

# Challenge of Allergic Rhinitis and multi-morbidity

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# Conflict of interest

- I have received lecture fees from ALK-Abello, GSK and the BSACI
- I have received financial support to attend two EAACI meetings from Meda (now Mylan)
- I am an investigator at a site in a multi-centre trial sponsored by GSK

# 'Multi-morbidity' in atopic disease

- *'Multimorbidity is the presence of one or more additional disorders (or diseases) co-occurring with a primary disease or disorder, or the effect of such additional disorders or diseases'*
- In allergic diseases, the term multimorbidity is favoured over co-morbidity

Cingi C et al Clin Transl Allergy (2017) 7:17

- But if you look up 'Multi-morbidities AND allergic rhinitis' on Pubmed you only get 1 hit! (5 if you lose the hyphen)
- 'Co-morbidities AND allergic rhinitis' gets many more

# ‘Multi-morbidity’ in allergic rhinitis

- Multi-morbidity of allergic disease/atopy
  - Presumably related to Th2 propensity
  - And/or to other genetic and/or environmental predisposing factors
  - ***Principally asthma, atopic dermatitis***; possibly food allergy, anaphylaxis, EOE
- Local multi-morbidity
  - In anatomical proximity to the nasal mucosa:
    - conjunctivitis, sinusitis, middle ear problems, cough, sleep impairment

But, likely to be overlap between these two divisions

# ‘Multi-morbidity’ in allergic disease/atopy - epidemiology

- Most epidemiological studies regard this as two or more of:
  - Rhinitis
  - Asthma
  - Eczema

