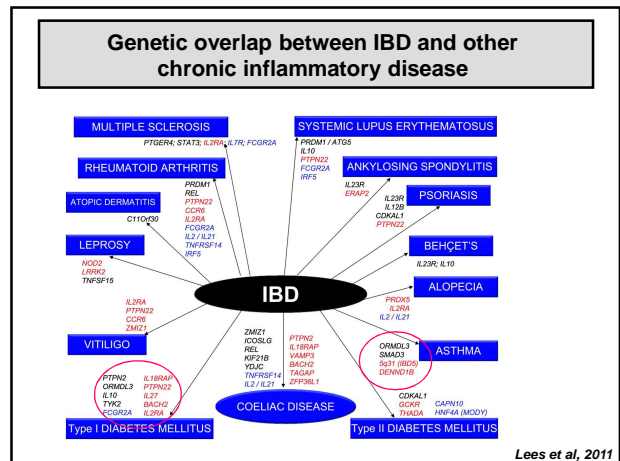
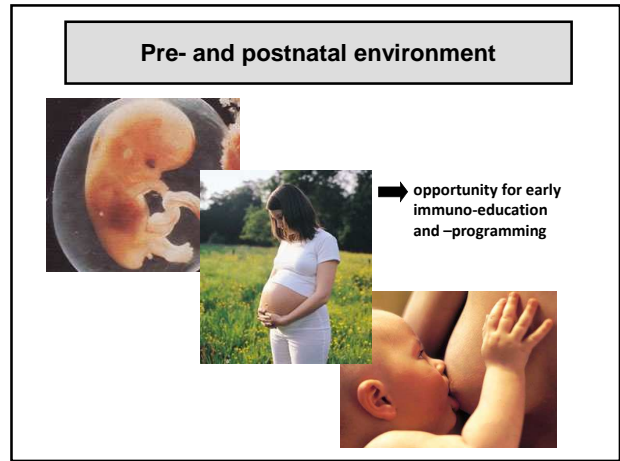
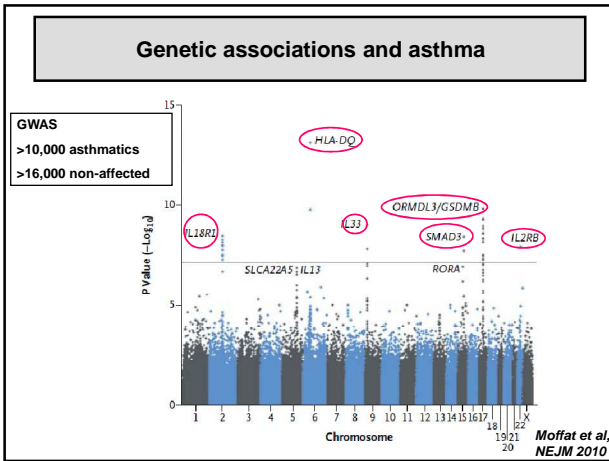


