

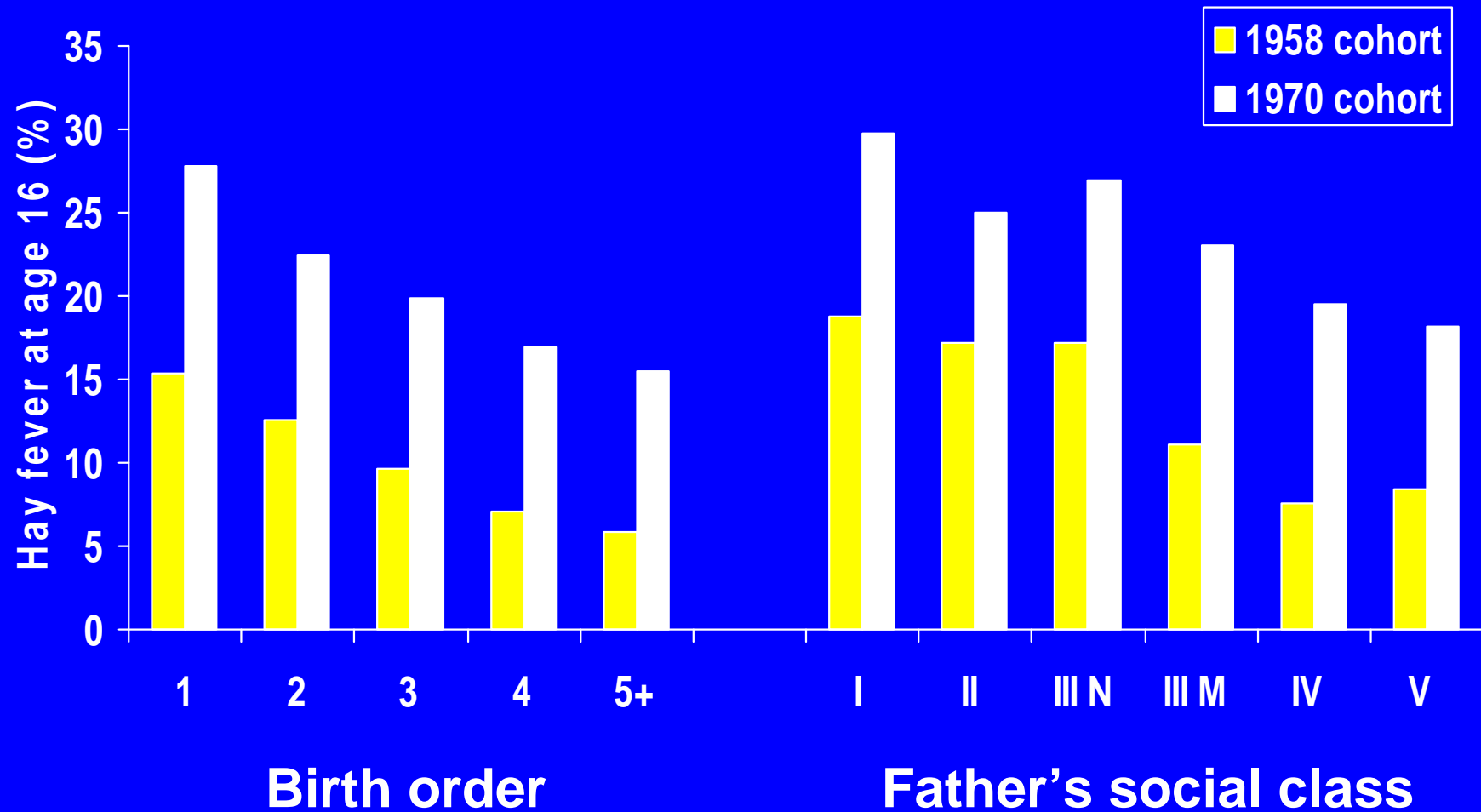
Twenty years of the hygiene hypothesis

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A little dirt never does any harm...



Hay fever, birth order & social class



The “hygiene hypothesis”

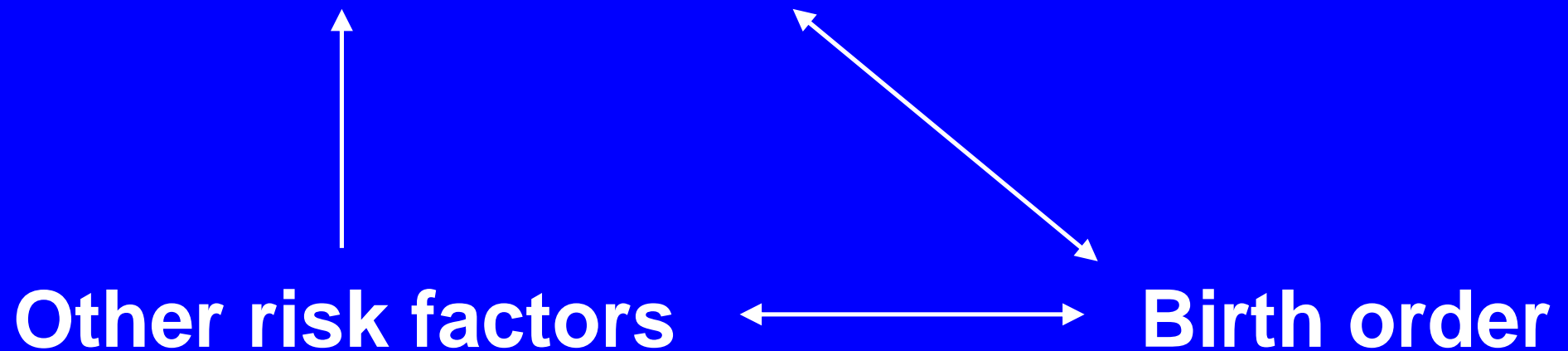
“ These observations ... could be explained if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings. ”

“ Over the past century ... reduced opportunities for cross-infection in young families ... may have resulted in more widespread expression of atopic disease. ”

Strachan D. Br Med J 1989;299:1259-60.

Interpreting the family size effect (2)

Allergic sensitisation





Ten years later ...

Immunologists are convinced (Th1/Th2)

Original association often been confirmed

No candidate agent or mode of infection

Hints that GI route may be important

Infection and allergy - hepatitis A

- Inverse association of specific IgE with seropositivity to hepatitis A among Italian air force recruits: a 50% reduction in risk (*Matricardi et al.*)
- Fairly specific to HAV: not found for CMV, measles, rubella, varicella, herpes simplex
- A similar association found in an Italian general population sample
- ... and in a case-control study in Scotland

Infection and allergy - bowel flora

- Reduced risk of allergy and specific IgE in children attending Rudolf Steiner schools in Sweden and New Zealand
- Fewer lactobacilli, more bifidobacteria and *Staph aureus* in commensal bowel flora of allergic children in Sweden and Estonia
- Increased risk of hay fever in German and UK children prescribed early antibiotics

