyl leukotriene receptor-1	Xq21.1	49
SYBL1	Synaptobrevin-like protein 1	Xq28	49
CD24	Signal transducer CD24 precursor	Yq11	49
SYBL1	Synaptobrevin-like protein 1	Yq12	49

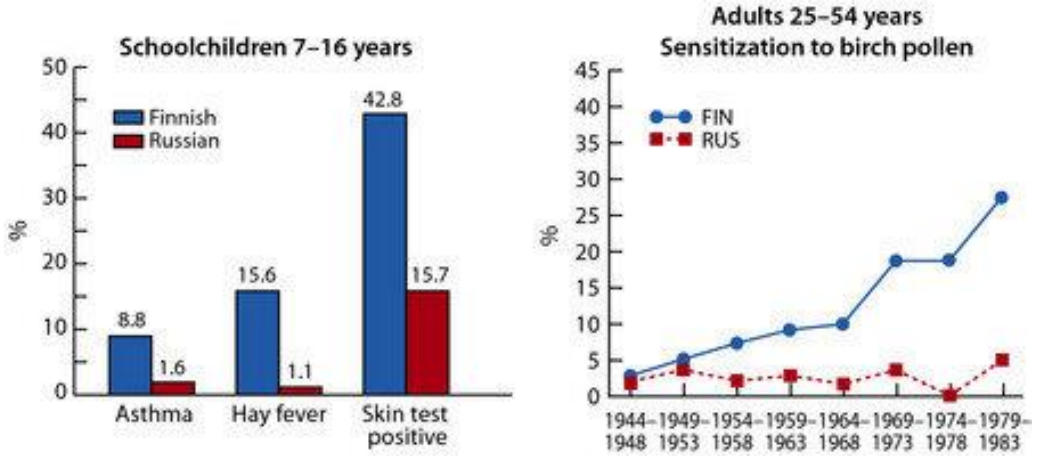
*Genes were arbitrarily ordered by location from chromosome 1 to the sex chromosomes; #NF-YB: CCAAT-binding transcription factor subunit A

Clean Hygiene Hypothesis

Modern lifestyle reduces the microbial stimulus necessary for the immune system to grow normally, causing an increased incidence of atopy Thus, children living in rural areas or with prolonged contact with animals are more likely to be infected and exposed to endotoxins in an unsanitary environment. Therefore, compared to others, they would experience fewer allergies by maintaining a healthy balanced immune system, where the T-helper 1 (Th1) response predominates on the Th2-driven proinflammatory state implicated in allergic reactions

Clean Hygiene Hypothesis

- Examples
  - Russian Vs Finish Karelia
  - Amish vs Hutterite Communities
  - East vs West Germany



