

# **Allergy: Risk factors and results from COPSAC**

**(Heterogeneity in Childhood Asthma  
and Allergy)**

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# Program

- **COPSAC**
- **Heterogeneity in childhood asthma and allergy**
- **Genetic heterogeneity**
- **Prevention**



# COPSAC (Copenhagen Prospective Study on Asthma in Childhood)

- Birth Cohort
  - 411 children
  - Asthmatic mothers
- Extensive objective phenotyping of atopic diseases (asthma, eczema, allergy)
  - Lung function from birth
  - Acute visits at lung and skin symptoms
- Environmental risk factors
- Genetics



# Asthma is a heterogenous disease

'Asthma. The word which properly signifies difficulty of breathing, has been as much misused, and has been made the cognomen of as many different diseases as any word in medicine.

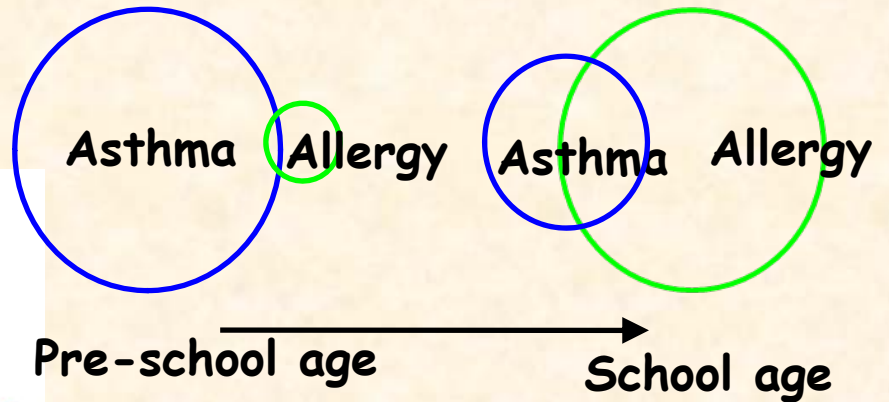
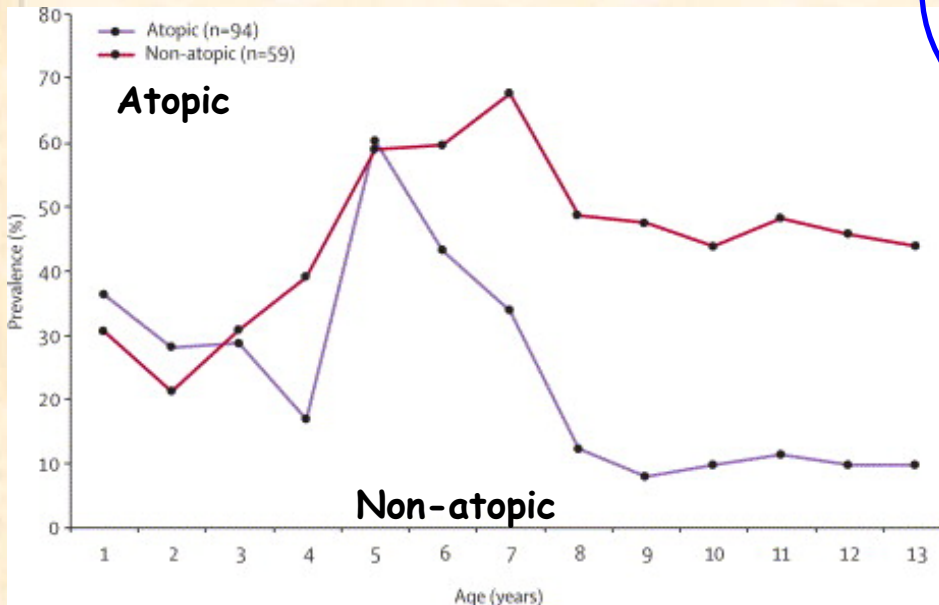
As in every other case, a more correct pathology in this disease will put us in the way of a more rational practice.'  
(Forbes 1834)

'Instead of wasting our efforts in attempting to ward off paroxysms of a purely spasmodic nature, by measures directed to the nervous system, our attention will be directed to the removal of the real disease, the structural alteration and pretematural sensibility of the bronchial membrane.'  
(Lancet 2006)  
(Forbes 1834)



# Heterogeneity of preschool Asthma

- **Course of disease**
  - Early transient, early persistent, late onset
- **Atopic vs non-atopic**



# Heterogeneity of preschool Asthma

- **Symptom inducing factors**
  - Viral vs multitrigger wheeze
- **Pathophysiology**
  - Neutrophilic vs eosinophilic inflammation
- **Etiology (?)**



