

CURRENT HOT ISSUE IN ASTHMA: AMISH DUST

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강의 내용

- **Amish and Hutterite farm dust**
- **Environment and local immunity at the lung barrier**
- **Conclusion**

THE AMISH

ANABAPTISM

- 오직 자신의 믿음을 고백하는 성인에게만 세례
 - 유아들은 선과 악을 분별할 수 없어 죄를 지을 수 없다고 생각했기 때문에 유아세례를 무시하고 재세례 주장
- 국가는 교회의 가르침과 행동을 지시 통제하면 안됨
- 카톨릭과 개신교 모두에게 이단으로 정죄

MENNO SIMONS: MENNONITES

- 재세례파는 유럽의 종교적, 사회적 관습과 제도를 위협하는 존재로 간주되어 모진 박해를 받음
- 스위스와 서부 독일지역의 산지로 피신:
 - 숨어서 가정예배를 드리며 산을 경작 -> 농토중시와 가정예배의 전통확립
- 박해에도 불구하고 유럽 전역으로 확산
- 네덜란드(1536)의 카톨릭 신부 메노 시몬스(Menno Simons) 참여.
- 메노나이트파(Mennonites)로 불림

JACOB AMMANN

- 스위스 메노나이트 파의 지도자 - 메모나이트파로부터 분리
- 엄격한 신앙 훈련과 단순한 의복 착용
- 의복에 대한 견해, 현대 물질문명의 기기 사용여부, 예배의 형태, 독일어의 사용, 회원의 규율 등에 차이 보임
- 국가로부터의 교회분리, 성인세례, 무저항, 성서근본주 신념 동일
- Ammann을 추종하는 사람을 Amish라고 함

THE AMISH

- The Amish are known for simple living, plain dress, and reluctance to adopt many conveniences of modern technology.
- In the early 18th century, many Amish and Mennonites immigrated to Pennsylvania for a variety of reasons.
- Most of the Amish continue to have 6–7 children while benefiting from the major decrease in infant and maternal mortality in the 20th century.
- Between 1992 and 2013, the Amish population increased by 120%, while the US population increased by only 23%.

THE AMISH

- The Amish value rural life, manual labor and humility, all under the auspices of living what they interpret to be God's word.
- Amish church membership begins with baptism, usually between the ages of 16 and 25..
- The rules of the church prohibitions or limitations on the use of power-line electricity, telephones, and automobiles, as well as regulations on clothing.
- Amish church members practice nonresistance and will not perform any type of military service.



AMISH FARM



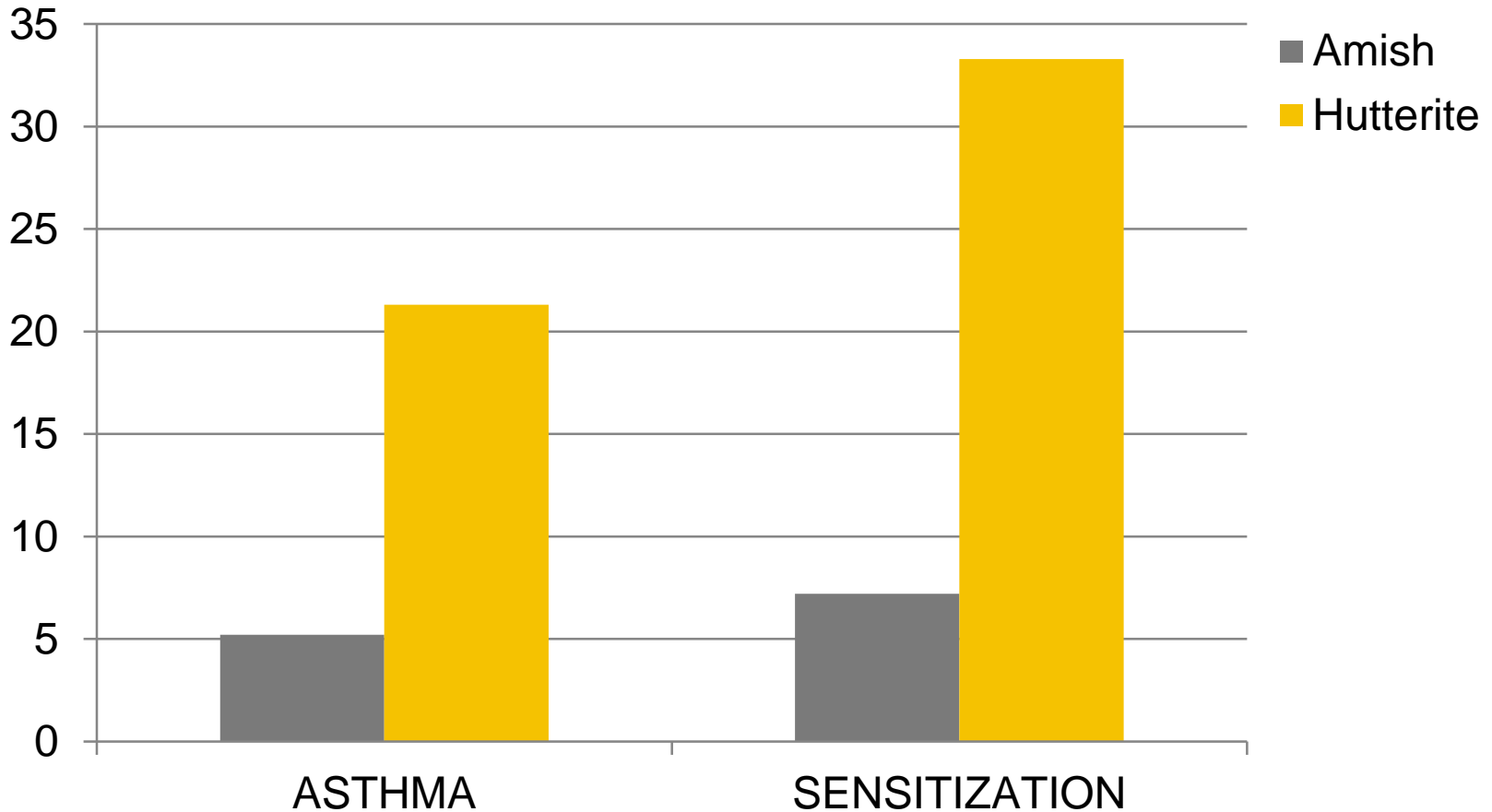
THE HUTTERITES

- Hutterites who also dress plain and speak German dialects emigrated from other European regions at a different time with different German dialects, separate cultures, and related but different religious traditions.
- Particularly, the Hutterites live communally[81] and are generally **accepting of modern technology**.

HUTTERITE COLONY



PREVALENCE OF ASTHMA & SENSITIZATION



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Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children

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STEIN M ET AL. NEJM, 2016;375:411-21

FARMING ENVIROMENT & ASTHMA

- Epidemiologic studies conducted in Central Europe that show significant protection from asthma and allergic disease in children raised on traditional dairy farms.
- In particular, children's contact with farm animals and the associated high microbial exposures have been related to the reduced risk.
- The effect of these traditional farming environments on immune responses is not well defined.