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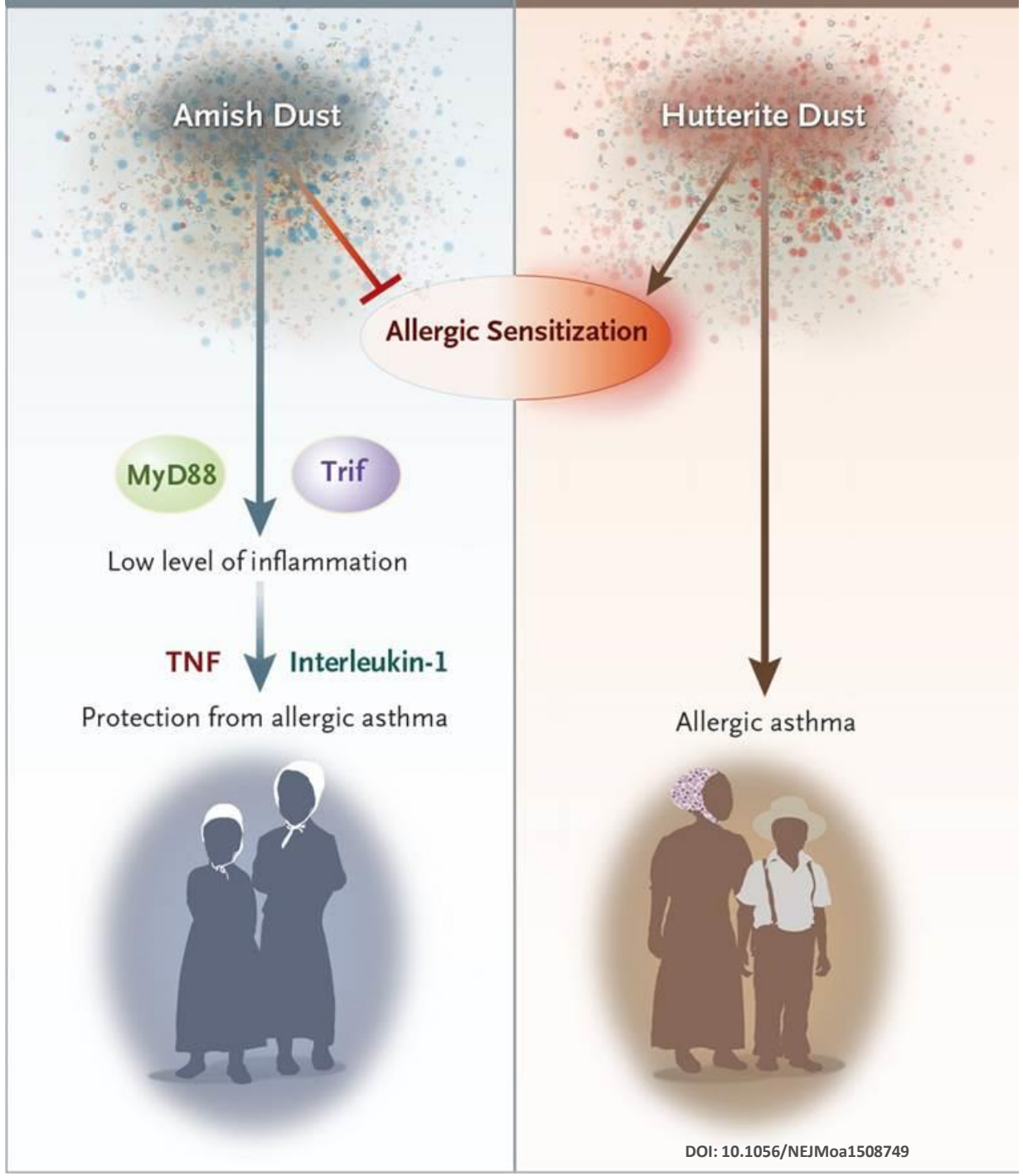
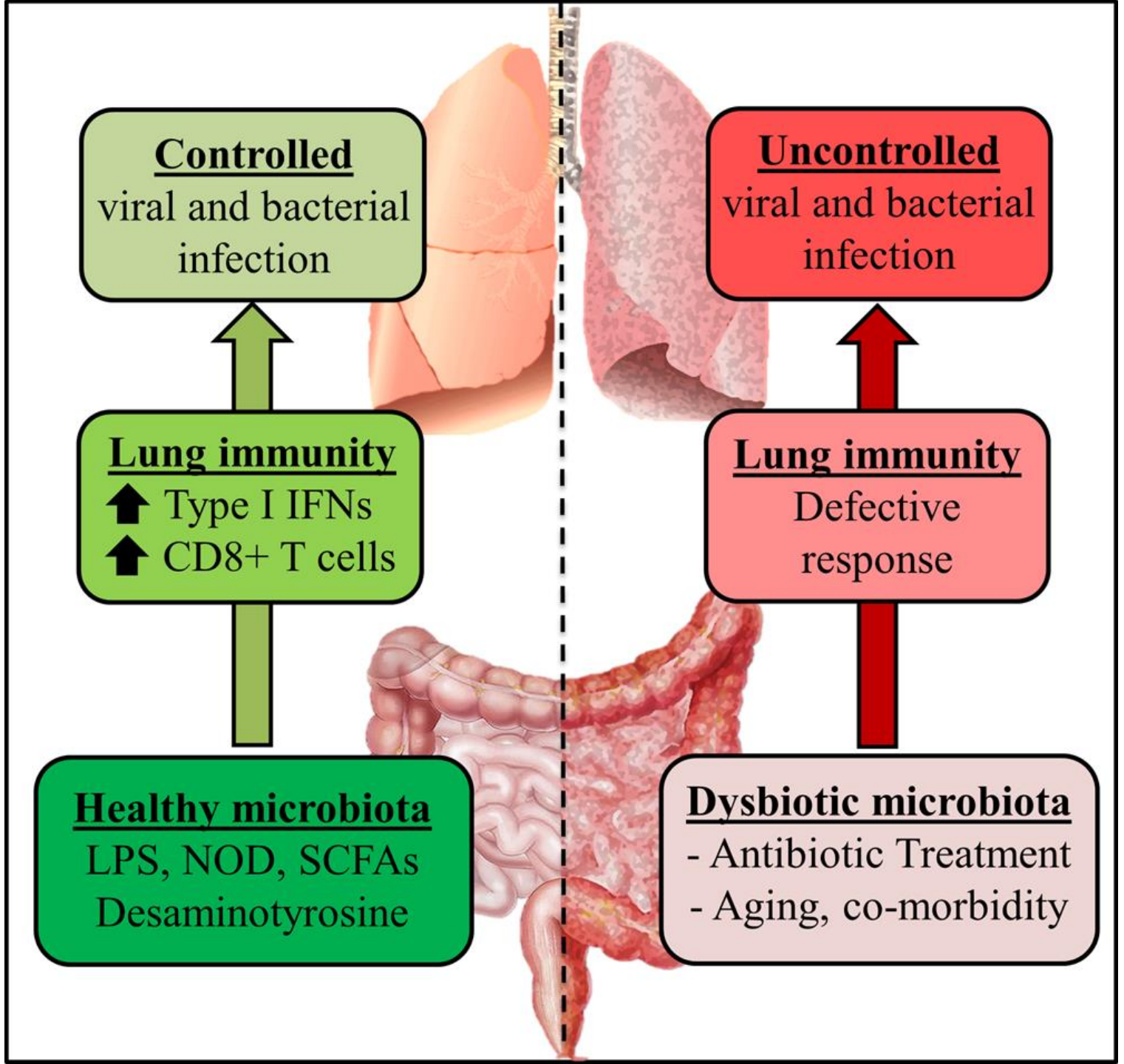


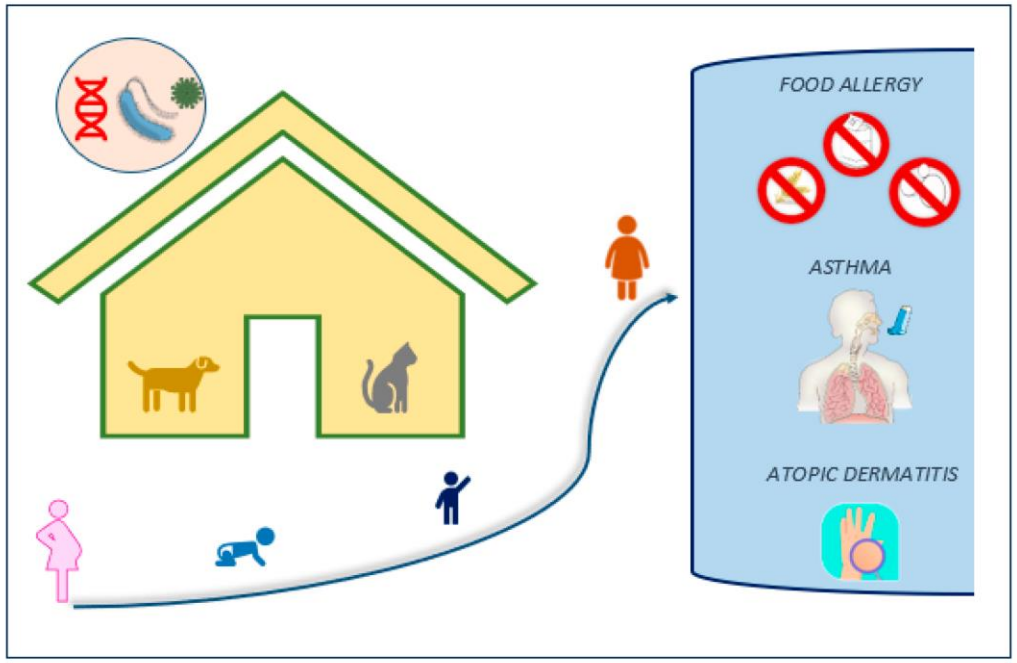
Gut lung axis



Pets in the home (mostly dog and/or cats)