# Problems with current phenotyping

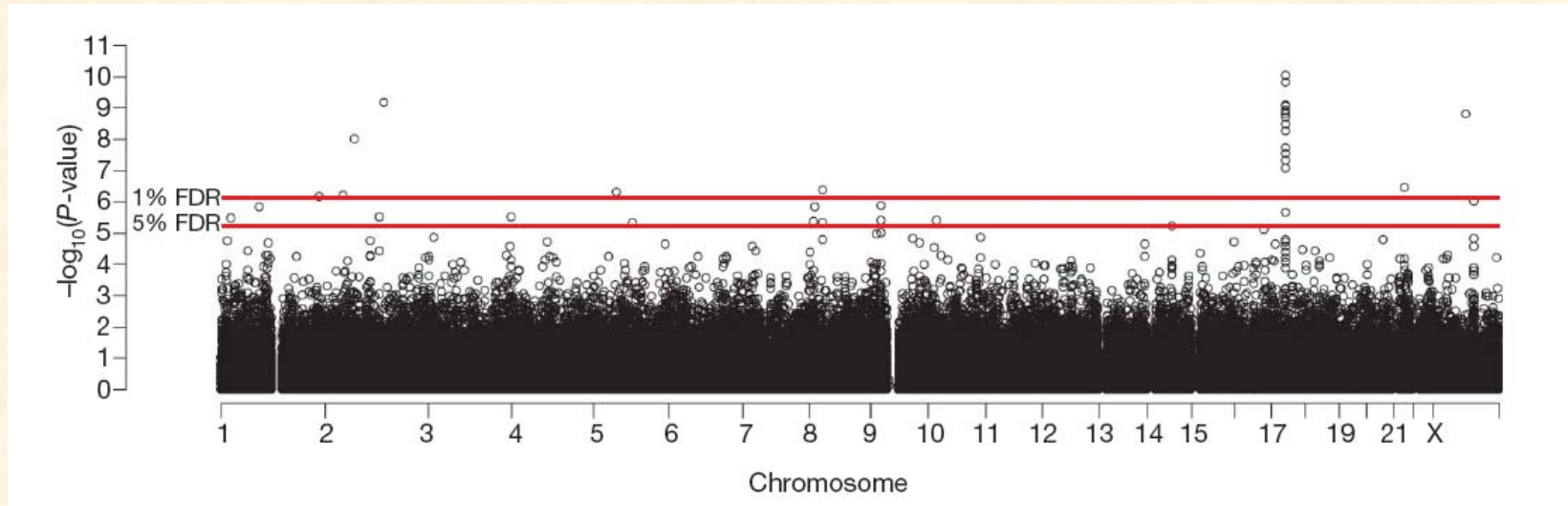
- Limited value value at the individual level factors
  - limited predictive value
  - mainly restrospective
  - does not predict treatment response
- Contributed little to understanding of the disease