2 US FARMING POPULATION

The Amish of Indiana

**The Hutterites of South
Dakoda**

Originated in Europe

Similar life style:
large sibship size,
high rates of childhood vaccination,
diets rich in fat, salt, and raw milk
childhood obesity , breast-feeding,
minimal exposure to tobacco smoke
and air pollution, Taboos against
indoor pets.

FARMING ENVIROMENT IN AMISH & HUTTERITE

- Amish practice traditional farming, live on single family dairy farms, and use horses for fieldwork and transportation.
- Hutterites live on large, highly industrialized, communal farms.

OVERVIEW

- Characterized environmental exposures, genetic ancestry, and immune profiles among 60 Amish and Hutterite children,
 - measuring levels of allergens and endotoxins
 - assessing the microbiome composition of indoor dust samples.
 - Whole blood was collected to measure serum IgE levels, cytokine responses, and gene expression
 - peripheral blood leukocytes were phenotyped with flow cytometry.
- Asthma mouse models: effects of dust extracts obtained from Amish
 - to study the effect of the environment on airway responses and to create a mechanistic framework for the interpretation of our observations in humans

STUDY PARTICIPANTS

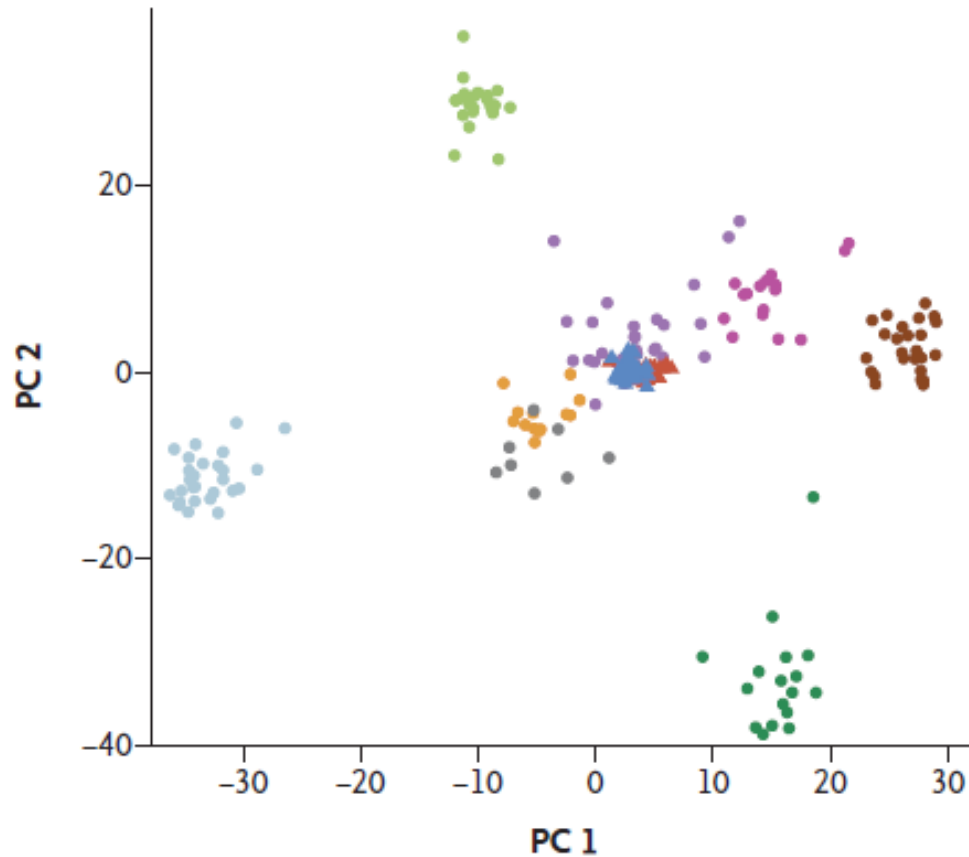
Table 1. Demographic and Clinical Characteristics of the Study Populations.*

Characteristic	Amish (N=30)	Hutterite (N=30)
Age (yr)		
Median	11	12
Range	8–14	7–14
Girls (no.)	10	10
Sibships (no.)	15	14
Children with asthma (no.)	0	6
Positivity for allergen-specific IgE (no.)		
>0.7 kUA/liter	5	9
>3.5 kUA/liter	2	9
Serum IgE (kU/liter)		
Median	21	64
Interquartile range	10–57	15–288

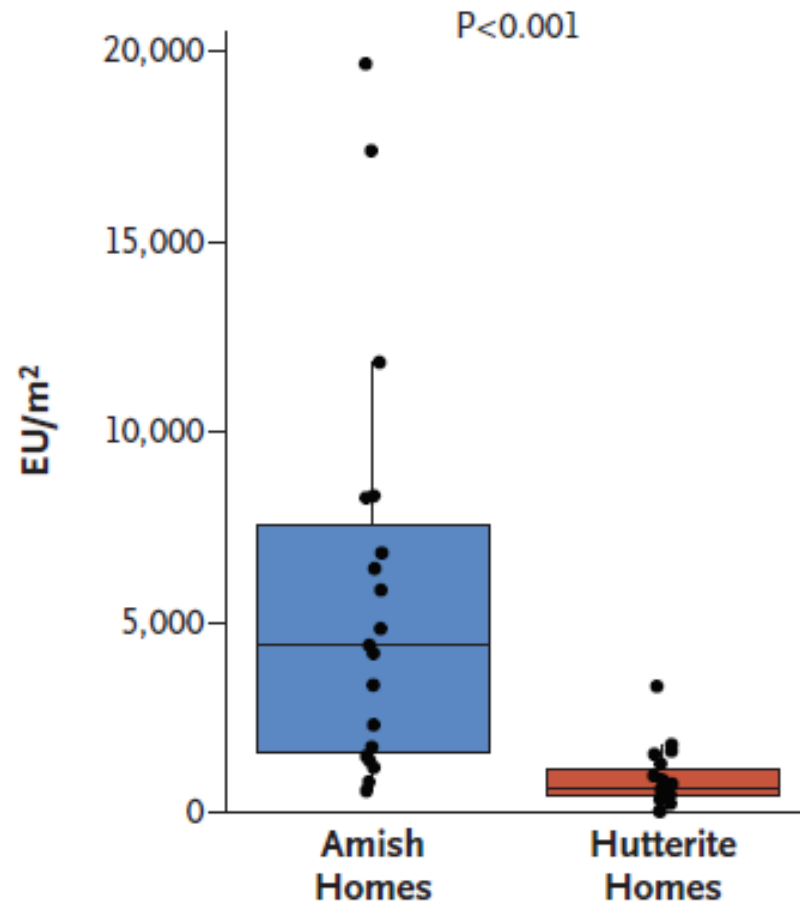
* UA denotes allergen-specific unit.