- Danish birth cohort: Dogs ownership lowered the risk of asthma and atopic dermatitis, and this was modified by timing of exposure and parental history of asthma and source of exposure

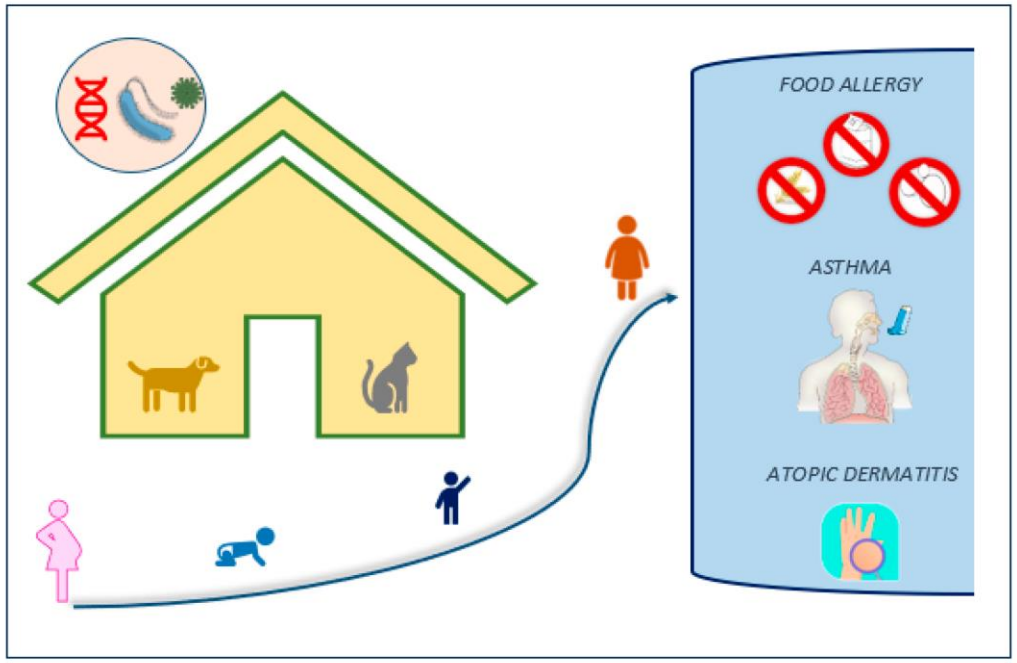
- Swedish Cohort: children with dogs for the first year of life had lower risk of asthma in kids 3 year or older but no difference in children under 3



Pets in the home (mostly dog and/or cats)

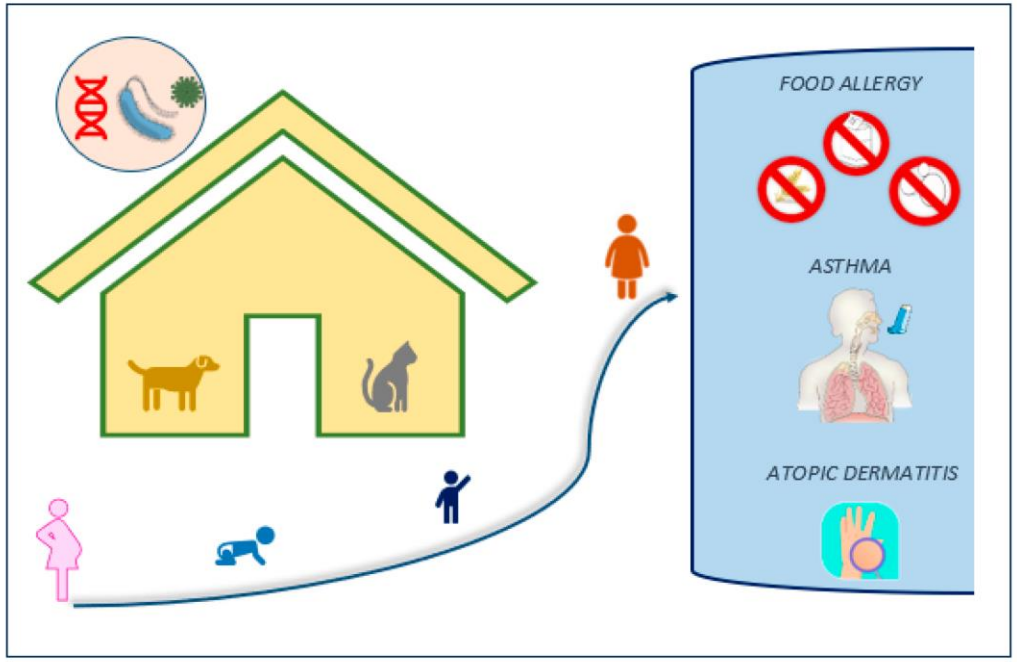
- EU child cohort network: having dog and cat ownership prenatally only was associated with greater odds of school age asthma but continuous ownership was associated with lower odds of asthma but when considering all time windows there was no association

- Polish cohort study using questionnaires: pets in rural regions prevented allergic disorders, while in cities, this increased symptoms of bronchial asthma, the risk of cough, and wheezing