**Is the answer  
Genetics?**

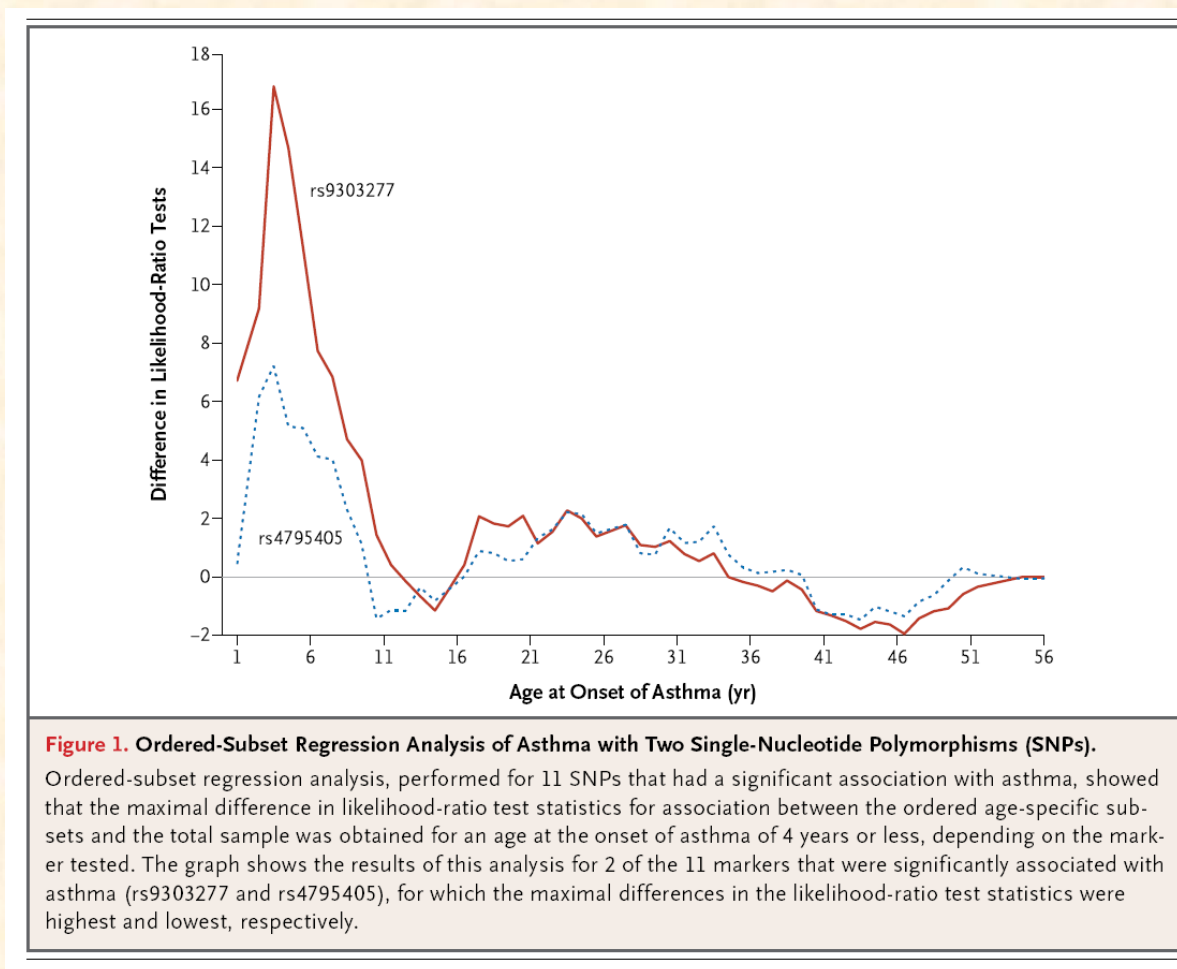


# ORMDL3 - genome wide association analyses



•Moffat et al Nature 2007

# ORMDL3 - Early onset asthma

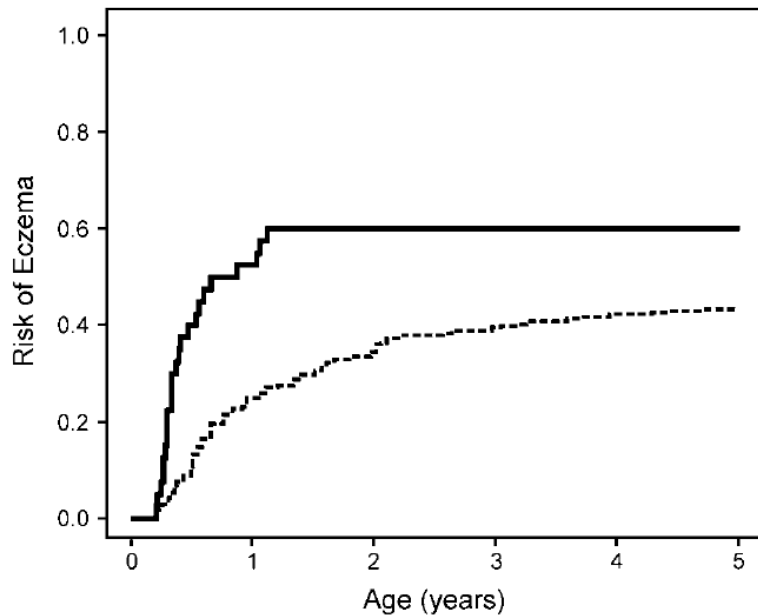


# 'ORMDL3' defined non-atopic asthma phenotype in early childhood (COPSAC)

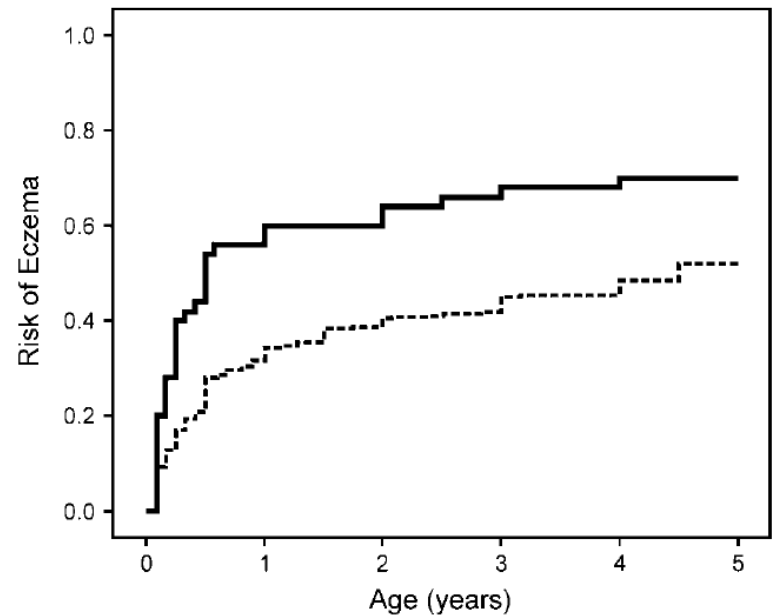
*Data confidential*

• Bisgaard et al submitted

# Filaggrin - a skin barrier protein



**Figure 1.** Kaplan-Meier Estimates of Cumulative Risk of Eczema in the COPSAC Cohort with and without FLG Mutation  
Numbers at risk at are given below the graph. Dashed line, no mutation; solid line, mutation.