A SNP Analysis of Genetic Association

▲ Amish ▲ Hutterite ● Basque ● French ● North Italian ● Russian
● Russian Caucasus ● Sardinian ● Scottish ● Tuscan

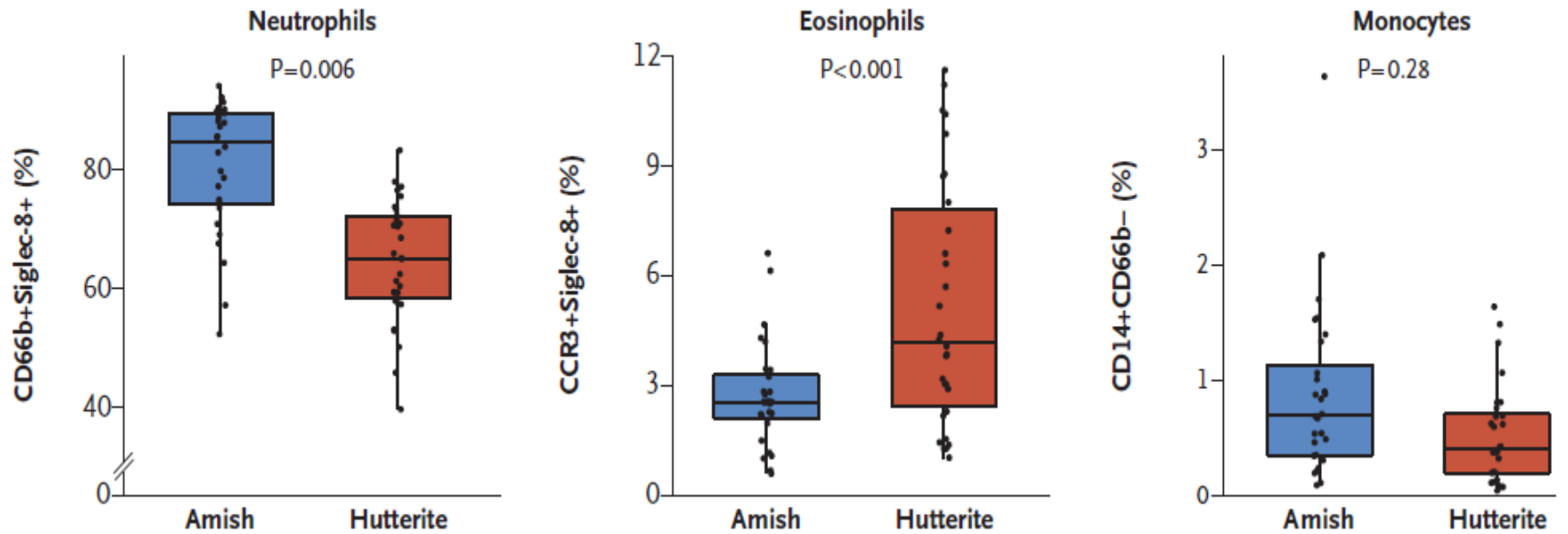


B Endotoxin Levels in Airborne Dust

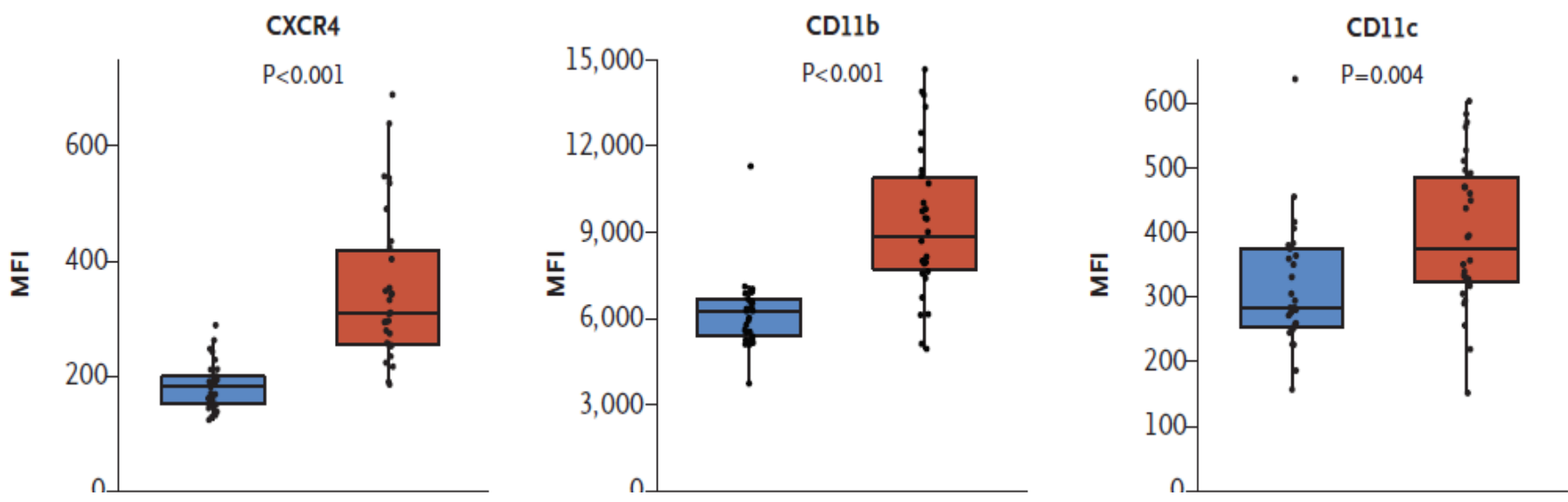