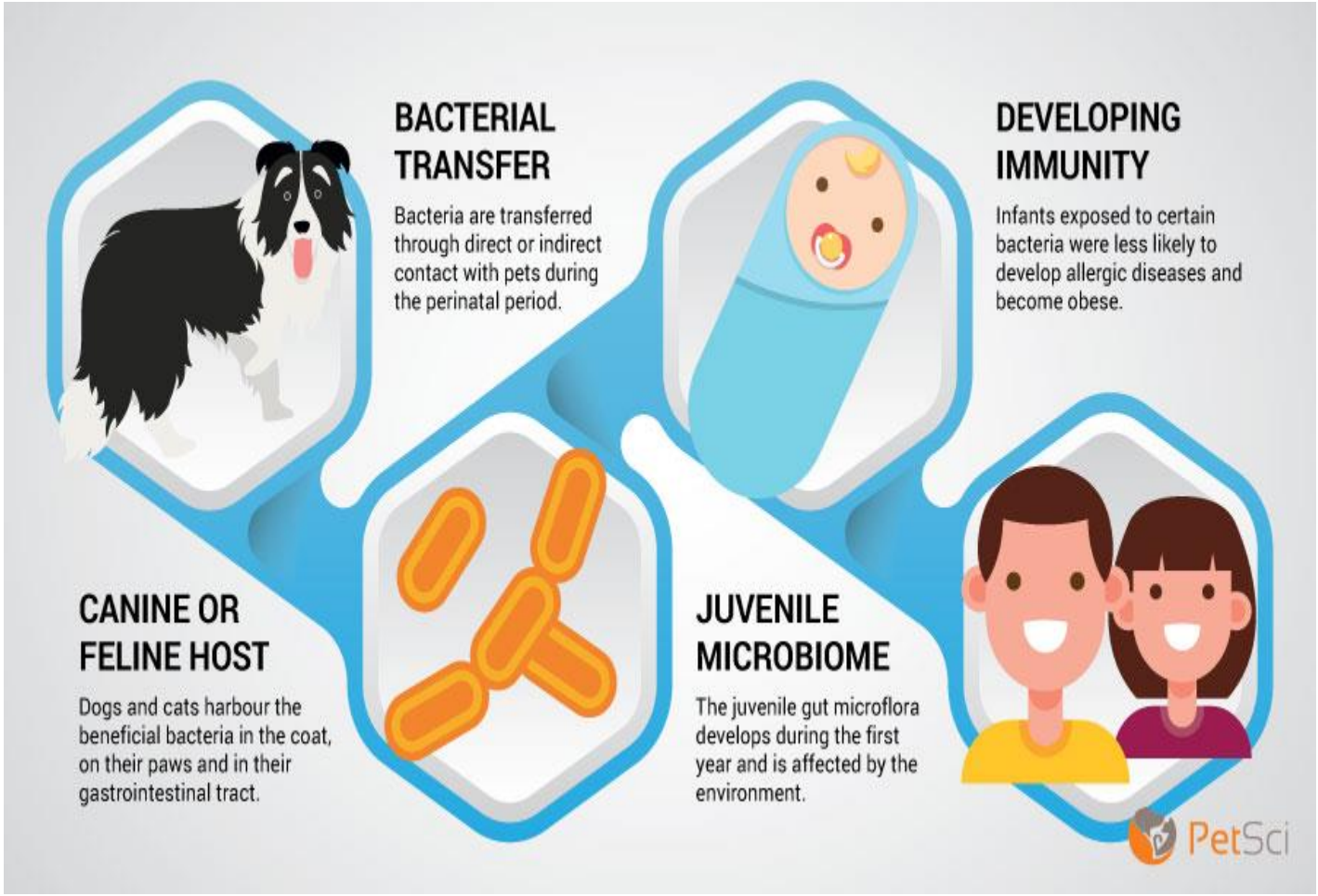
Pets in the home (mostly dog and/or cats): systematic review of literature

- 2 studies found no association between dog and cat housekeeping and the development of asthma in preschool and school-aged children
- 3 studies found that pet ownership was linked to the onset of nonatopic asthma and wheeze in school- and preschool-age children
- 3 studies found that keeping a dog/cat in the household in infancy was inversely associated with the chance of asthma (one article found an association only for female dogs).



Pets in the home effect on asthma proposed mechanisms

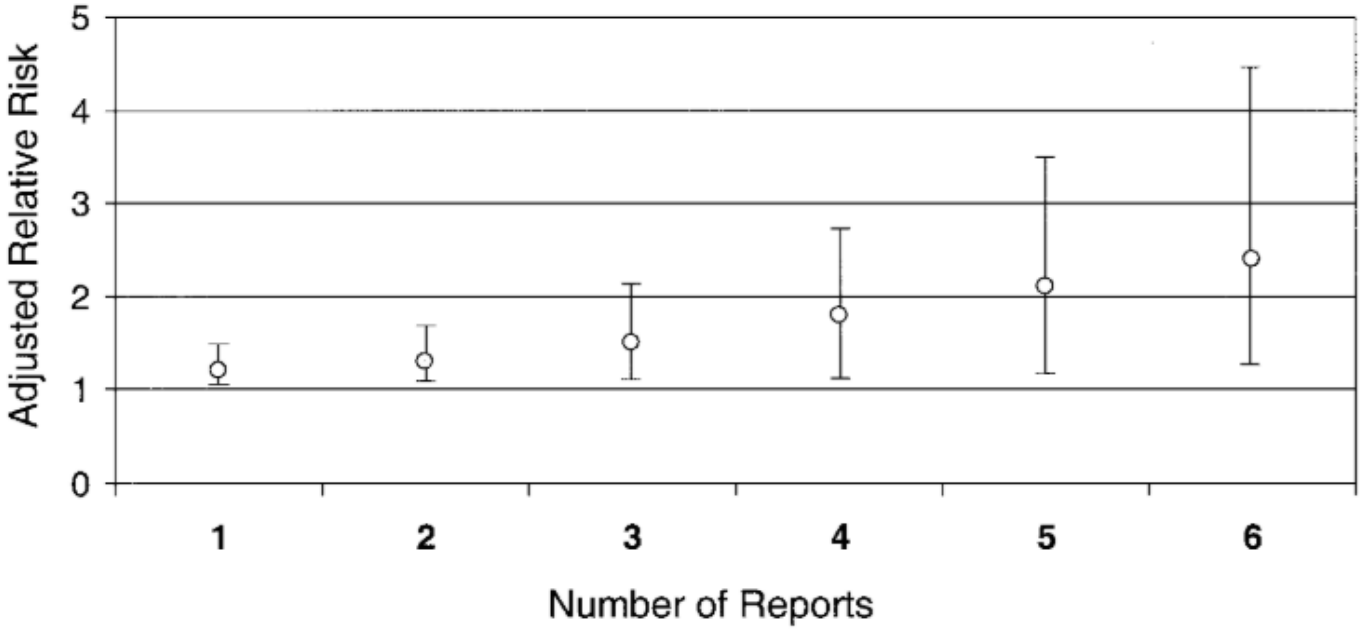
- Having pets improves microbial exposures and increases level of endotoxin → alter human microbiome → enhances type 1 immunity and alter immune maturation through trained immunity → decreases likelihood of atopy
- Changes in immune regulation
  - Dogs during infancy increased IL-10 and IL-13 cytokine secretion patterns,
  - Thymus-derived Treg (tTreg) levels in the venous blood during fetal development vary based on the levels of pet exposure and presence of atopic conditions