**Figure 2.** Kaplan-Meier Estimates of Cumulative Risk of Eczema in the MAAS Cohort with and without FLG Mutation  
Numbers at risk at are given below the graph. Dashed line, no mutation; solid line, mutation.

# 'Filaggrin' defined atopic asthma phenotype in early childhood

Asthma exacerbations

Sensitization

• *Data confidential*

# **Genetics and prevention?**

**(gene environment interaction)**



# Primary prevention of asthma and allergy

- Environmental risk factors have caused increased disease prevalence

- Which environmental risk factors are largely unknown

- Passive smoking

- Pet exposure

- House dust exposure

- Breeding

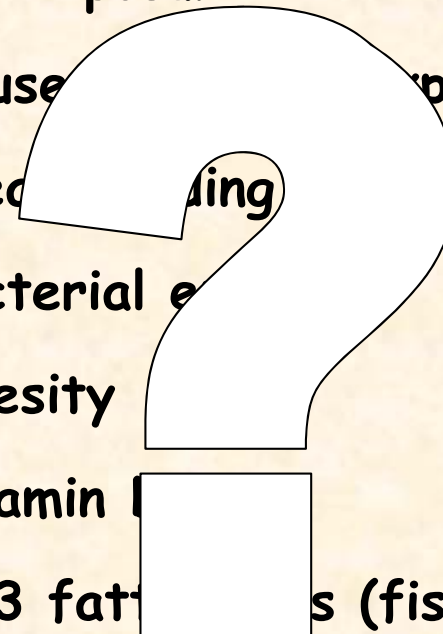
- Bacterial exposure

- Obesity

- Vitamin D

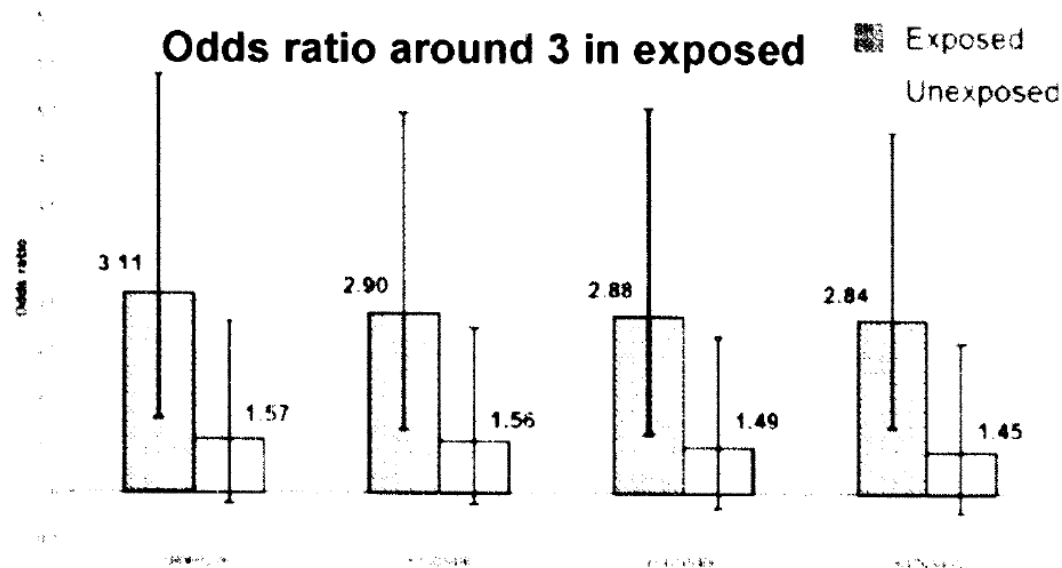
- N-3 fatty acids (fish oil)