PROPORTIONS OF PERIPHERAL-BLOOD LEUKOCYTES AND CELL-SURFACE-MARKER PHENOTYPES IN AMISH AND HUTTERITE CHILDREN

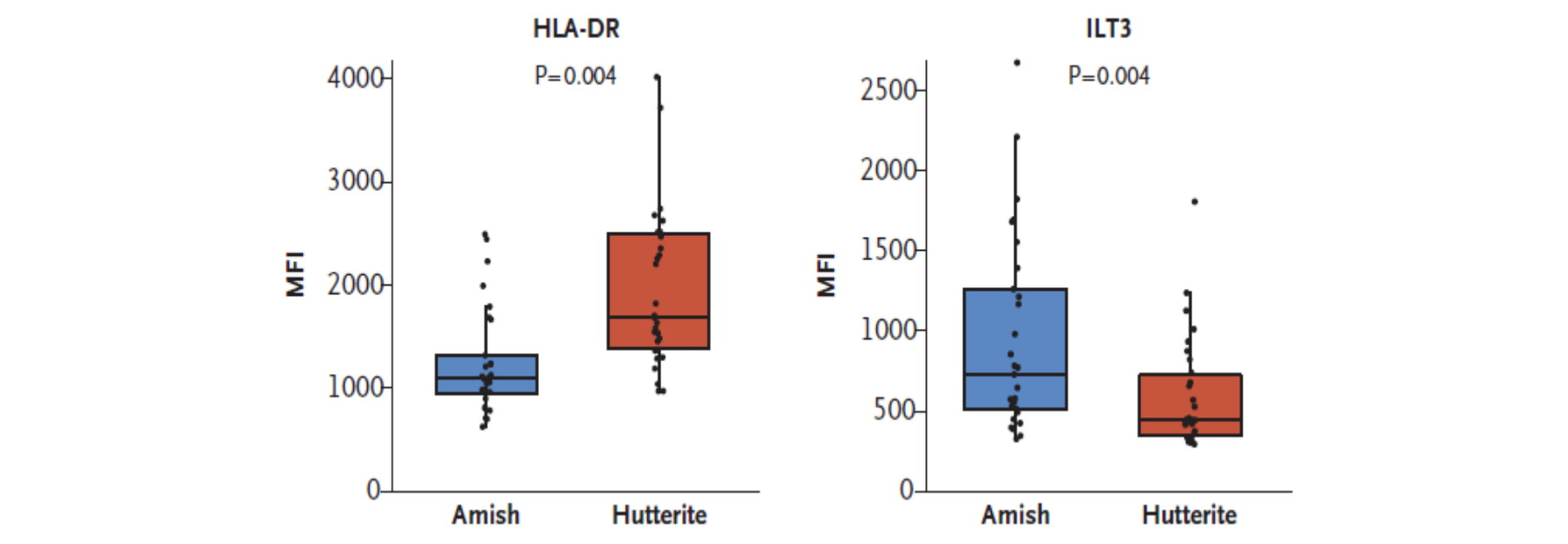
A Cell Proportions of Peripheral-Blood Leukocytes



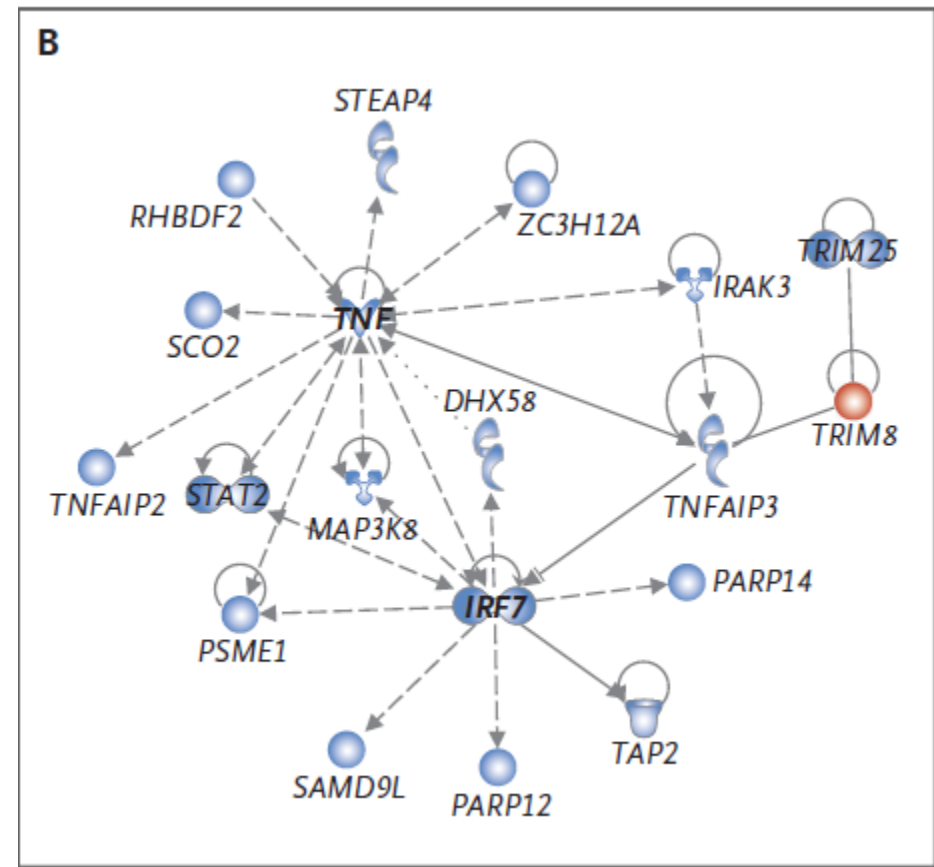
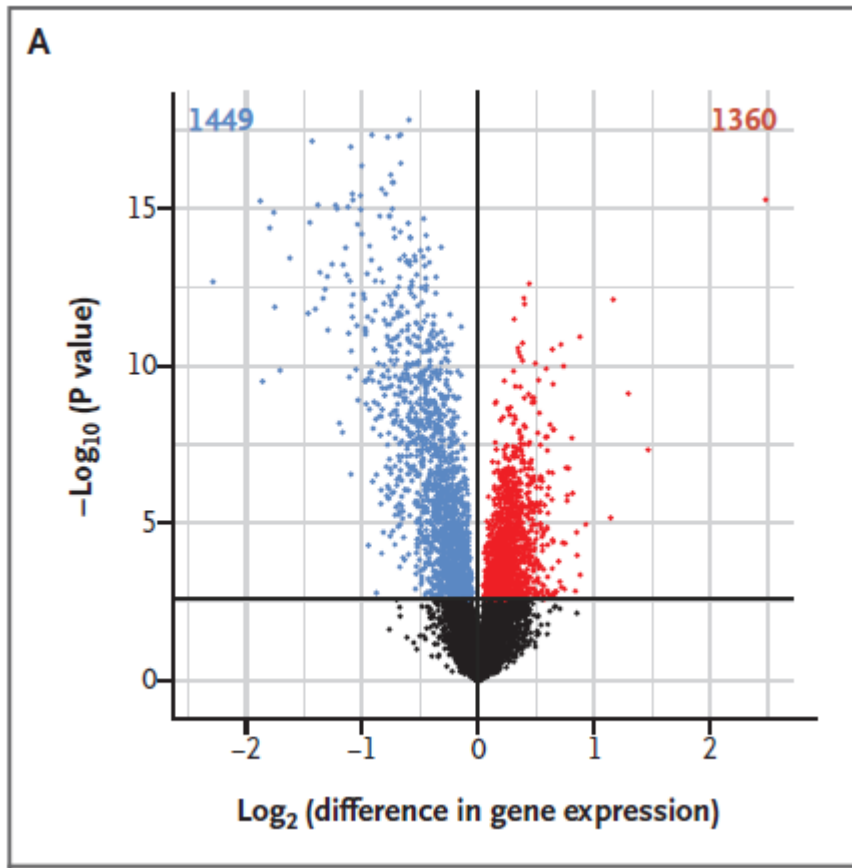
B Cell-Surface Markers on Neutrophils