Pets in the home effect on asthma proposed mechanisms

- Epigenetic changes
  - Having a pet altered the methylation of the ADAM33 region
  - Allergic rhinitis is related to the level of methylation of ADAM33
- Genetic mutations may modulate effect of pet ownership on asthma and allergic sensitization
  - FLG mutations = increased likelihood of cat allergic sensitization
  - FLG mutations + dog exposure= lower risk of sensitization to any allergen

Bottles in or just before bed



Celedón JC, Litonjua AA, Ryan L, Weiss ST, Gold DR. Bottle feeding in the bed or crib before sleep time and wheezing in early childhood. Pediatrics. 2002 Dec;110(6):e77. doi: 10.1542/peds.110.6.e77. PMID: 12456944.

TABLE 2. Relation Between Bottle Feeding in the Bed or Crib Before Sleep Time in the First Year of Life and Recurrent Wheezing and Asthma at Age 5 Years Among 448 Study Participants

Number of Reports of Bottle Feeding in the Bed or Crib Before Sleep Time	OR (95% CI)			
	Recurrent Wheezing (n = 38)*		Asthma (n = 38)†	
	Unadjusted	Adjusted‡	Unadjusted	Adjusted‡
0	1.0	1.0	1.0	1.0
1	1.3 (1.08–1.66)	1.3 (1.05–1.66)	1.4 (1.12–1.72)	1.3 (1.07–1.69)
2	1.8 (1.16–2.77)	1.8 (1.11–2.77)	1.9 (1.25–2.95)	1.8 (1.13–2.86)
3	2.4 (1.25–4.62)	2.3 (1.17–4.61)	2.7 (1.40–5.06)	2.4 (1.21–4.84)
4	3.2 (1.35–7.70)	3.1 (1.23–7.67)	3.7 (1.57–8.68)	3.3 (1.29–8.18)
5	4.3 (1.46–12.82)	4.1 (1.30–12.76)	5.1 (1.76–14.89)	4.4 (1.37–13.83)
6	5.8 (1.57–21.35)	5.4 (1.36–21.23)	7.1 (1.97–25.55)	5.9 (1.46–23.39)

* At least 2 episodes of wheezing in the previous 12 months.
† Physician-diagnosed asthma and at least 1 episode of wheezing in the previous 12 months.
‡ Adjusted for gender, household income, and active maternal history of asthma.

Early Respiratory infections

- Previous individual observational studies have an associations of respiratory tract infections in early life with the risk of wheezing or asthma in later life, which ranges from a 1.5- to 10-fold increased risk
  - cohort studies of severe bronchiolitis demonstrate that approximately 30% of infants with severe bronchiolitis develop asthma by age 6–7 years
- Early-life respiratory tract infections were associated with a lower lung function in childhood or adulthood

TABLE I. Pathogens detected in the NPA samples[23]

Positive for	Infectious NPA (n = 815) No. (%)	Control NPA (n = 366) No. (%)	URI (n = 548) No. (%)	Nonwheezy LRI (n = 193) No. (%)	wLRI (n = 74) No. (%)	Febrile LRI (n = 68) No. (%)
Any virus	562 (69.0)	88 (24.0)	376 (68.6)	135 (69.9)	51 (68.9)	42 (61.8)
Rhinovirus	394 (48.3)	42 (11.3)	284 (51.8)	76 (39.4)	34 (46.0)	19 (27.9)
RSV	89 (10.9)	18 (4.9)	47 (8.6)	30 (15.5)	12 (16.2)	14 (20.6)
Coronavirus	47 (5.8)	19 (5.2)	34 (6.2)	11 (5.7)	2 (2.7)	1 (1.5)
PIF	44 (5.4)	4 (1.1)	26 (4.7)	12 (6.2)	6 (8.1)	5 (7.4)
Influenza	35 (4.3)	0	24 (4.4)	8 (4.1)	3 (4.1)	6 (8.8)
HMPV	17 (2.1)	1 (0.3)	7 (1.3)	9 (4.7)	1 (1.4)	2 (2.9)
Adenovirus	13 (1.6)	5 (1.4)	9 (1.6)	2 (2.7)	2 (2.7)	3 (4.4)
Mycoplasma pneumoniae	11 (1.3)	8 (2.2)	7 (1.3)	4 (2.1)	0	1 (1.5)
Chlamydia pneumoniae	11 (1.3)	5 (1.4)	7 (1.3)	2 (1.0)	2 (2.7)	0

PIF, Parainfluenza viruses 1-3; *HMPV*, human metapneumovirus.