Infection and allergy - farming



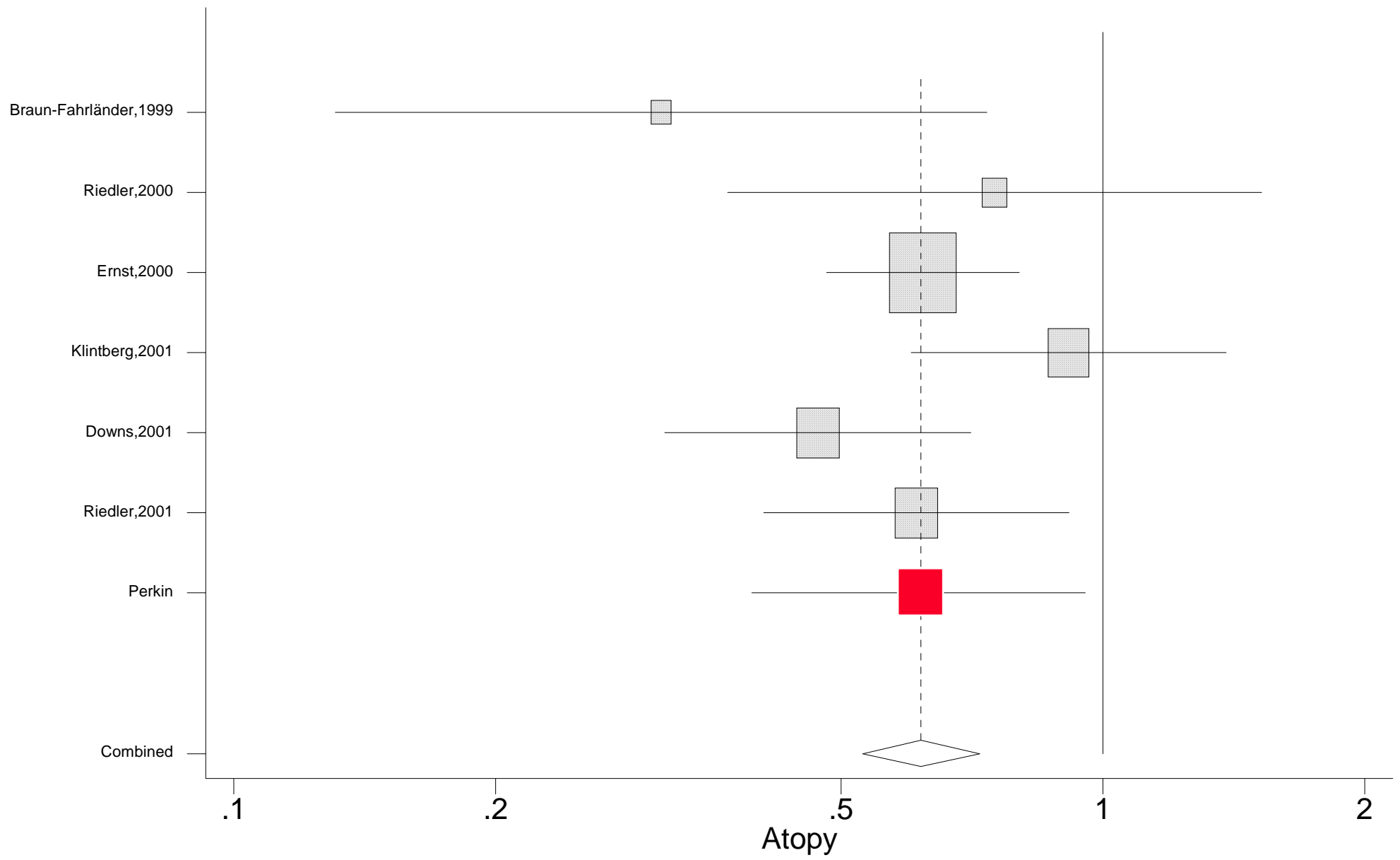
Infection and allergy - farming

Less allergy in farmer's children:

- **Swiss, Austrian and Bavarian Alps**
- **Finland and Sweden**
- **Quebec, Canada**
(mainly livestock)

Possible explanations:

- **“Poor hygiene”**
- **Animal contact**
- **Endotoxins**
- **Mycobacteria**
- **Unprocessed or unpasteurised foods**



The Shropshire Asthma & Allergy Study

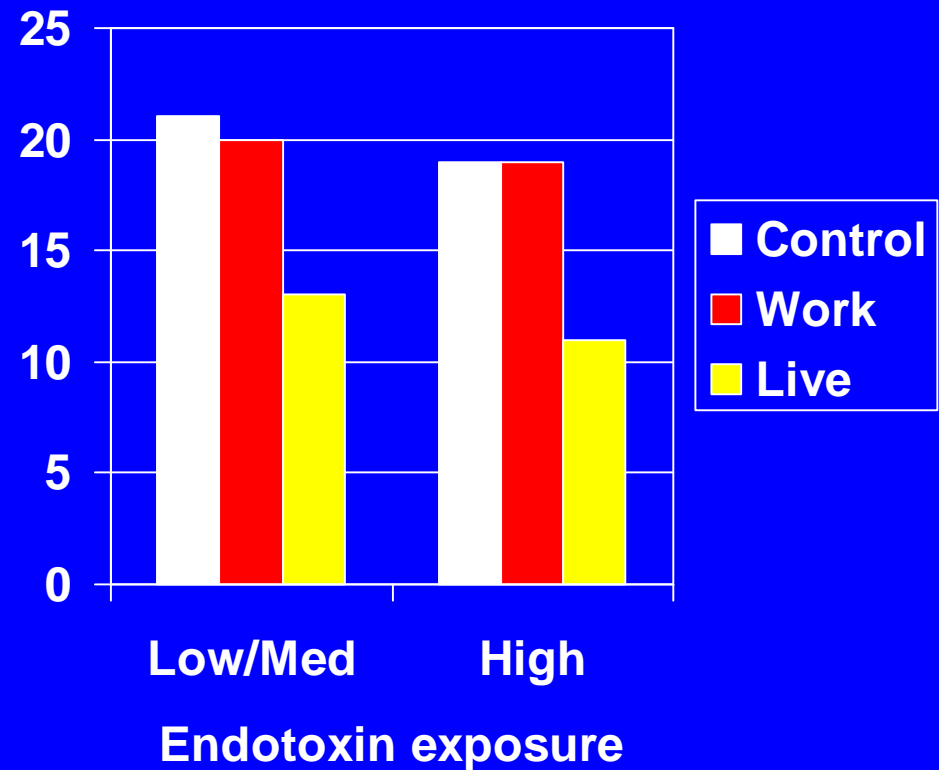
- First study of farmers' children in the UK
- Questionnaire survey of 4767 children aged 5-11 years in a rural area with mixed farming
- Clinical examination and environmental measures in stratified samples of children:
 - Parents live and work on a farm (n = 246)
 - Parents work on a farm, but live elsewhere (n = 118)
 - Non-farm workers, living in the same villages (n = 422)