C Cell-Surface Markers on Monocytes



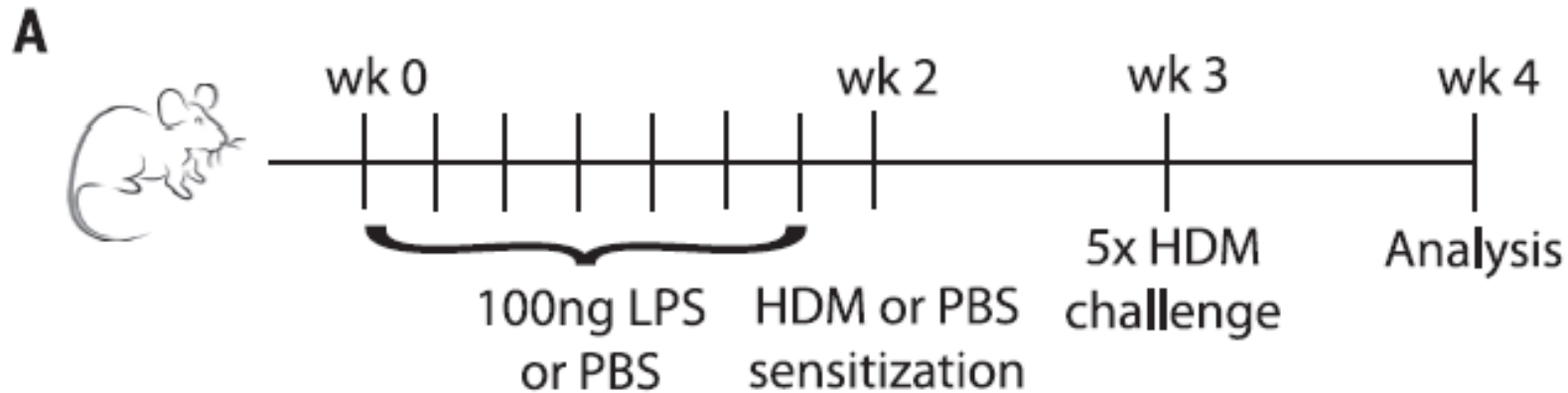
GENE-EXPRESSION PROFILES IN PERIPHERAL-BLOOD LEUKOCYTES FROM AMISH AND HUTTERITE CHILDREN

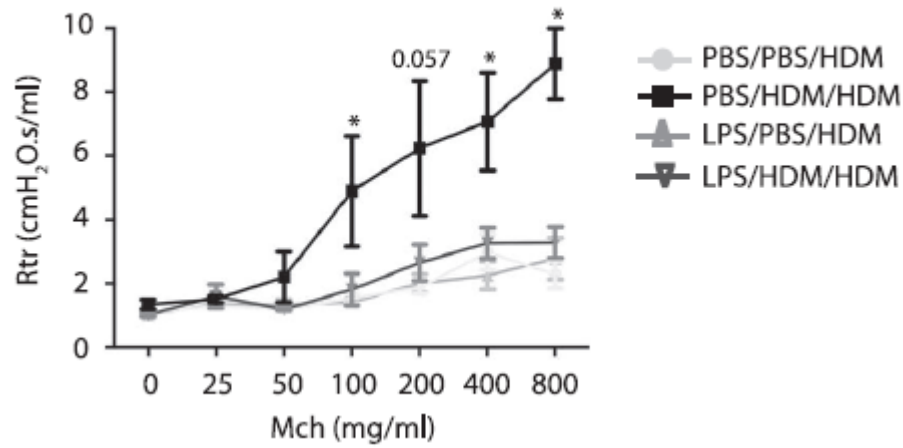
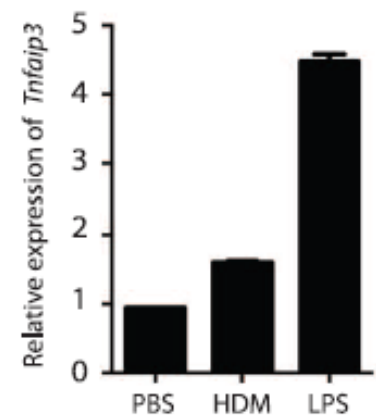
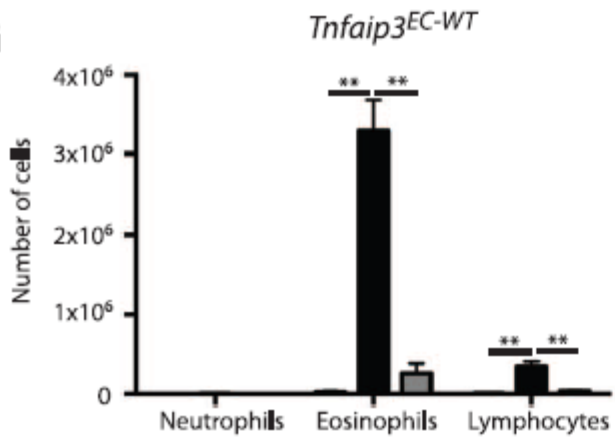
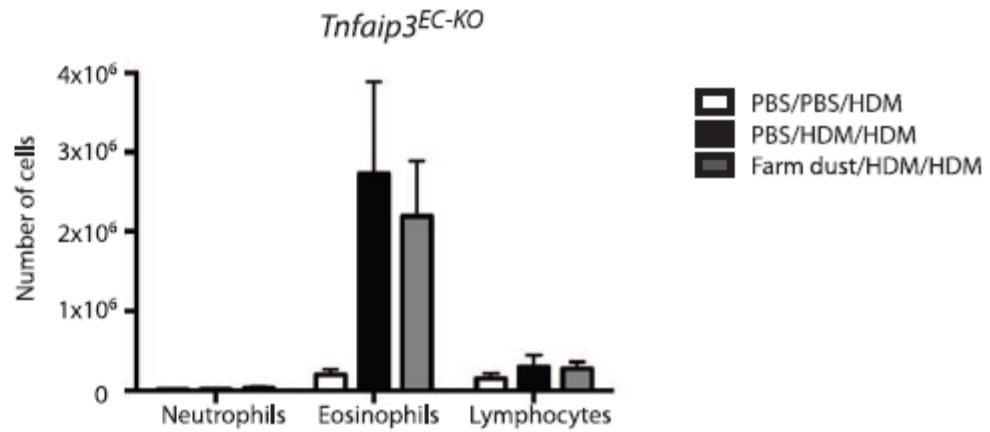