Early Respiratory infections

TABLE III. Predictors of current wheeze at 5 years of age in relation to time of atopic sensitization

Type of ARI	Never atopic OR (95% CI) *P* value	Atopic by age of 2 years OR (95% CI) *P* value	Atopic after 2 years OR (95% CI) *P* value
Whole population regardless of ARI history	**0.4 (0.2-0.8) 0.006***	**3.1 (1.5-6.4) 0.05**	**2.9 (1.4-5.8) 0.05**
Any wheezy LRI in first year	1.4 (0.4-5.1) 0.6	**3.4 (1.2-9.7) 0.02**	0.5 (0.1-3.5) 0.5
No. of wheezy LRI *(linear model)*	1.1 (0.5-2.8) 0.8	**2.4 (1.2-4.7) 0.01**	0.9 (0.2-4.1)0.9
0	Comparison group	Comparison group	Comparison group
1	1.6 (0.4-6.9) 0.5	1.9 (0.7-5.5) 0.2	**(≥1)** 0.5 (0.1-3.4) 0.5
≥2	1.0 (0.1-9.1) 1.0	**7.1 (1.3-38.4) 0.02**	NA
Any febrile infections in first year	1.2 (0.4-3.8) 0.8	1.2 (0.8-1.8) 0.4	1.8 (0.3-9.6) 0.5
Any febrile URI	1.3 (0.4-4.1) 0.7	0.9 (0.5-1.5) 0.9	1.4 (0.3-7.1) 0.7
Any febrile LRI	1.0 (0.2-3.8) 1.0	**4.2 (1.5-11.8) 0.006**	1.3 (0.2-9.9) 0.8
Any wheezy or febrile LRI	1.0 (0.3-3.4) 1.0	**3.9 (1.4-10.5) 0.007**	0.7 (0.1-3.9) 0.7
Any wLRI associated with rhinovirus or RSV	0.8 (0.2-4.0) 0.8	**4.1 (1.3-12.6) 0.02**	0.9 (0.1-6.4) 0.9
Any wLRI associated with rhinovirus	1.6 (0.3-8.7) 0.6	**3.2 (1.1-9.5) 0.03**	2.1 (0.3-18.5) 0.5
Any wLRI associated with RSV	1.6 (0.3-8.7) 0.6	3.6 (1.0-13.3) 0.06	Insufficient number

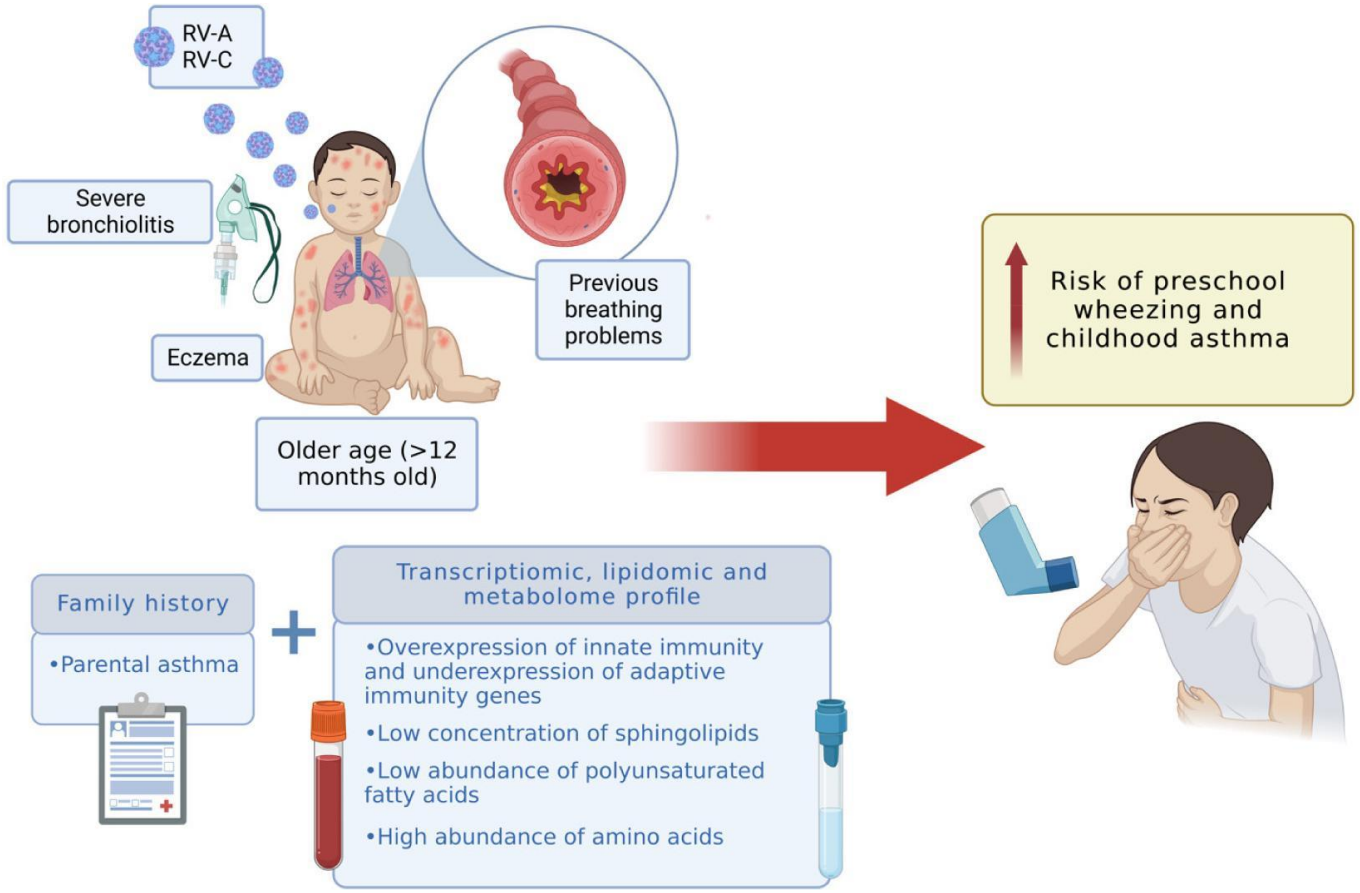
Early Respiratory infections

Table 1: Risk of asthma development with wheeze associate respiratory tract infection (wLRI), atopic sensitization, or febrile lower respiratory tract infection (fLRI). OR-odds ratio ARR=adjusted risk ratio CI= confidence interval (Kusel et al, 2008 and Kusel et al 2012)