Endotoxin and atopy in Shropshire

Endotoxin exposure



Skin prick positivity

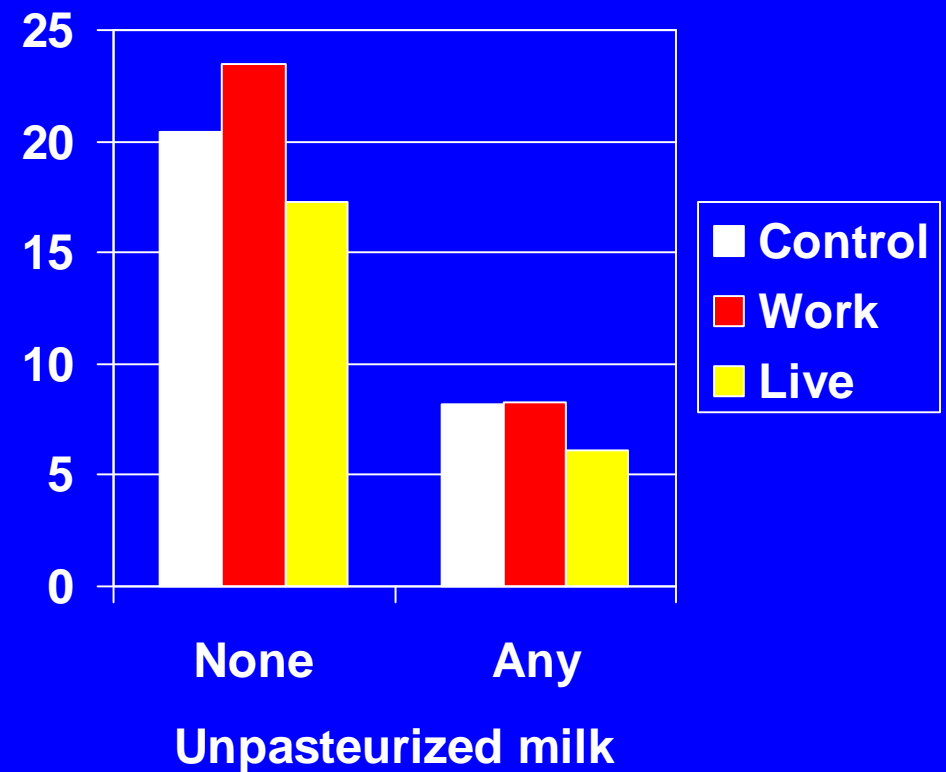


Unpasteurized milk & atopy in Shropshire

Unpasteurized milk



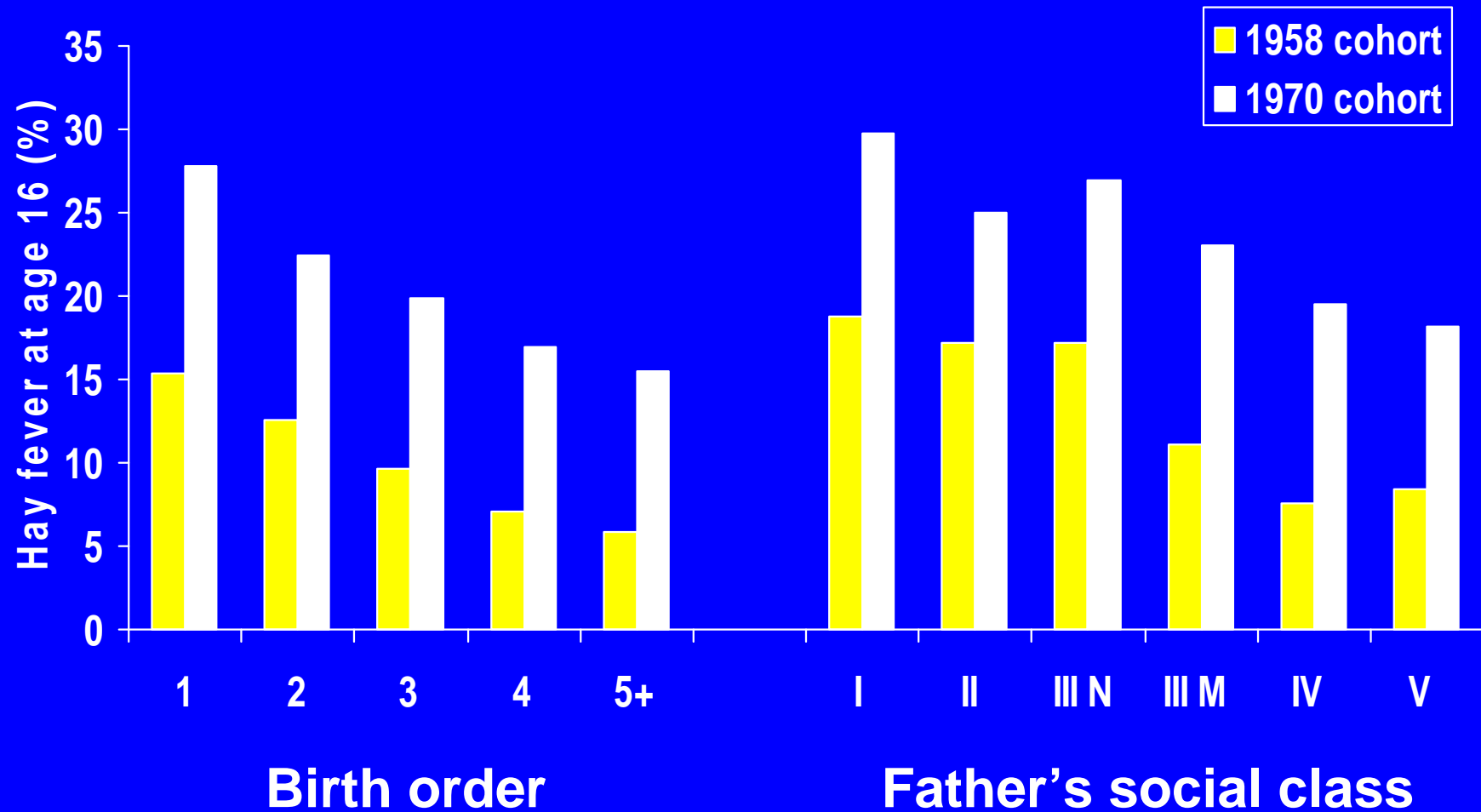
Skin prick positivity



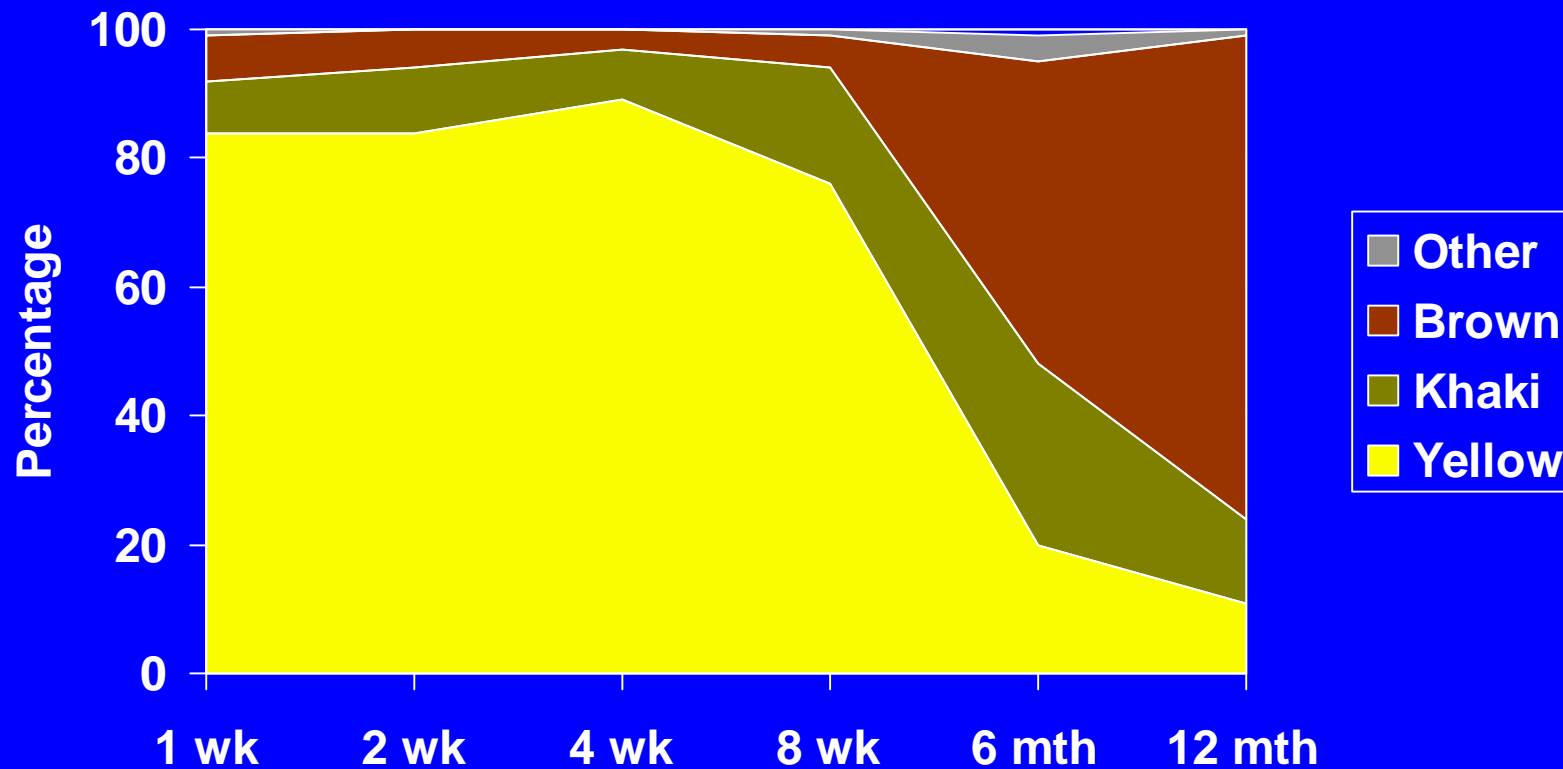
Allergy and infant bowel flora



Hay fever, birth order & social class

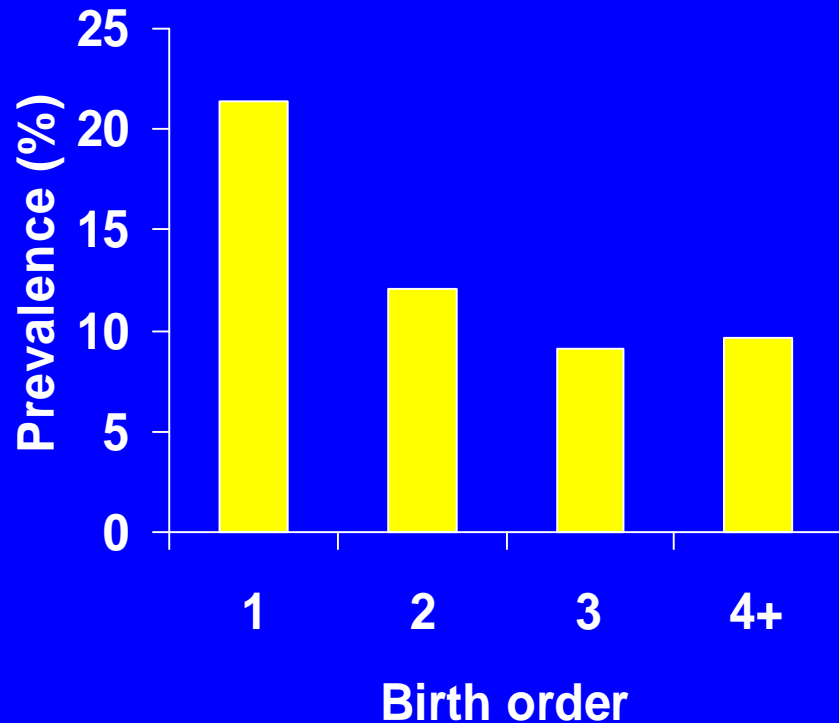


Stool colour change with age

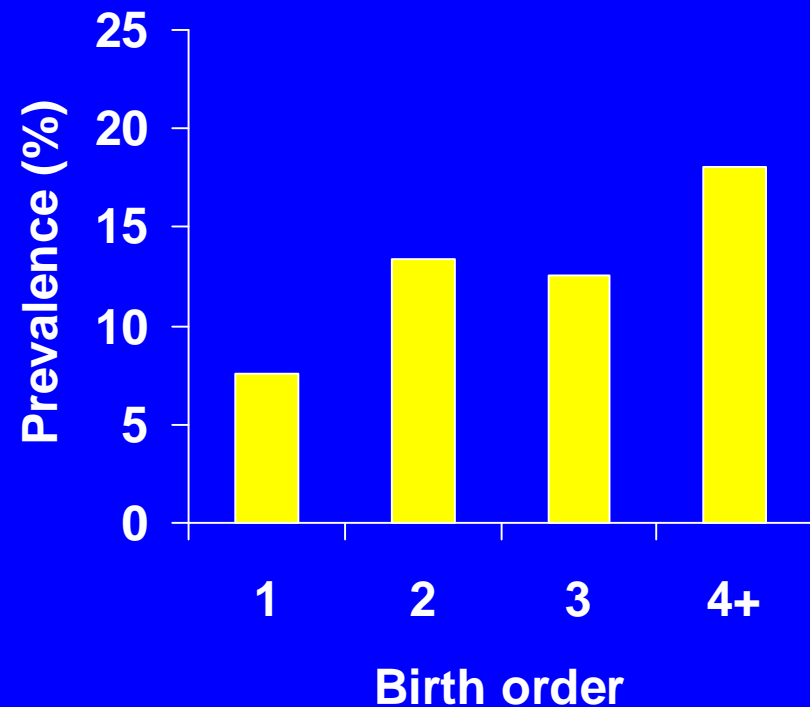


Brown infant faeces and birth order

Brown stools by 4 weeks



Never brown by 6 months



Avon Longitudinal Study of Parents and Children (ALSPAC)

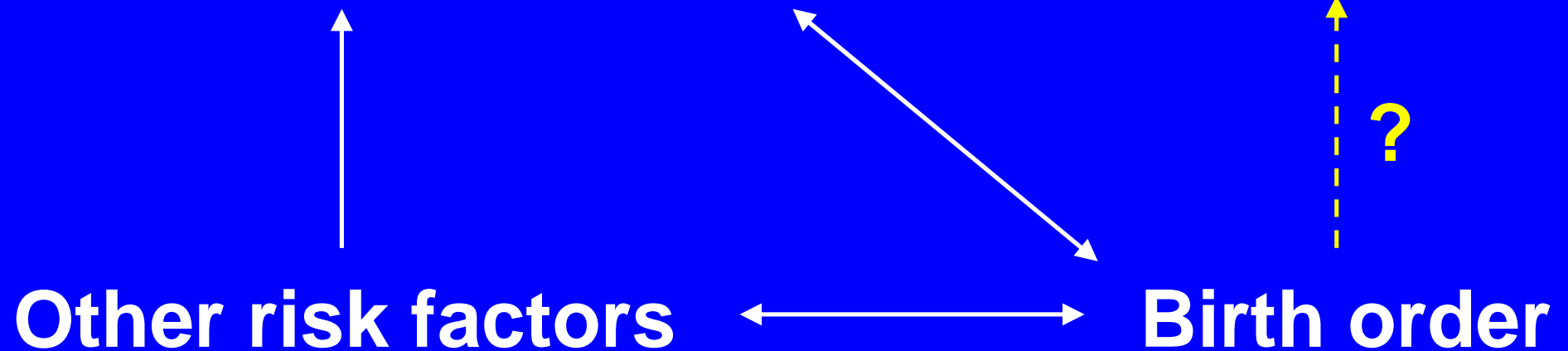
Birth order and infant bowel flora (1)

ALLERGY