ALLERGY

Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells

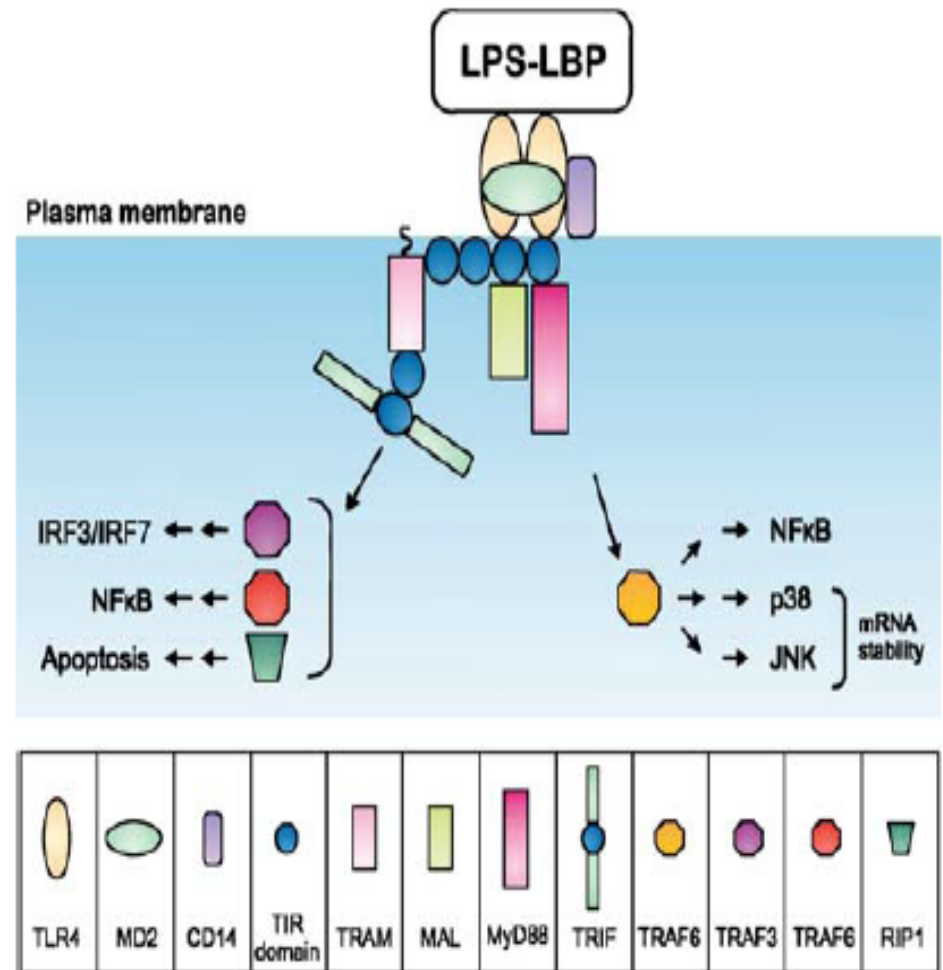
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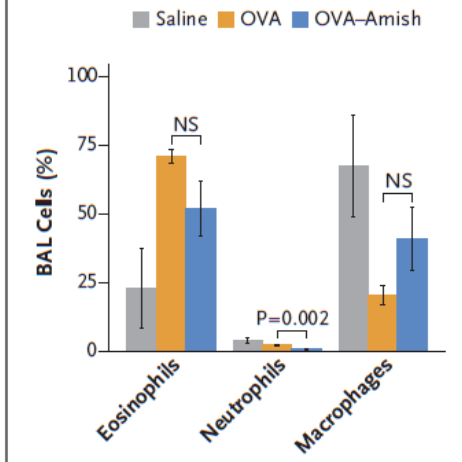
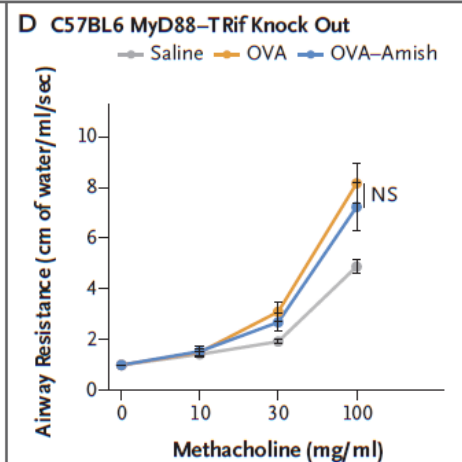
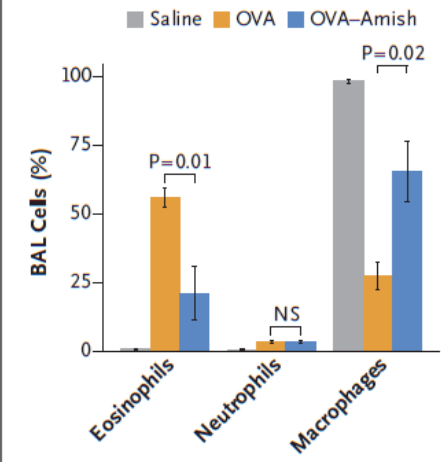
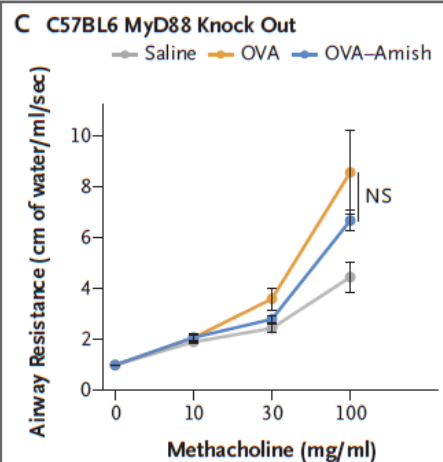
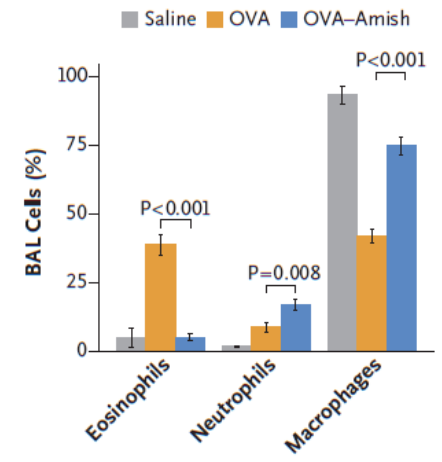
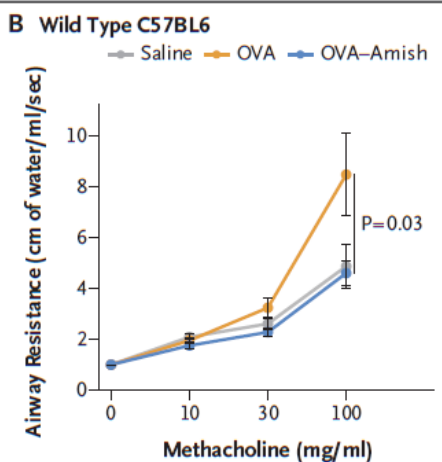
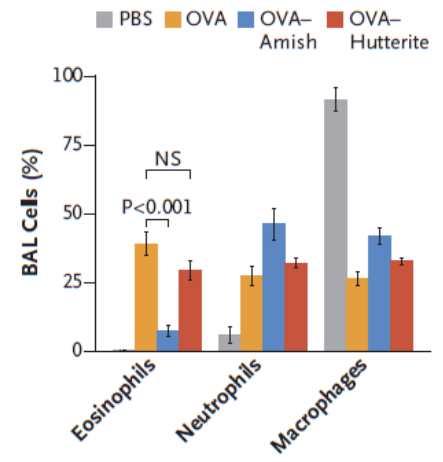
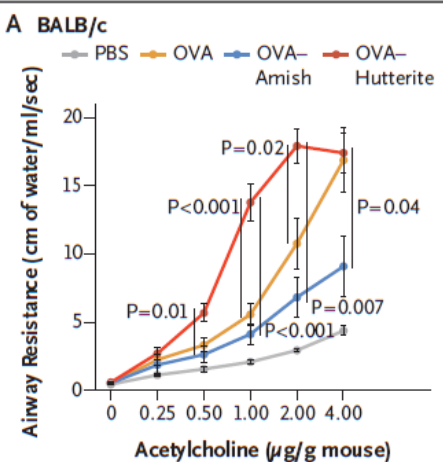
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MOUSE ASTHMA MODEL