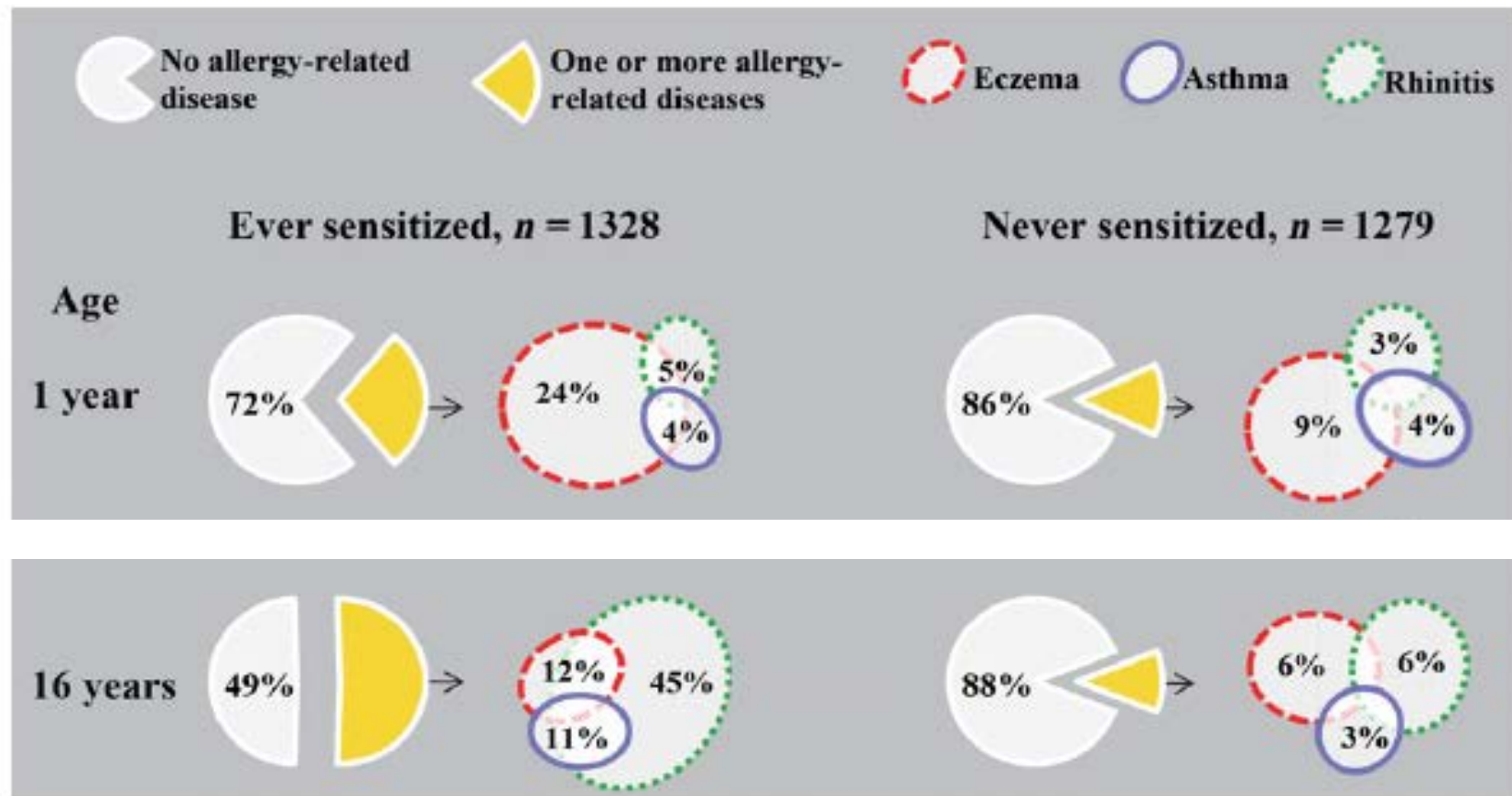
# 'Multi-morbidity' in atopic disease

- Multicentre Allergy Study (MAS) cohort
- 1,314 newborns in 1990, 'risk-enriched' for allergic disease
- 942 followed up to age 20
- Multi-allergic morbidity (2 or 3 of A, AR, AD) in 11.6% males and 12.7% females
- Increased in those with at least one atopic parent

# 'Multi-morbidity' in atopic disease

- Swedish BAMSE cohort: 2,607 children
- Prevalence of atopic disease by parental report
- Blood for sIgE at 4, 8, 16 years of age
- 51% had  $\geq 1$  sensitisation  $\geq 1$  time point
- Sensitisation associated with
  - asthma and rhinitis from 4-16 years
  - multi-morbidity of eczema, rhinitis and asthma
  - eczema throughout childhood
- But 23% with sensitisation never had an atopic disease

# 'Multi-morbidity' in atopic disease





# 'Multi-morbidity' in atopic disease

- **Shared genetic origin:**
- Genome-wide association study (GWAS) of 'allergic disease phenotype' including any of A, AR, AD
- 360,838 individuals from 13 different European studies
- 180,129 cases reporting having ever had asthma and/or AR and/or AD
- 180,709 controls
- 8,307,659 genetic variants tested for association
- 136 independent risk variants ( $p < 3 \times 10^{-8}$ ), 132 nearby genes
- *130 of 136 variants were shared risk factors for each condition*