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FLORA

Allergic sensitisation  Intestinal flora



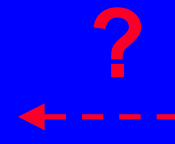
Birth order and infant bowel flora (2)

ALLERGY

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FLORA

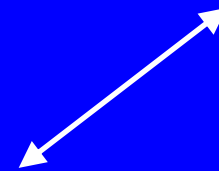
Allergic sensitisation



Intestinal flora



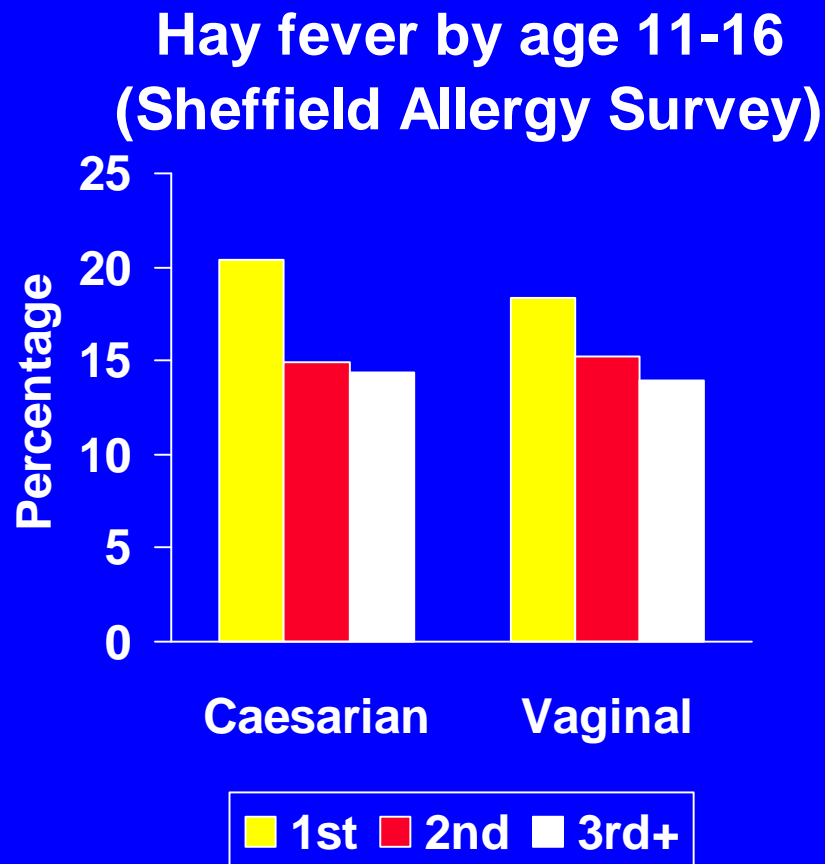
Birth order



Caesarian
delivery



Allergy by birth order and delivery



**B 1958 C
(HF, SPT)**

**Birth order Caesarian
order delivery**

Inverse None

**Sheffield
(Hay fever)**

Inverse None

**ALSPAC
(SPT)**

Inverse None



**What was known
about bowel flora
in normal infants?**

**Very little! (apart
from in Sweden)**

Plenty of bacteria ...