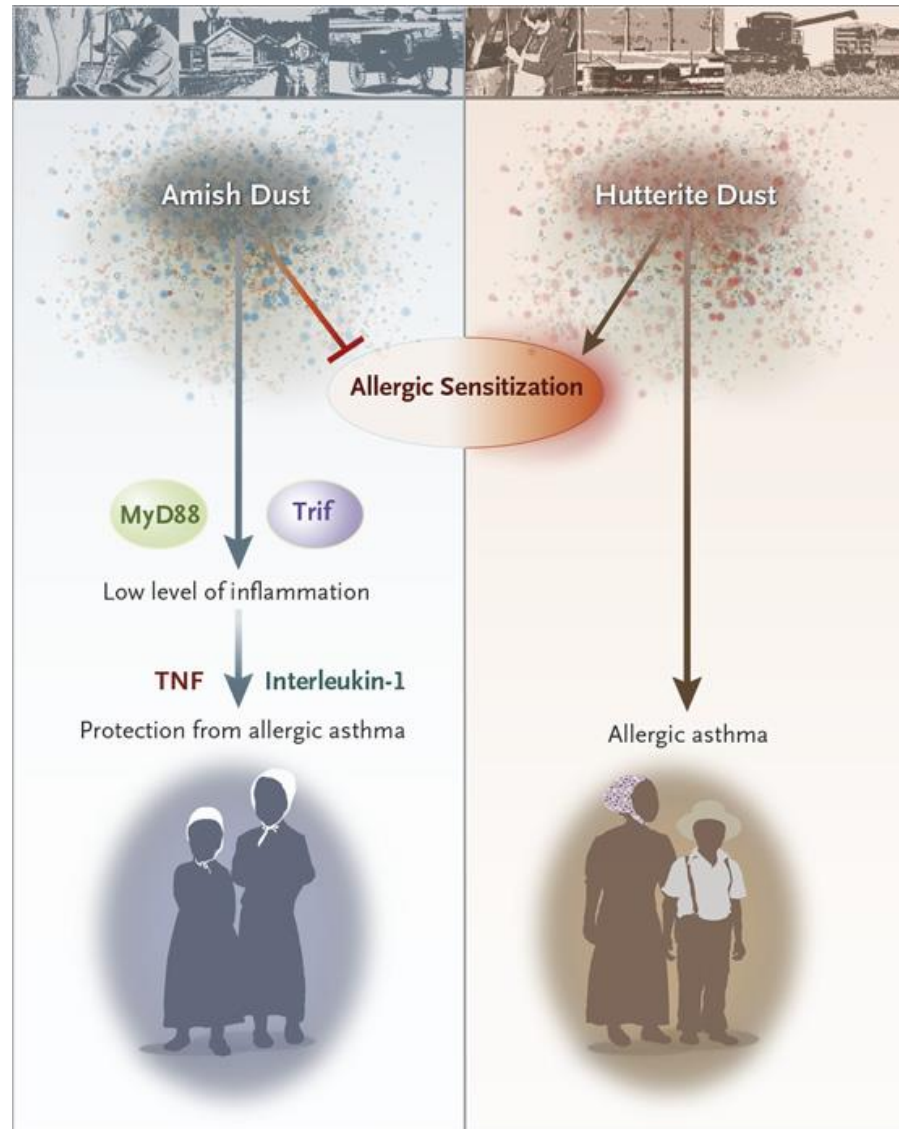
- Instilled 50 μ l of house-dust extract intranasally every 2 to 3 days (for a total of 14 times)
- **7-week old** BALB/c mice (Harlan Laboratories), C57BL6 wild-type, **MyD88**-deficient mice and in mice deficient in both **MyD88 and Trif**



EFFECTS OF AMISH AND HUTTERITE HOUSE-DUST EXTRACTS ON AIRWAY RESPONSES IN MOUSE MODELS OF ALLERGIC ASTHMA



INNATE IMMUNITY IN ASTHMA



**ENVIRONMENTAL
MICROBIAL EXPOSURE &
ASTHMA**

GROWING UP IN TRADITIONAL FAMILY BASED FARMS

- Protects against allergies, asthma and early virus-triggered wheeze
- Explained by the exposure to certain gram negative bacteria and fungi that were found in animal sheds
- Chronic exposure of microbial compounds in farm dust
 - Enhanced expression of A20, an ubiquitin-modifying enzyme that inhibits production of pro-inflammatory mediators via attenuation of NF-kB signaling.
 - SNP A20 encoding gene of farm children – asthma risk
- Increased barrier resistance in cultured human primary bronchial epithelial cells (PBEC) in response to farm dust

ACINETOBACTER IWOFFII IN SKIN MICROBIOME

- more abundant presence in the skin microbiome of healthy individuals compared to allergic ones
 - correlated with a higher expression of anti-inflammatory molecules by their peripheral blood mononuclear cells
- Isolated from farm cowsheds : transmaternal protection against allergic airway inflammation in mice
- Exposure to the commensal flora is currently considered as one of the first and strongest signals in this perspective.