# ‘Multi-morbidity’ in atopic disease

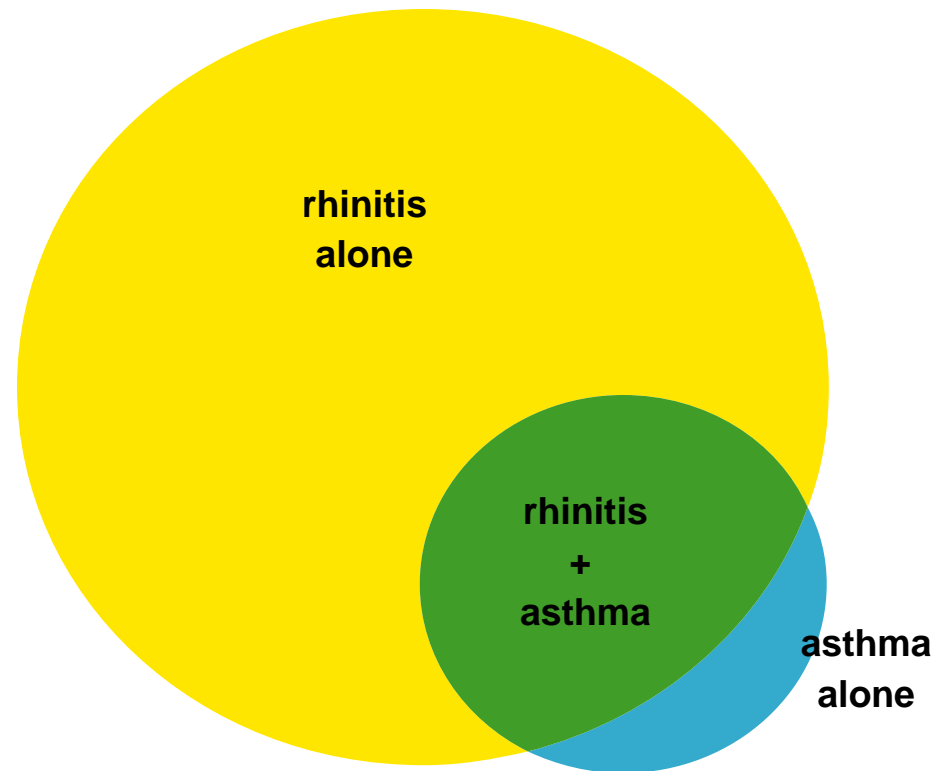
- **Not all down to IgE sensitisation:**
- MeDALL – Mechanisms of Development of Allergy
- 12 European birth cohort studies
- Questionnaire and sIgE to 6 allergens at 4 and 8 years
- Coexistence of eczema, rhinitis and asthma occurs more commonly than expected by chance alone...
- ...both in the presence and absence of IgE sensitisation
- *IgE sensitisation accounted for just 38% of comorbidity*