... plenty of mucosa

**Interest in probiotics
and novel species**

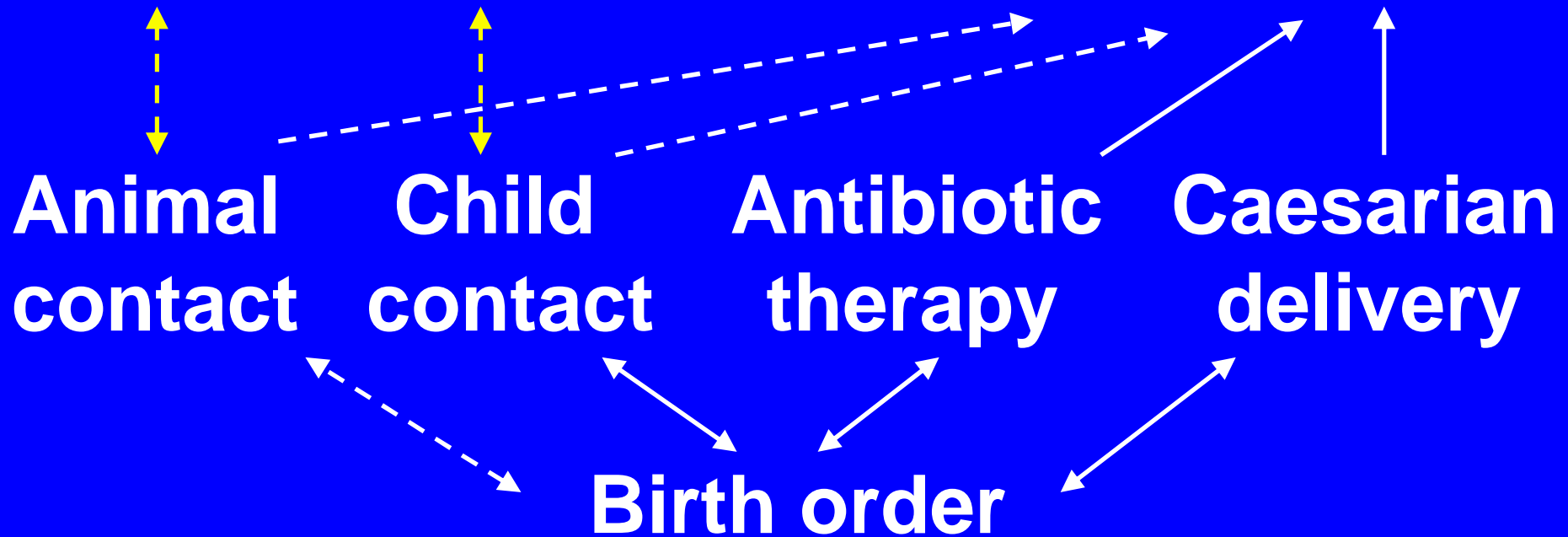
Allergy and infant bowel flora

ALLERGY

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FLORA

Allergic sensitisation ← - - - **Intestinal flora**



The Allergyflora Study

- Three birth cohorts (London, Goteborg, Rome), totalling 324 children followed to age 18 months
- Faecal aerobic and anaerobic bacteria cultured at 3, 7 & 14 days and 1, 2, 6 & 12 months
- Clinical examination at age 18 months:
 - Atopic eczema
 - Total IgE (analysed as continuum and ≥ 100 kU/L)
 - Food-specific IgE (FX5)
 - Inhalant-specific IgE (Phadiatop)

ALLERGYFLORA microbiology

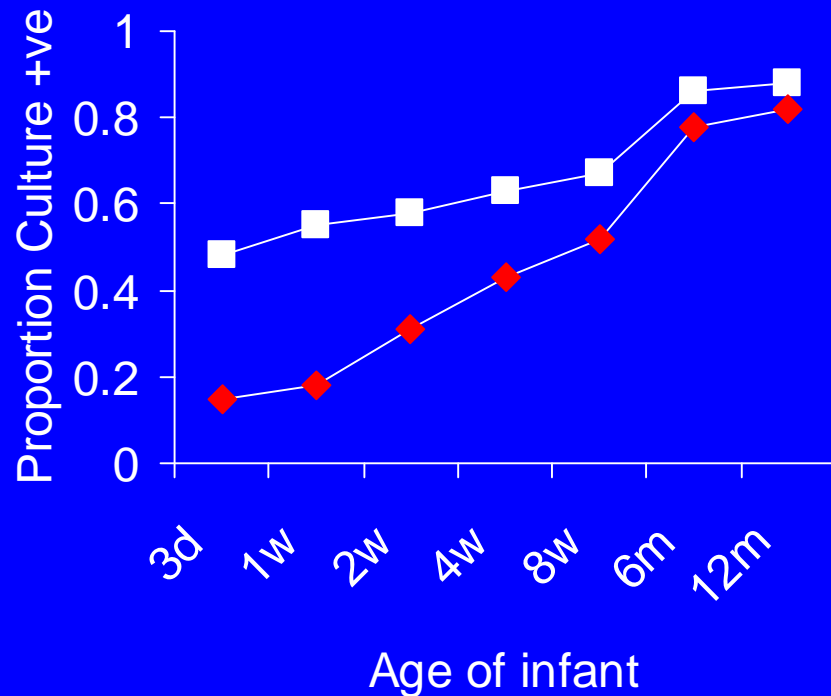
- Samples refrigerated at home, transported anaerobically to lab within 24 hours
- Aerobic cultures:
 - Blood agar
 - Drigalski (plus API)
 - Staphylococcal agar
 - Enterococcosel agar
- Anaerobic cultures:
 - Brucella blood agar
 - Bile esculin (plus API)
 - Beerens agar (plus PCR)
 - Rogosa agar (plus PCR)
 - Brucella alcohol agar
- Phage typing of E. coli (for strain turnover)