Genetics and rheumatoid arthritis

Candidate Gene and Pathway	SNP Locus	Function Relevant to Pathogenesis
T-cell activation		
HLA-DRE1	6p21	HLA-DRE1 allele (also known as the shared epitope) involved in MHC molecule-based antigen presentation and responsible for self-peptide selection and T-cell response; first discovered and still by far the strongest genetic risk for rheumatoid arthritis
PTPN22	1p13.2	Lymphocyte-specific tyrosine phosphatase involved in regulation of activation threshold of lymphocytes; second genetic hit described in rheumatoid arthritis
AP33	2q11.2	Transcription factor for lymphoid development
CD28	2q31.2	Costimulatory molecule for T-cell activation
CD40	20q13.12	Costimulatory molecule that enhances interactions between T and B cells and increases auto-antibody production
CTLA4	2q31.2	Costimulation suppressor that regulates interactions between T cells and antigen-presenting cells
IL2RA	10p15.1	High-affinity receptor for interleukin-2 on lymphocyte subsets
IL2	4q27	Cytokine that regulates activation of T cells, particularly regulatory T cells
IL-21	4q27	Cytokine that regulates differentiation of T cells, particularly Th17, and activation of B cells
PRKCE	10p15.1	Member of the protein kinase C family that regulates T-cell and macrophage activation
STAT4	2q31.3	Transducer of cytokine signals that regulate proliferation, survival, and differentiation of lymphocytes
TAGAP	6q25.3	Rho GTPase enzyme involved in T-cell activation
NF-κB pathway		
REL	2q31.1	Proto-oncogene member of the NF-κB family that regulates leukocyte activation and survival
TNFAIP3	6q21.3	Signaling protein and negative regulator of TNF-α-induced NF-κB activation
TNFA17	9q31.1	Regulator of TNF-α-receptor superfamily signaling (e.g., to NF-κB and JNK)
Other pathways		
BLK	8p23.1	B-lymphoid tyrosine kinase involved in B-cell receptor signaling and B-cell development
CCLE1	9p13.1	Chemokine implicated in germinal center formation
CCR2A	10q13.2	Low-affinity IGF-1 receptor that regulates macrophage and neutrophil activation and immune-complex clearance
RAD51	17q36.2	Enzyme that converts epigenetic to chromatin, creating autoantigens in rheumatoid arthritis
PRDM1	6q21	Protein that acts as a repressor of interferon gene expression
TNFRSF14	12p13.32	TNF-α-receptor superfamily member with proinflammatory activity

McInnes and Schett, NEJM 2011





The fetal origins of adult disease: Barker Hypothesis

is strongly associated with

Reduced birthweight and infant weight

→

Coronary heart disease

Study population:

- 5654 men
- born in East Hertfordshire
- between 1911 and 1930

Dr. David Barker

D.J.P. Barker; *British Medical Journal*, 1992
 D.J.P. Barker; *The Lancet* 1989

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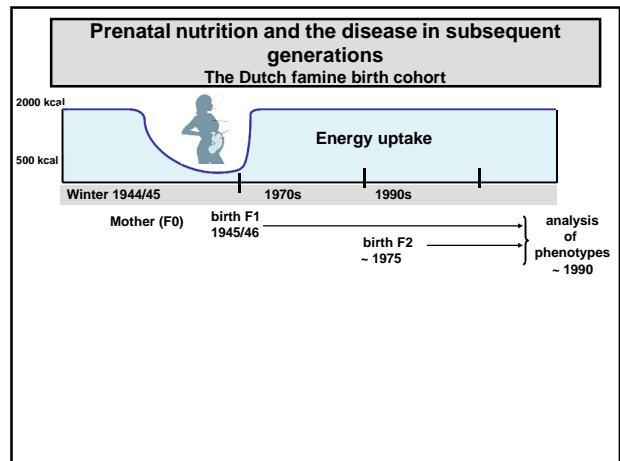
Study population:

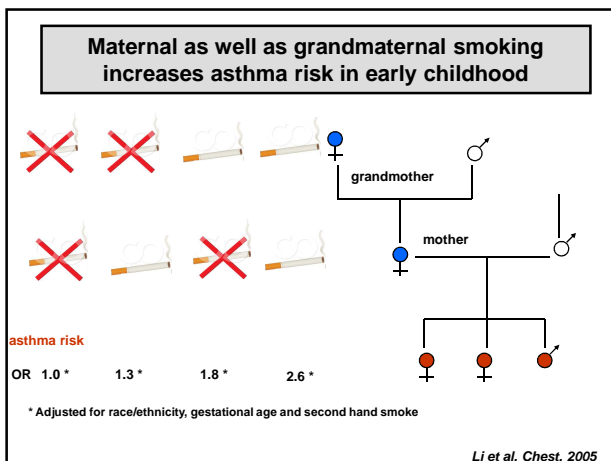
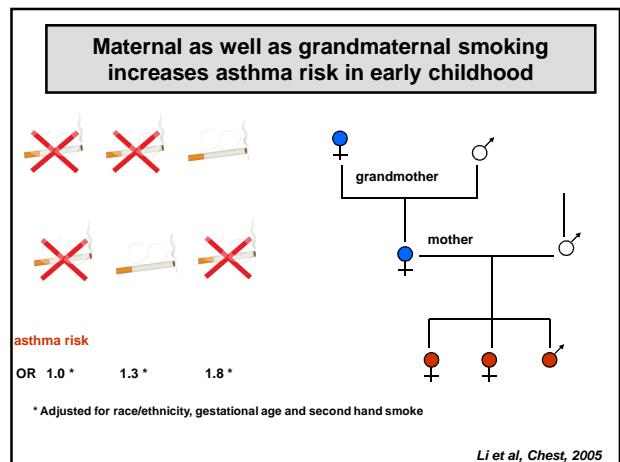
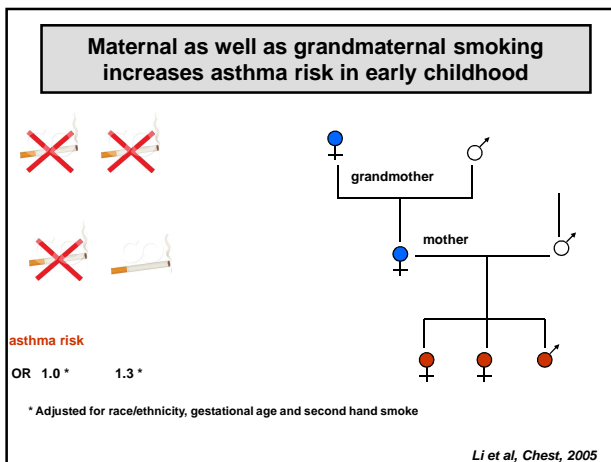
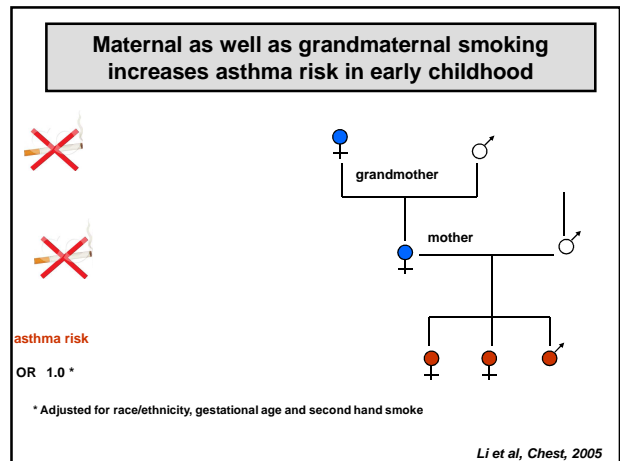
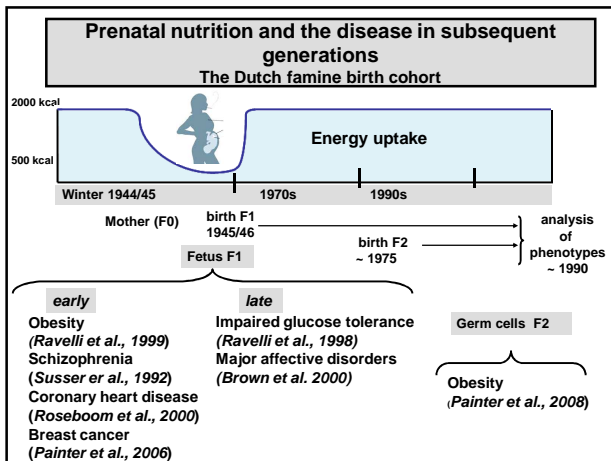
- 5654 men
- born in East Hertfordshire
- between 1911 and 1930