Characteristic	OR of persistent wheeze at 5 years of age (95% CI)	p	ARR of current asthma at 10 years of age (95% CI)	p
wLRI by 1 year of age	2.9 (1.0-8.3)	0.05	1.17 (0.56-2.44)	0.684
fLRI by 1 year of age	3.6 (1.2-10.7)	0.02	2.57 (1.33-4.98)	0.005
Atopic sensitization by 2 years of age	3.1 (1.5-6.4)	0.05	2.67 (1.28-5.54)	0.008
Atopic sensitization by 2 years of and fLRI by 1 year of age	4.2 (1.5-11.8)	0.01	4.92 (2.59-9.36)	<0.001

Early Respiratory infections

- Infants with rhinovirus bronchiolitis have higher risk of asthma compared to those with RSV bronchiolitis
- the COAST and COPSAC studies revealed an interaction between 17q21 polymorphisms (TT genotype at rs7216389), rhinovirus-related wheezing illnesses, and the development of asthma.
- Viral specific, microbiome interactions, metabolomics, interferon regulation are important influencers on asthma risk after bronchiolitis
  - variability in ORMDL3 gene
  - sphingolipid metabolism
  - type I and II IFN regulation
  - fatty acid and amino acid metabolism pathways



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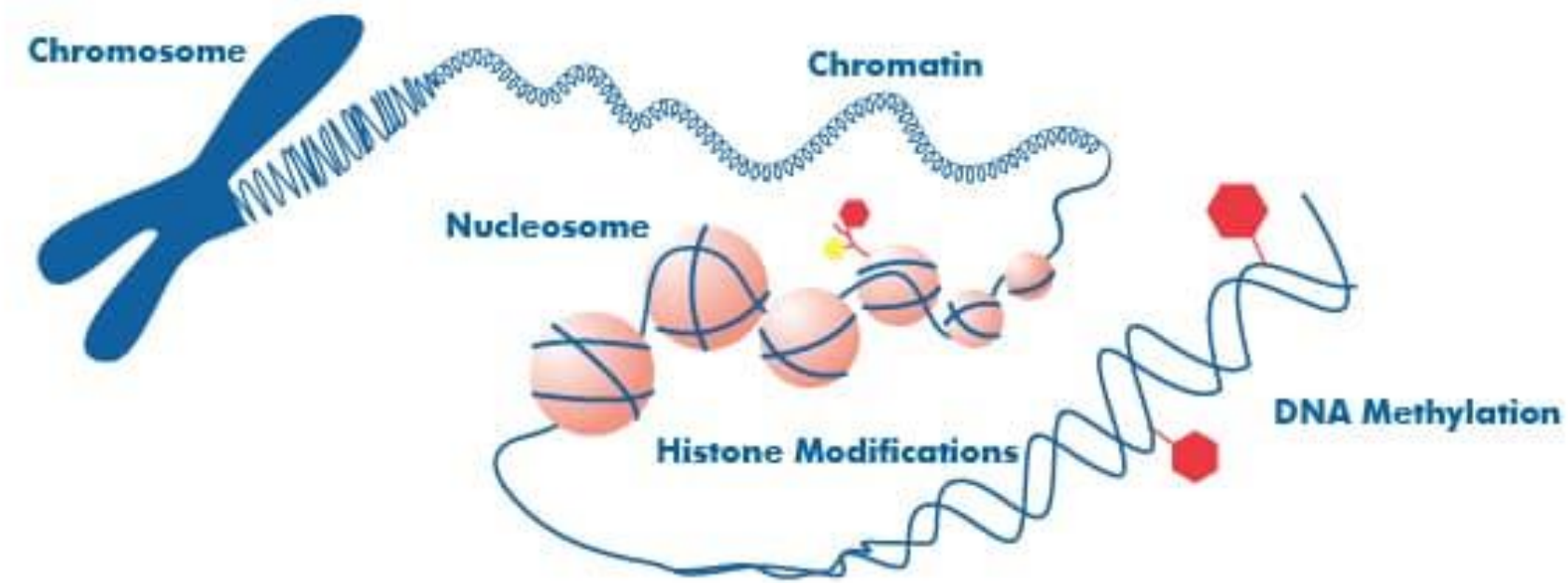
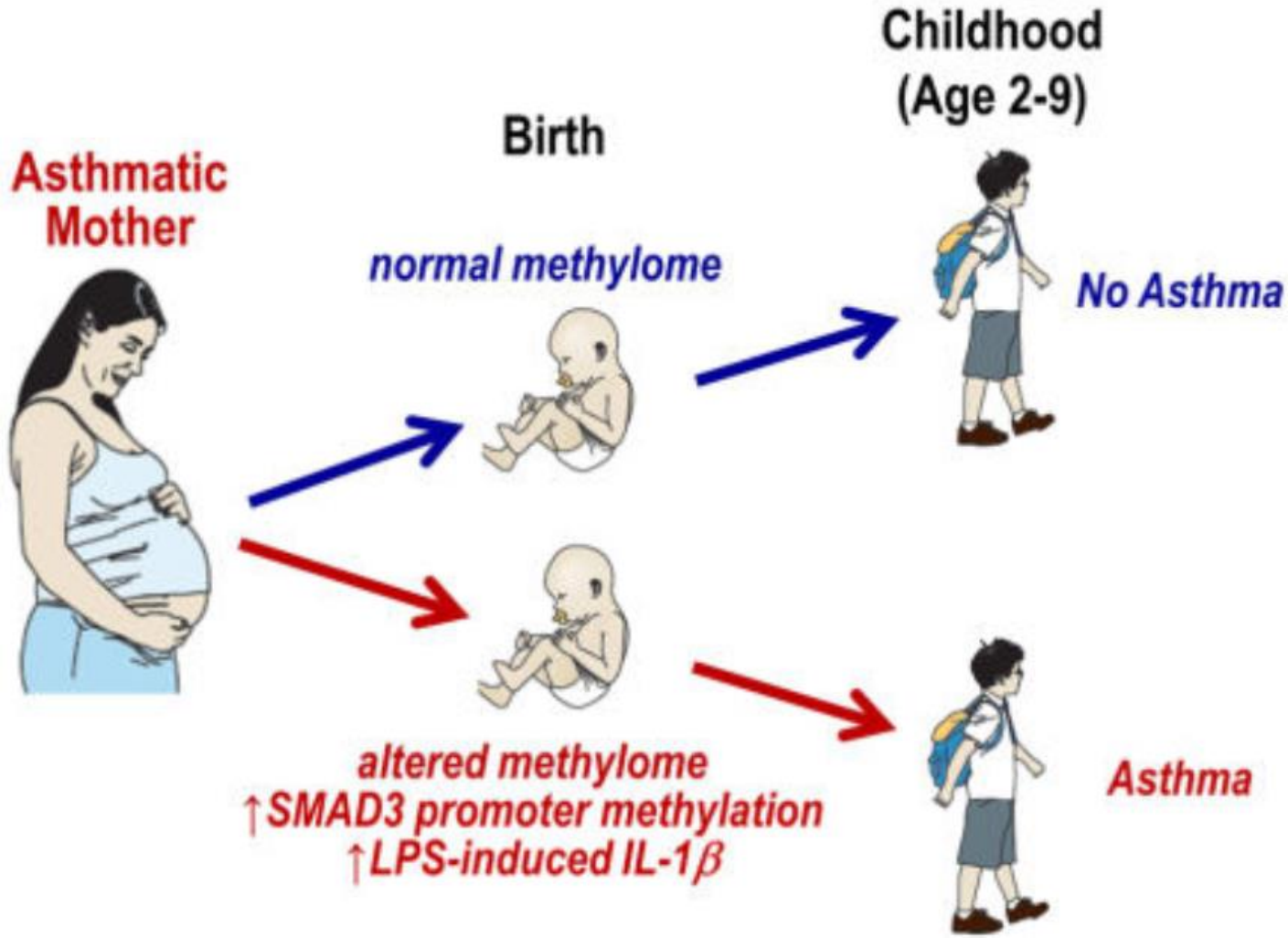
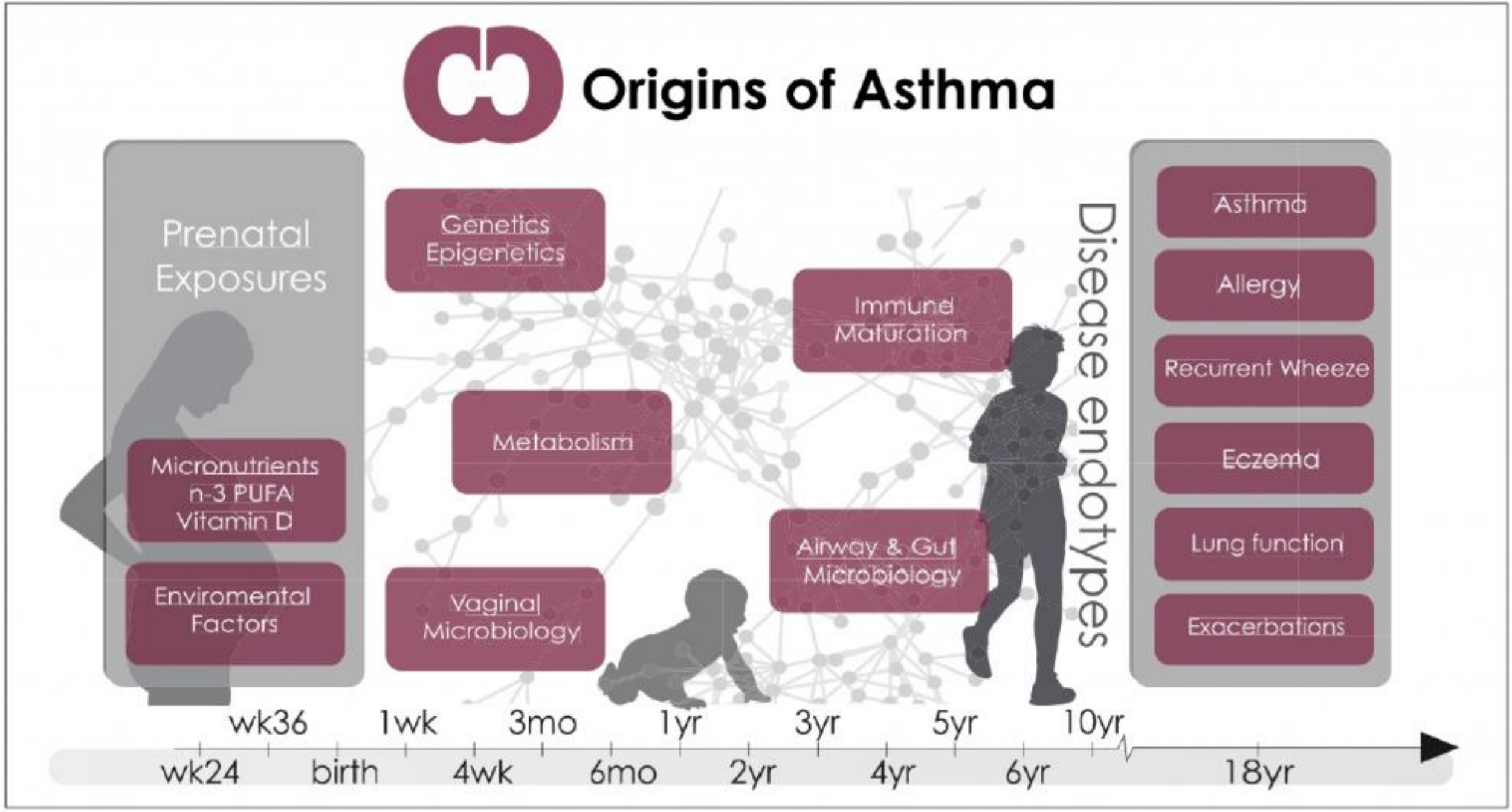
Environment meets genetics: Epigenetics and asthma



https://www.novusbio.com/research-areas/epigenetics


Childhood
(Age 2-9)
Birth
Asthmatic
Mother
normal methylome
No Asthma
altered methylome
↑SMAD3 promoter methylation
↑LPS-induced IL-1β
Asthma



https://copsac.com/the-origins-of-asthma/

Thank you

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