Two years going through the motions



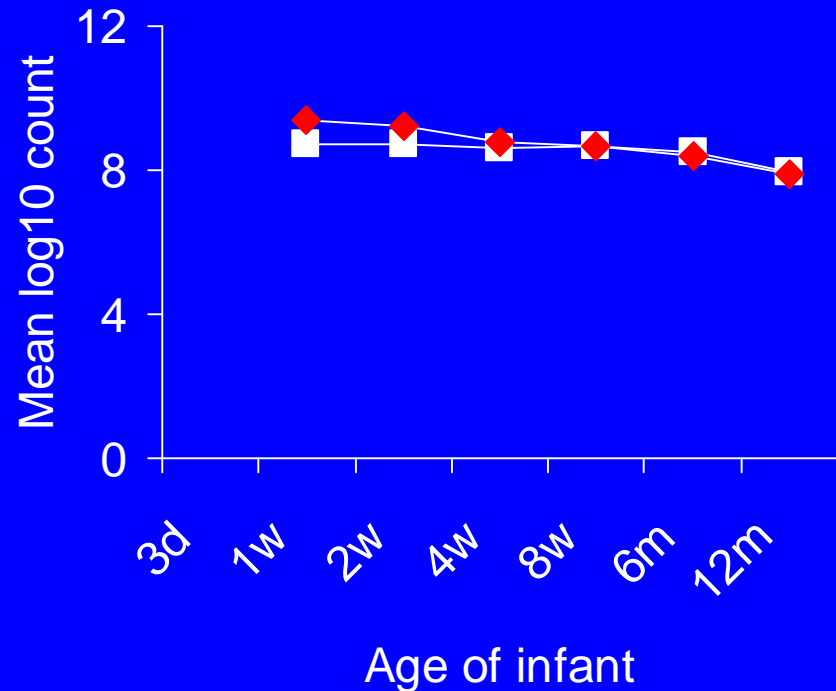
Escherichia v. mode of delivery

Positive cultures



■ Vaginal delivery

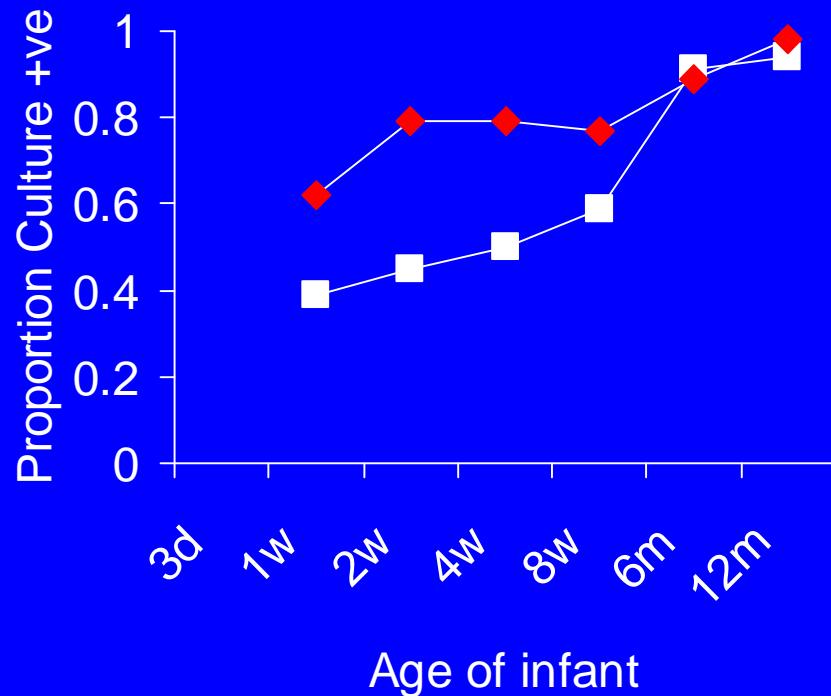
Mean log counts (if +ve)



■ Caesarian section

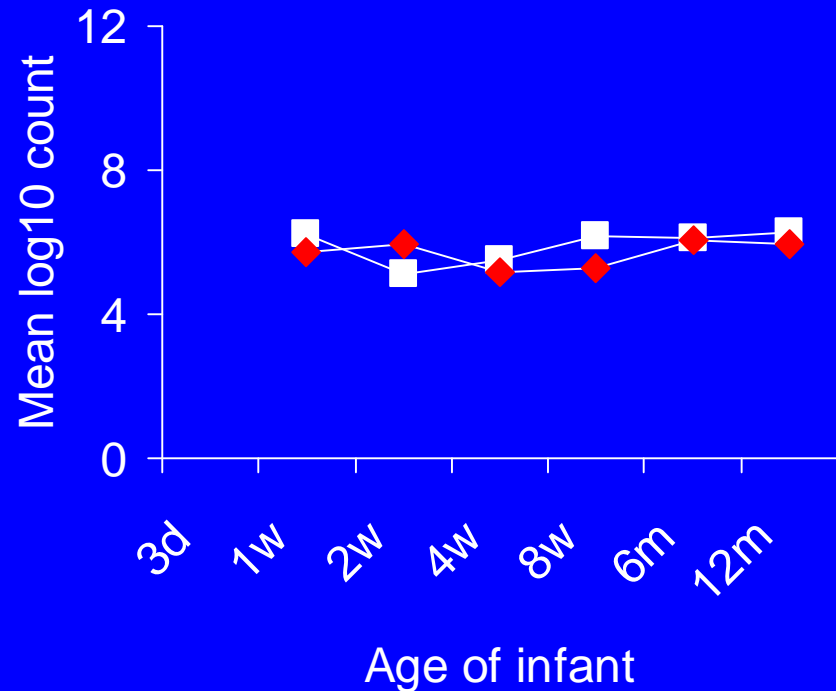
Clostridia v. mode of delivery

Positive cultures



■ Vaginal delivery

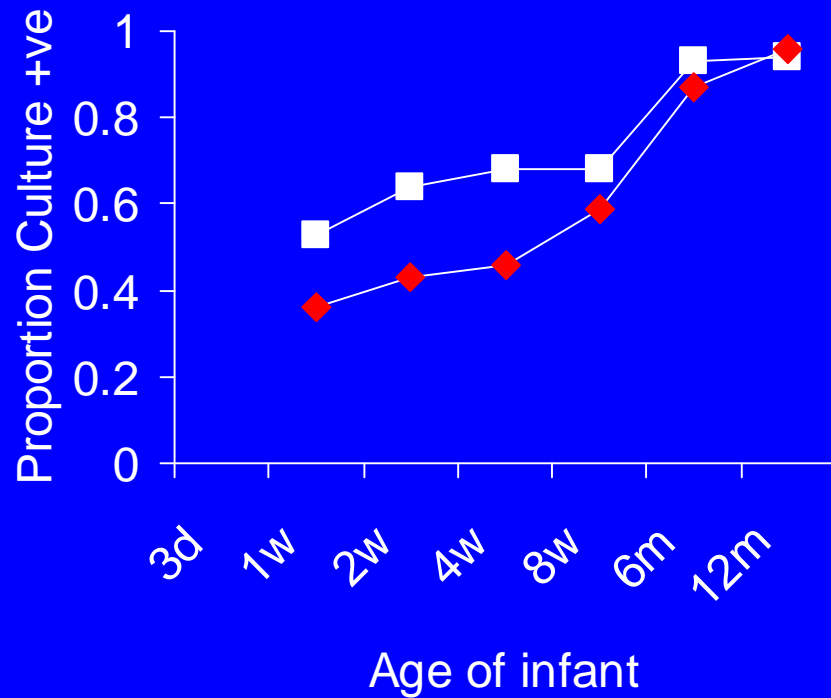
Mean log counts (if +ve)



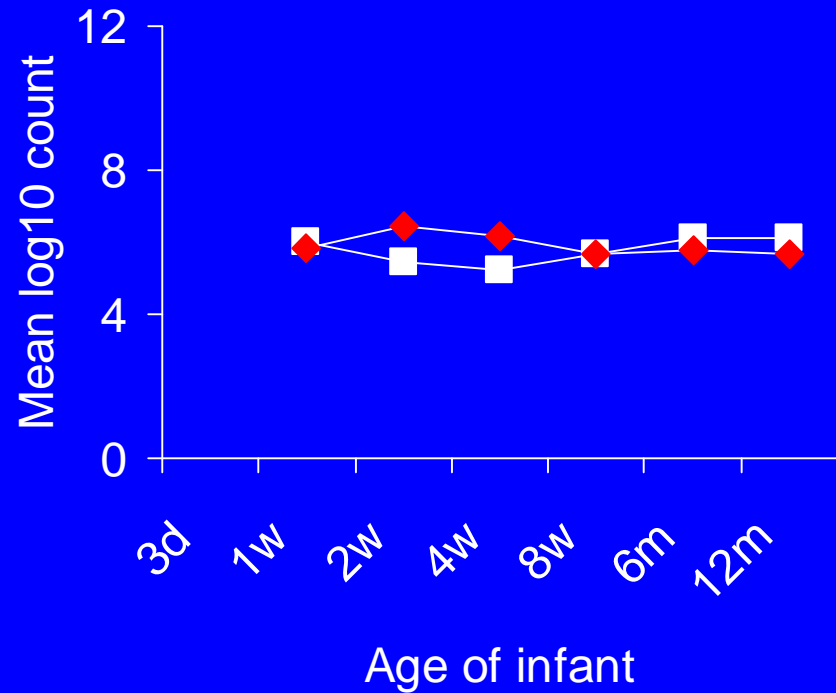
■ Caesarian section

Clostridia v. siblings

Positive cultures



Mean log counts (if +ve)