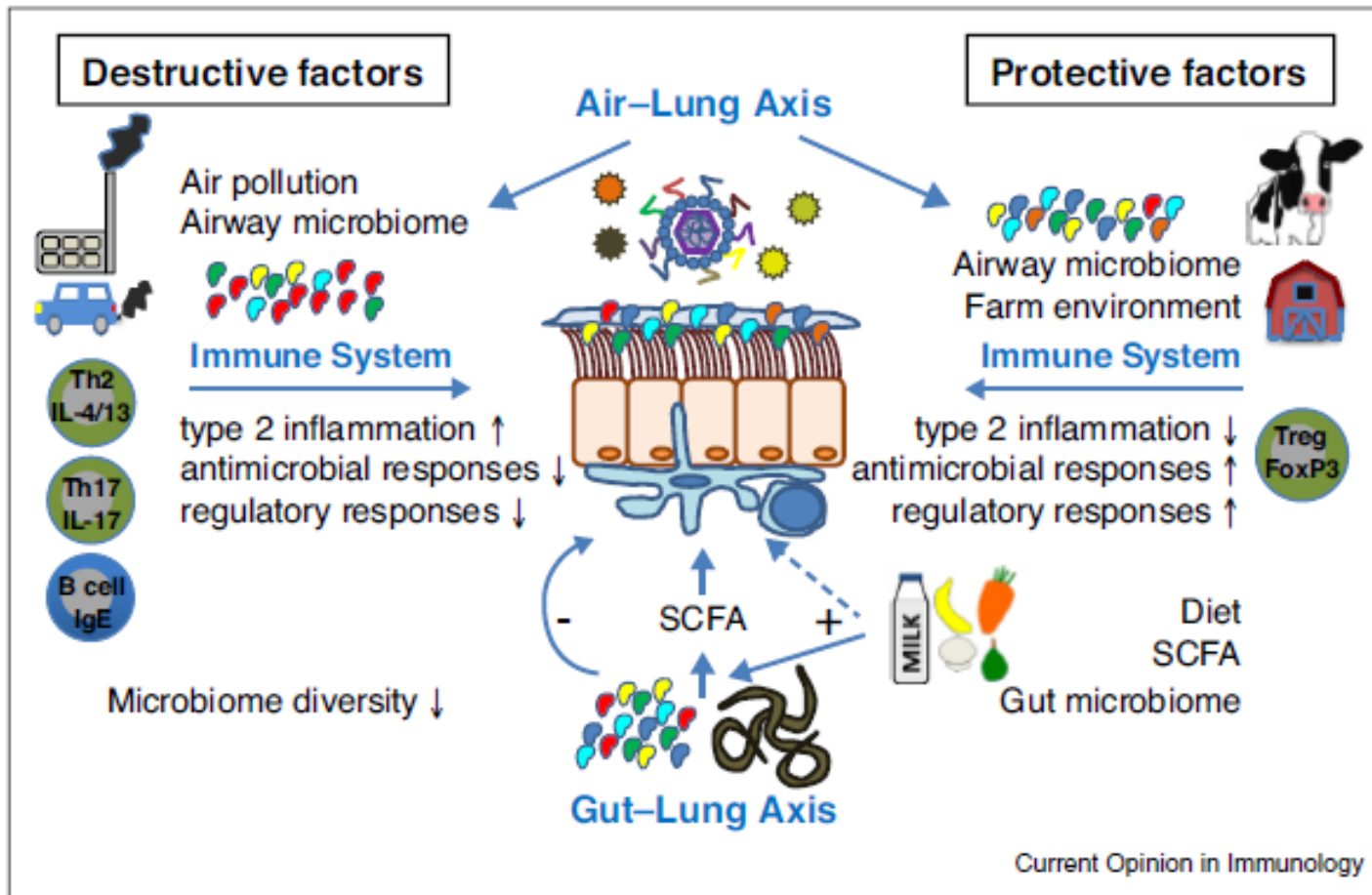
CAESAREAN DELIVERIES

- Increased risk to develop allergies and asthma during childhood for children born by C-sections
 - the composition of the gut microbiome from children delivered by C-section could partially be restored by immediate exposure to maternal vaginal fluids after birth
- Process of labor may 'stress' the immune system and form the first signal to drive immune activation

EXPOSURE TO ENVIRONMENTAL MICROBES: SUMMARY

- Exposure to environmental microbes at early age is a determinant in the risk to develop asthma and allergies.
- may be explained by
 - the microbiome composition at mucosal surfaces
 - a shifted maturation of the (innate) neonatal immune system

EARLY ENVIRONMENTAL FACTORS SHAPING CHILDHOOD ASTHMA AND ALLERGY

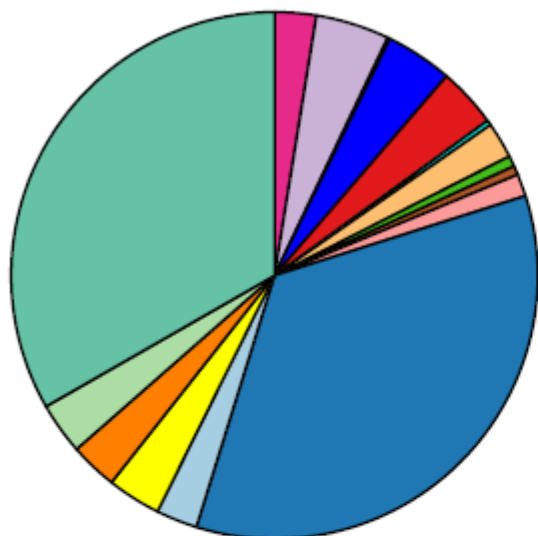


TAKE HOME MESSAGE

환경 중 미생물의 노출에 의한 선천면역(기
도상피세포의 mucosal immunity 포함)의 활
성화는 천식 및 알레르기의 예방에 중요.

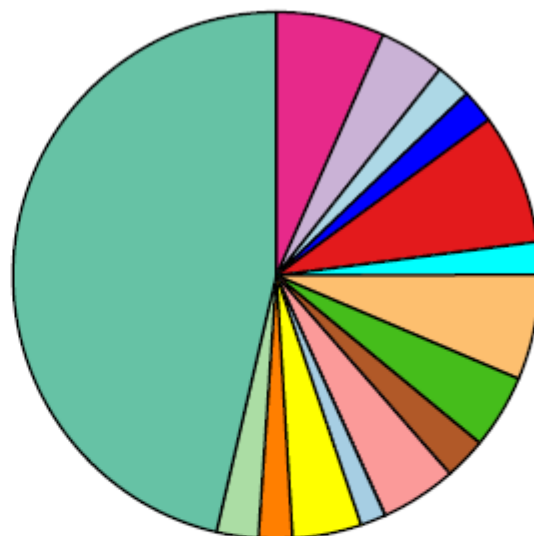
경청해 주셔서 감사합니다

Amish



- *Corynebacteriaceae* (0.026 vs. 0.067)
- *Micrococcaceae* (0.045 vs. 0.04)
- *Prevotellaceae* (0.001 vs. 0.022)
- *Bacillaceae* (0.041 vs. 0.021)
- *Staphylococcaceae* (0.037 vs. 0.08)
- *Lactobacillaceae* (0.003 vs. 0.02)
- *Streptococcaceae* (0.022 vs. 0.065)
- *Clostridiaceae* (0.007 vs. 0.046)

Hutterite



- *Lachnospiraceae* (0.005 vs. 0.026)
- *Ruminococcaceae* (0.014 vs. 0.047)
- *Bartonellaceae* (0.347 vs. 0)
- *Rhodobacteraceae* (0.025 vs. 0.016)
- *Sphingomonadaceae* (0.033 vs. 0.042)
- *Enterobacteriaceae* (0.029 vs. 0.021)
- *Moraxellaceae* (0.032 vs. 0.026)
- *Other* (0.333 vs. 0.463)