- Paracetamol



# ORMDL3 genotype and passive smoking

◆ Early-onset asthma odds-ratios (ORs) for 17q21 SNPs showing evidence for heterogeneity ( $P < 0.01$ ) according to ETS exposure



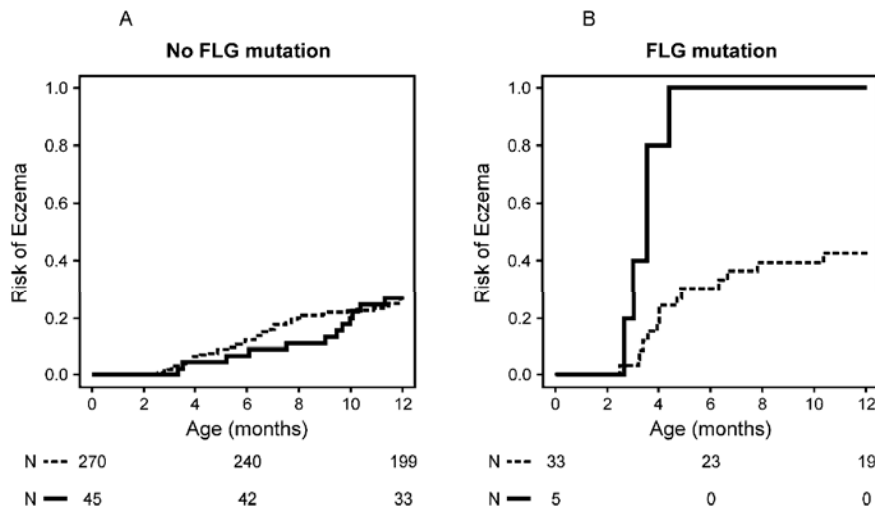
**Heterogeneity according to ETS:**

Association only significant in ETS-exposed offspring

Bouzigon *et al*/ IGES meeting sept 2008



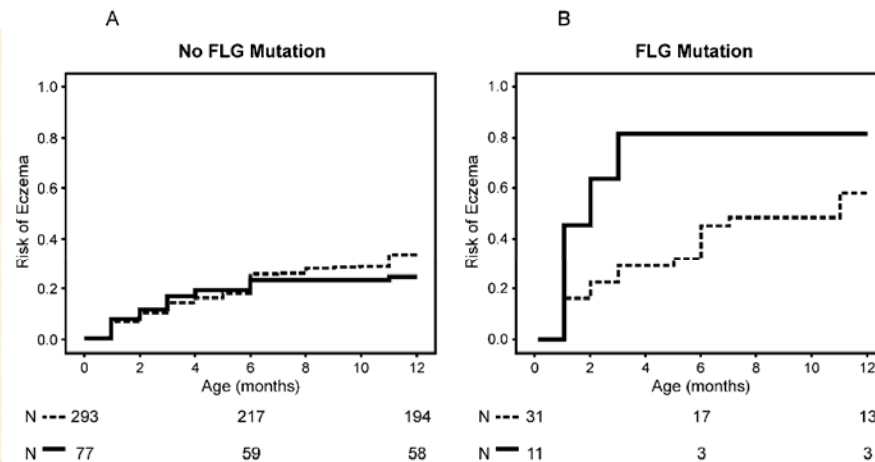
# Filaggrin genotype and cat at birth



**Figure 3.** COPSAC: Kaplan-Meier Estimates of Cumulative Risk of Eczema during the First Year of Life Stratified on Mutation and Cat at Birth Status. Numbers at risk at birth, 6, and 12 mo are given below the graph. Dashed line, no cat at birth; solid line, cat at birth. doi:10.1371/journal.pmed.0050131.g003

• **COPSAC**

• **MAAS**



**Figure 4.** MAAS: Kaplan-Meier Estimates of Cumulative Risk of Eczema during the First Year of Life Stratified on Mutation and Cat at Birth Status. Numbers at risk at birth, 6, and 12 mo are given below the graph. Dashed line, no cat at birth; solid line, cat at birth.

• **Bisgaard et al PLoS 2008**

# Conclusion

- **Childhood allergic diseases are highly heterogeneous**
- **Objective and detailed phenotyping is essential**
- **Genetics may be the key to improved understanding, diagnosis, prevention and treatment of disease**