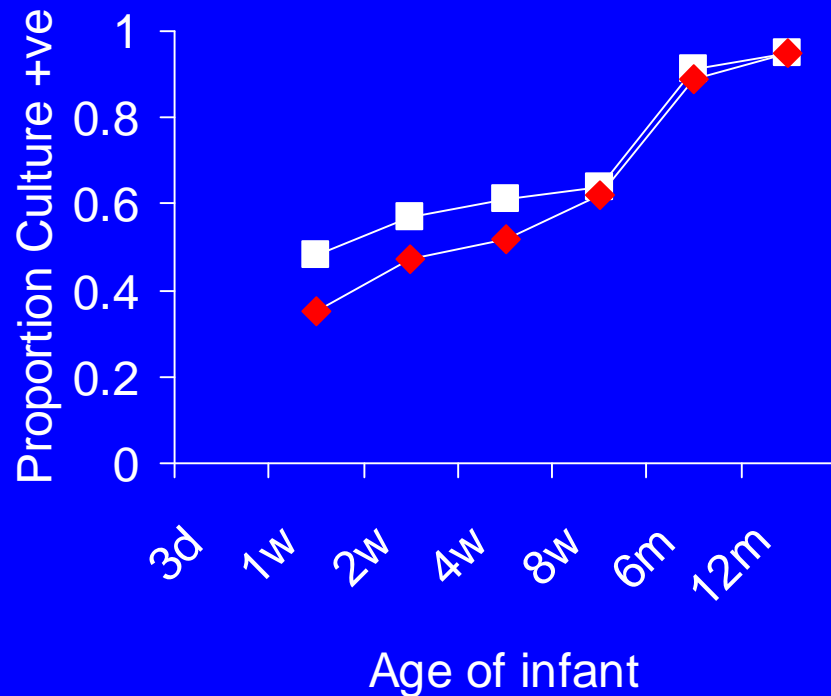
No siblings



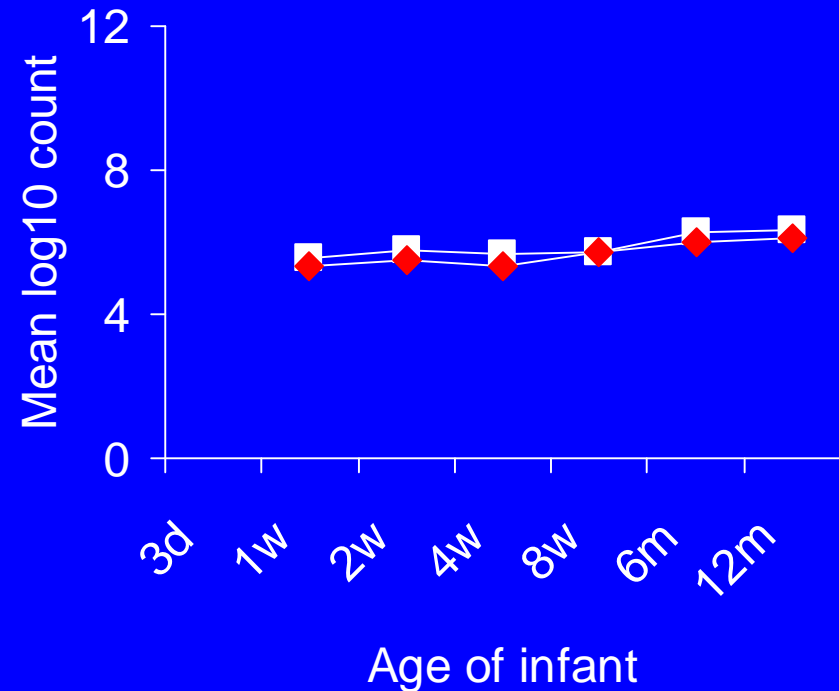
Any siblings

Clostridia v. eczema 18m

Positive cultures



Mean log counts (if +ve)



■ No eczema at 18 months

■ Eczema at 18 months

Bowel flora v allergy at 18m (1)

	Eczema	Food IgE	Total IgE
Age at acquisition of:			
Escherichia	-	-	-
Klebsiella	-	-	-
Other Enterobacteria	-	-	-
Staph. aureus	-	-	-
Enterococci	-	-	-

Bowel flora v allergy at 18m (2)

Eczema Food IgE Total IgE

Age at acquisition of:

Bacteroides	-	-	-
Bifidobacteria	-	-	-
Lactobacilli	-	-	p = 0.03
Clostridia	-	-	-

Bowel flora v allergy at 18m (3)

	Eczema	Food IgE	Total IgE
Number of species of:			
Enterobacteria	-	-	-
Bacteroides & related	-	-	-
Log counts for:			
All species	-	-	-
Gram - / gram +	-	-	-
Anaerobes / aerobes	-	-	-

A pessimistic conclusion!

ALLERGY

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FLORA

Allergic sensitisation  Intestinal flora

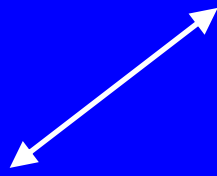
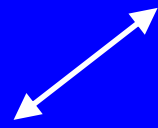
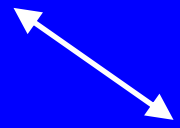
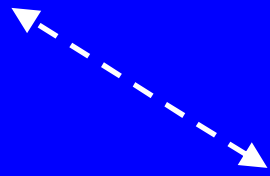


Pets in house

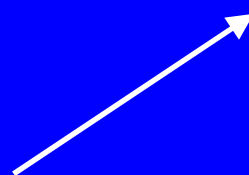
Child contact

Antibiotic therapy

Caesarian delivery



Birth order





Twenty years on...

**Infant bowel flora
does not explain
birth order effect**

**Major determinants
of flora are not risk
factors for allergy**

**Continuing interest
in the hygiene
hypothesis...!**

Vaccination, infections and allergy



Infection and allergy - TB / BCG

- **Inverse association of specific IgE with tuberculin reactivity in Japanese children routinely receiving BCG vaccine neonatally**
- **No such association found in Norwegian adults routinely vaccinated as adolescents**
- **One small Swedish trial suggests no large protective effect of neonatal BCG on atopy**
- **Clinical TB independent of atopy in Finland**

Does early BCG protect against allergy?

- 76,310 children born 'into' two large UK databases (GPRD and DIN)
- Followed for >5 years
- 7098 cases of hay fever
- Controls matched for age and general practice
- Adjustments for 'ghosts' & consultation frequency

2.5% BCG by age 2
(and 0.2% thereafter)

Pooled adjusted odds
ratio for hay fever:

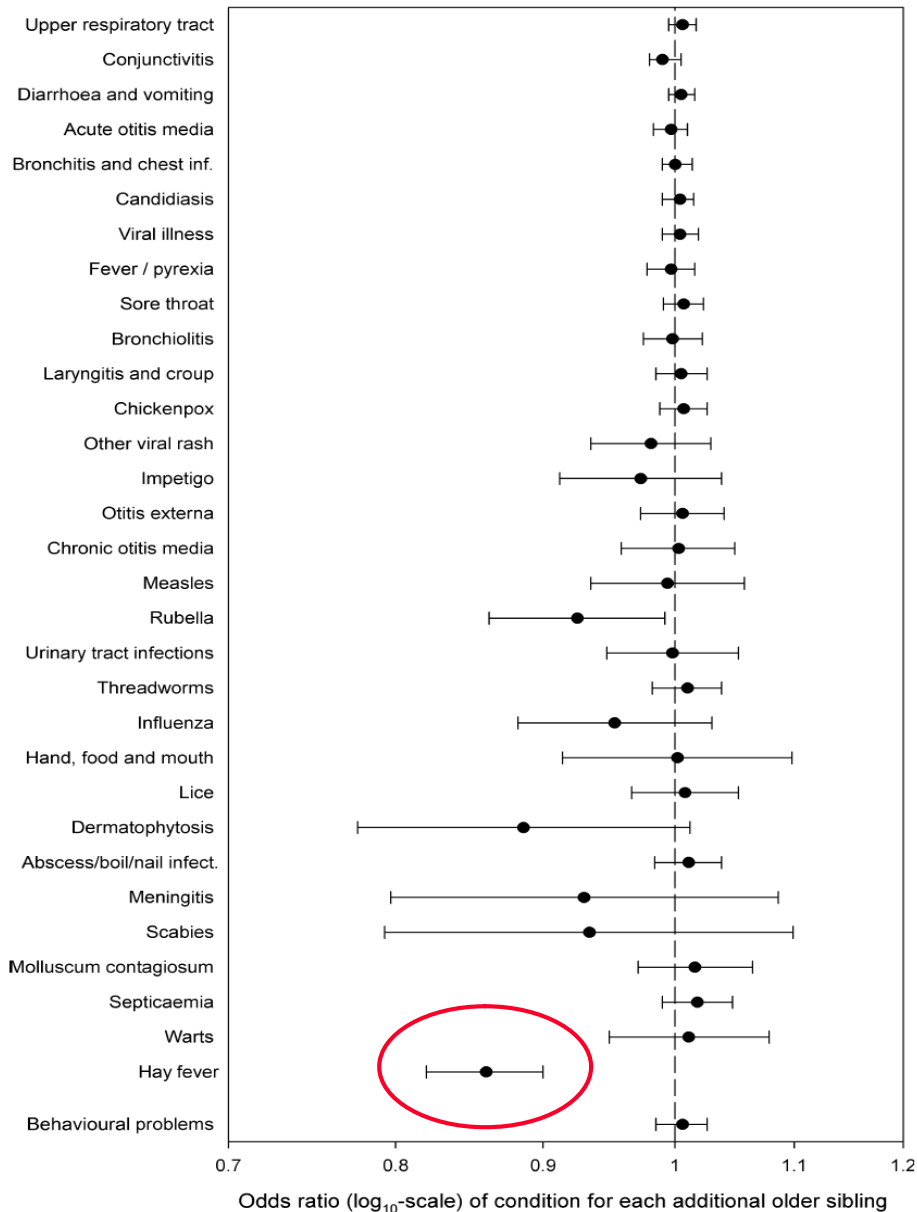
1.28 (0.96 - 1.73)