- Hypertension
- Stroke
- T2D
- Osteoporosis
- Aging
- Breast and ovarian cancer

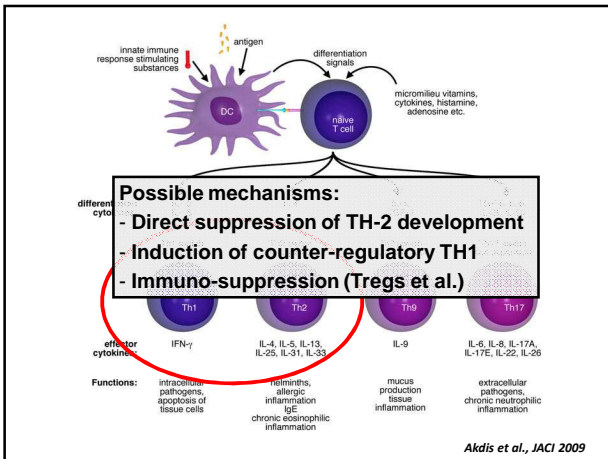
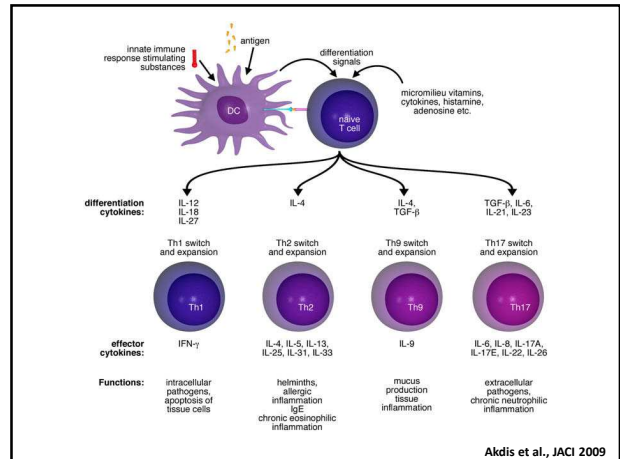
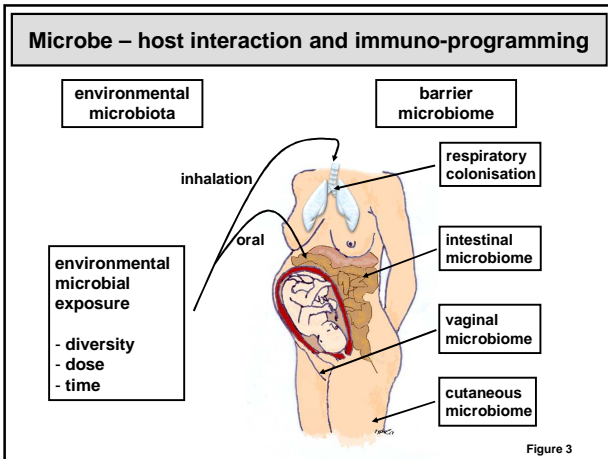
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D.J.P. Barker; *British Medical Journal*, 1992
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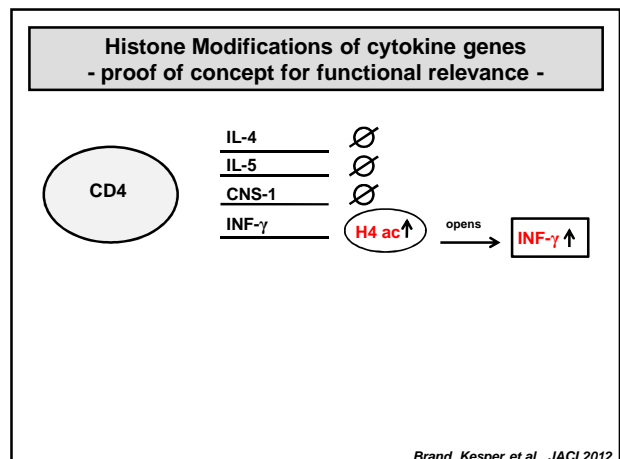
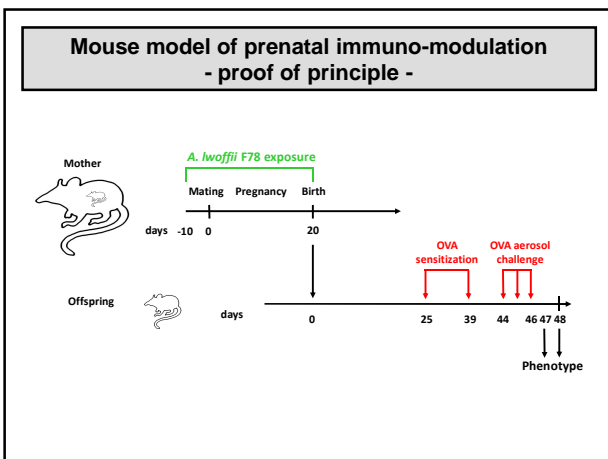
- ### Loss of clinical and immunological tolerance
- ➔ Hygiene hypothesis
 - Lack of infectious microbes in early childhood
 - Altered exposure to environmental microbes
 - Examples:
 - having older siblings
 - frequent viral infections
 - anthroposophical life style
 - early day care
 - traditional farming