# Allergic rhinitis and asthma



# Asthma and rhinitis

- Up to **80%** of asthmatics have rhinitis

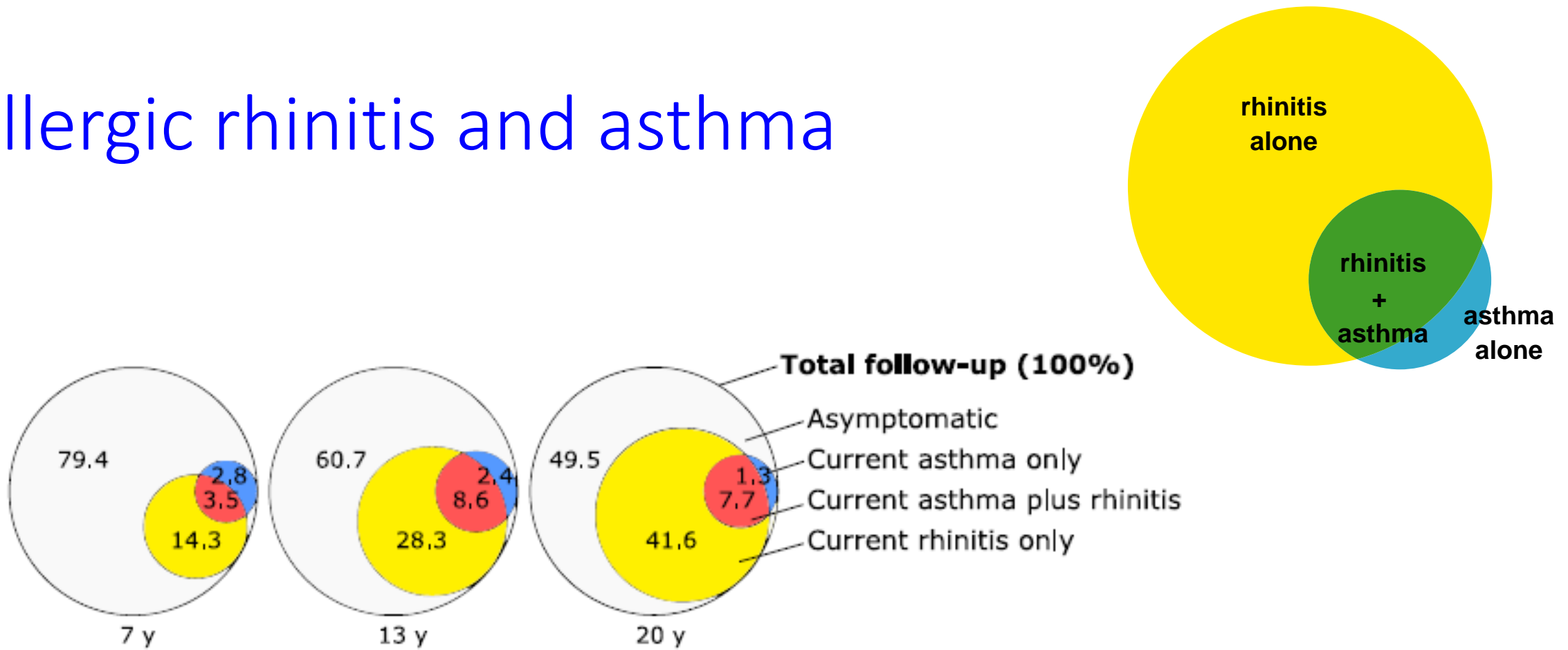


Adapted from The Workshop Expert Panel. *Management of Allergic Rhinitis and its Impact on Asthma (ARIA) Pocket Guide. A Pocket Guide for Physicians and Nurses*. 2001; Bousquet J and the ARIA Workshop Group *J Allergy Clin Immunol* 2001;108(5):S147-S334; Sibbald B, Rink E *Thorax* 1991;46:895-901; Leynaert B et al *Am J Respir Crit Care Med* 2000;162:1391-1396.

# Allergic rhinitis and asthma

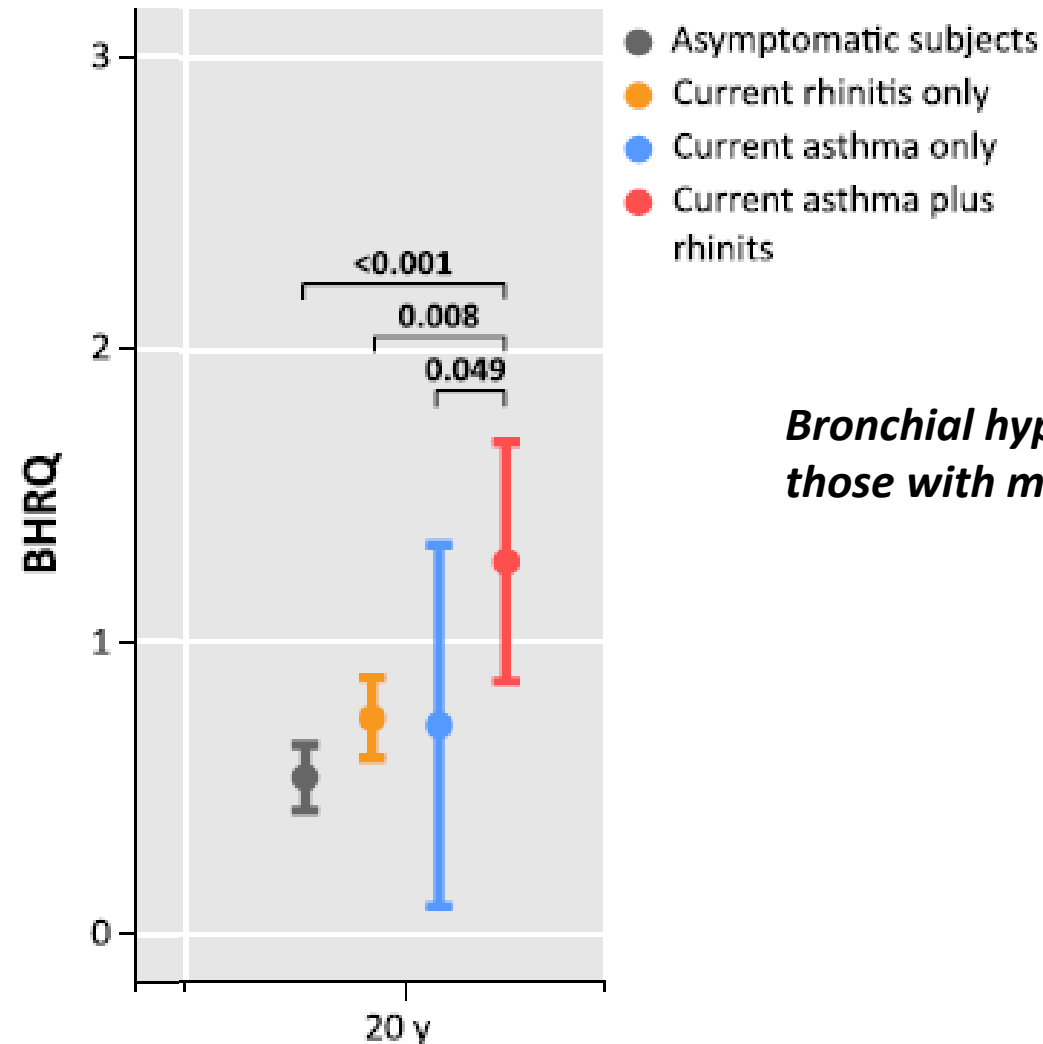
- Multicentre Allergy Study (MAS) cohort
- Lung function and bronchial challenge tests at 7, 13 and 20
- Asthma only, rhinitis only, both ('multi-morbidity')
  - Multi-morbidity: 3.5% aged 7, 7.7% aged 20
  - Asthma only: 2.8% aged 7, 1.3% aged 20
  - Rhinitis only: 14.3% aged 7, 41.6% aged 20
- i.e. by age 20, asthma largely seen with co-existing rhinitis