Protection unlikely

Illnesses v older siblings in the GPRD database

Common infectious illnesses not associated with position in sibship!

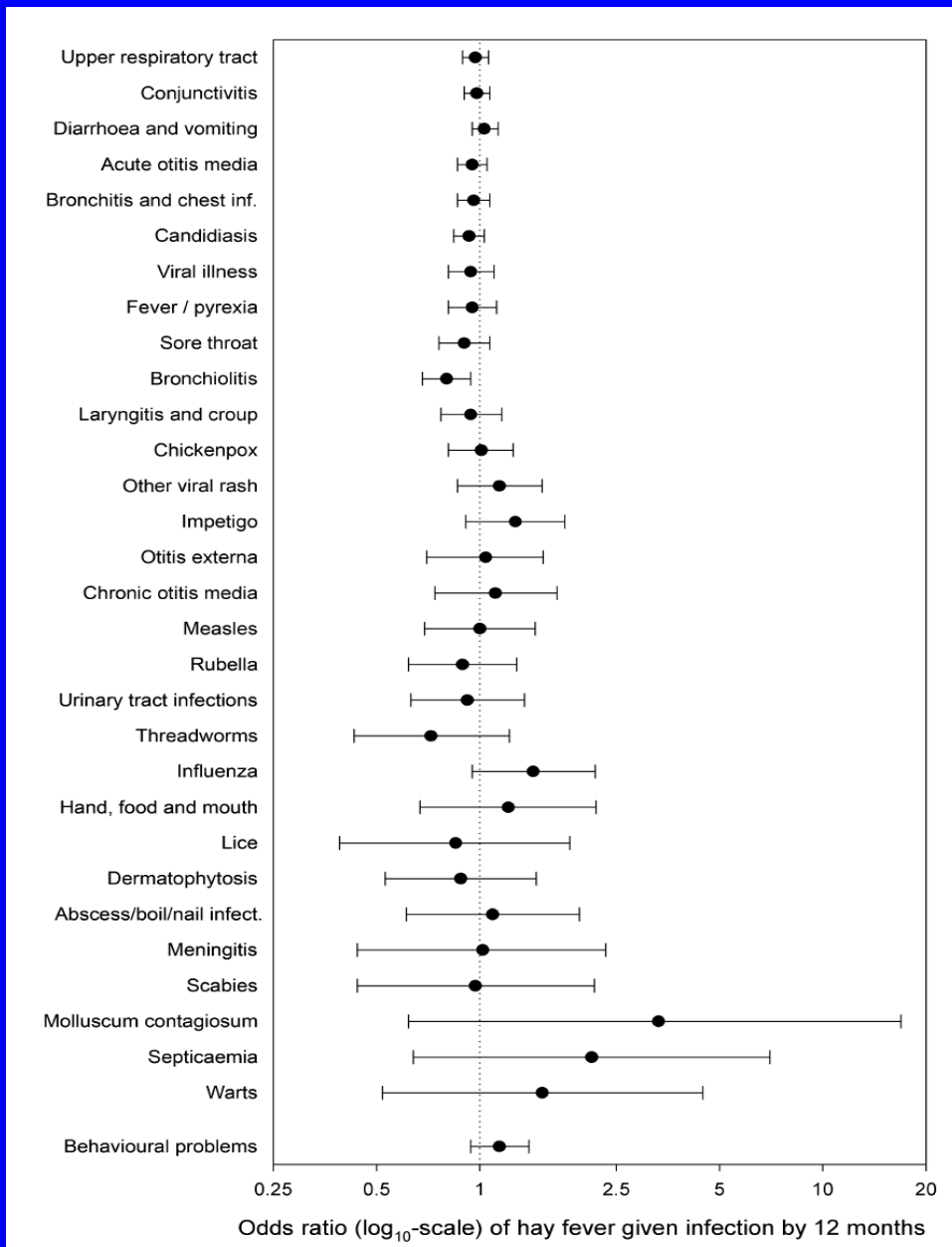
Inverse association with hay fever confirmed



Illnesses v hay fever in the combined GPRD and DIN databases

Common infectious illnesses not associated with hay fever, therefore:

... they can't explain the association of hay fever with older siblings.



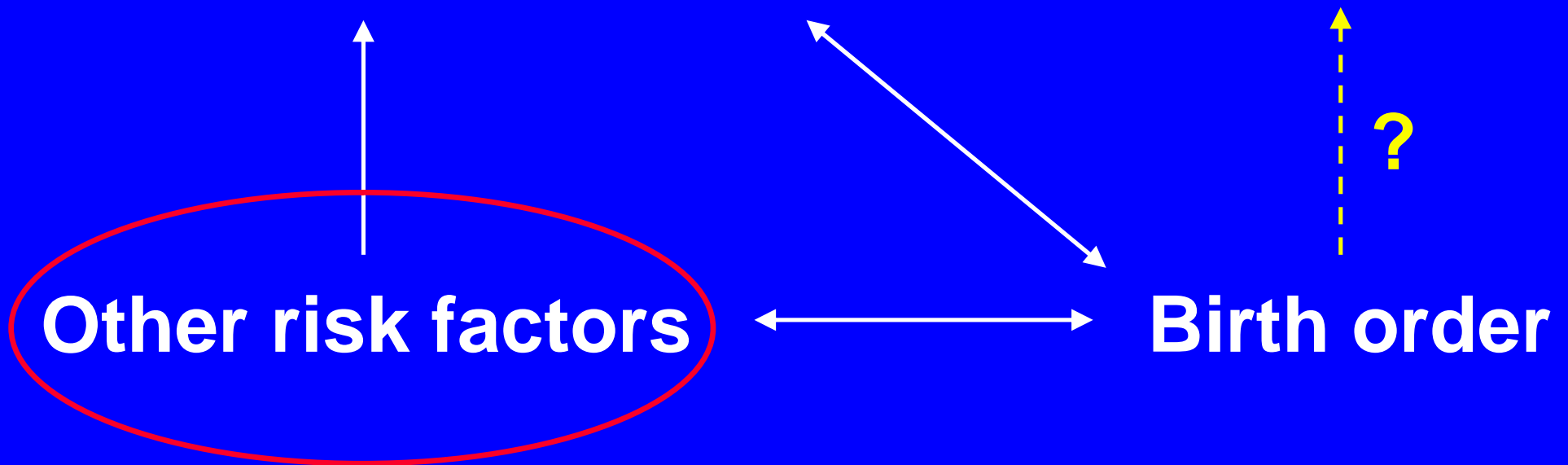
Birth order and infectious illness

ALLERGY

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INFECTION

Allergic sensitisation \leftarrow [?] Early illnesses



A little dirt never does any harm...

Farms



Nappies

Illnesses

Vaccines

The appliance of science?

I learned long ago,
never to wrestle with a pig.

You get dirty, and besides,
the pig likes it.

George Bernard Shaw



Original caption...

“Mum decided to see how long it would take before the kids did the housework for her on Mother’s Day.”