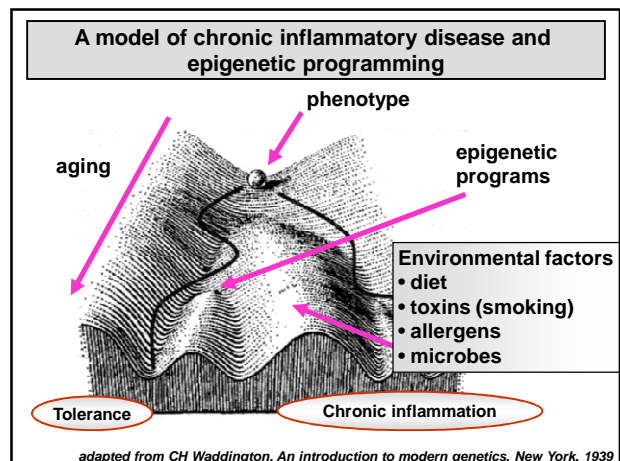
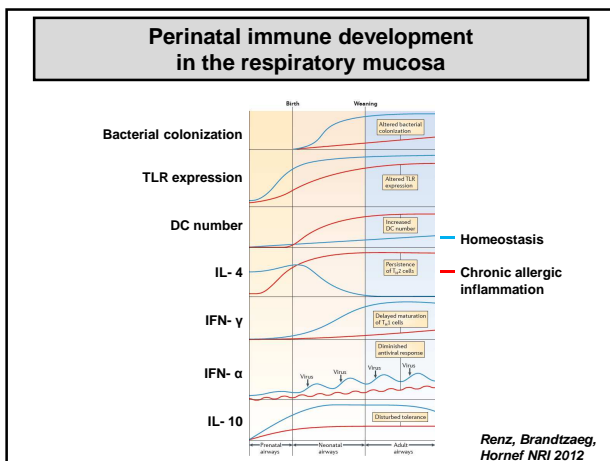
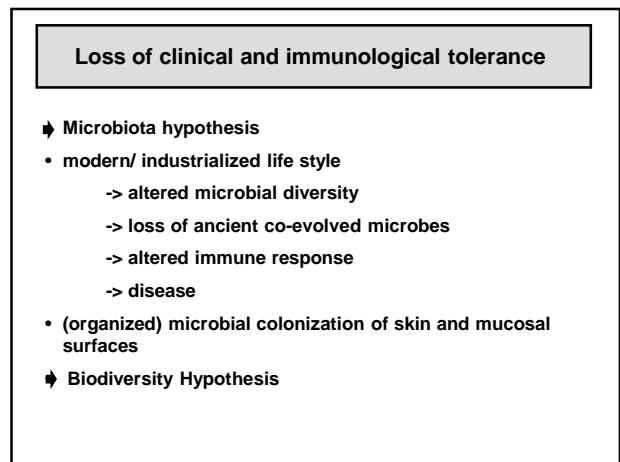
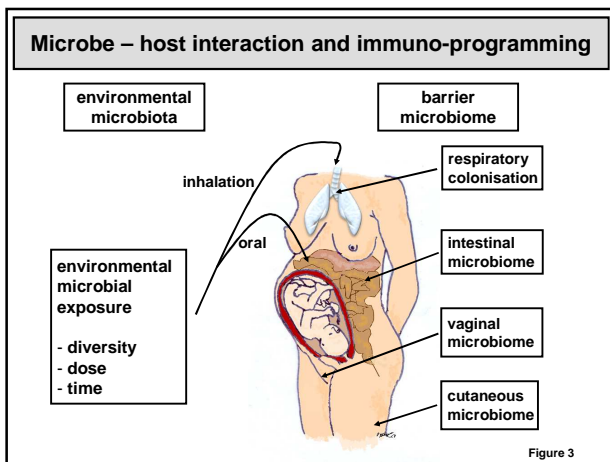
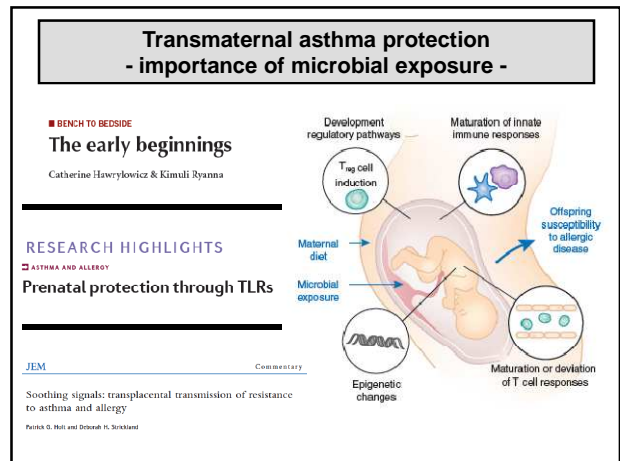
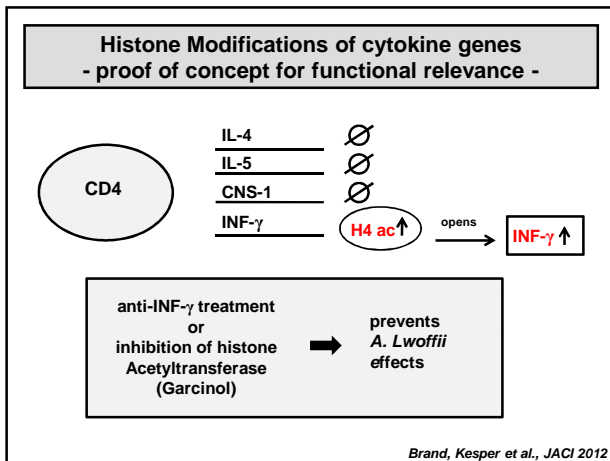


Environmental microbes with asthma protective properties

Acinetobacter lowffii	-	TH1 / IFN γ	↑	1)
Staphylococcus sciuri	+	T-cell activation	↓	2)
Lactococcus lactis	+	TH2 ↓ (IFN γ) ↑		3)
Bacillus licheniformis	+	TH1 pathology		4)
Lactobacillus GG	+	(T-cell activation ↓)		5)
LPS	-	IL-12 ↑ / gram mechanism	TH1 ↑	5)

1. Conrad et al, JEM 2009
 2. Hagner-Benes et al, submitted
 3. Debarry et al, JACI 2007
 4. Vogel et al, JACI 2008
 5. Blume et al, Clin Exp Res, 2007





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