# Allergic rhinitis and asthma



# Allergic rhinitis and asthma

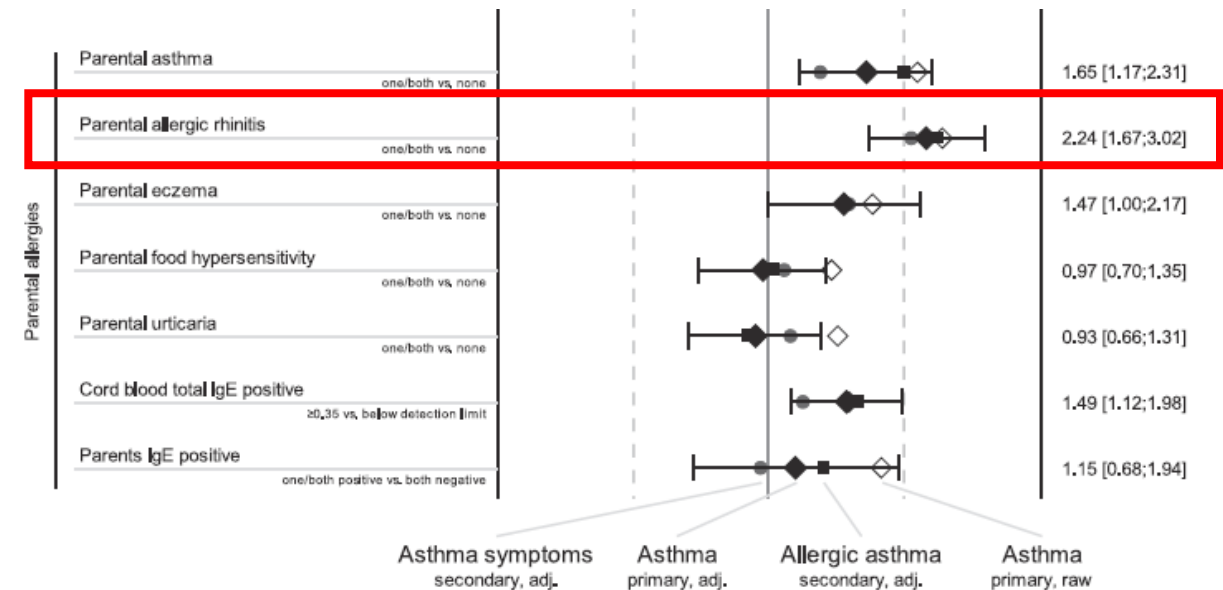
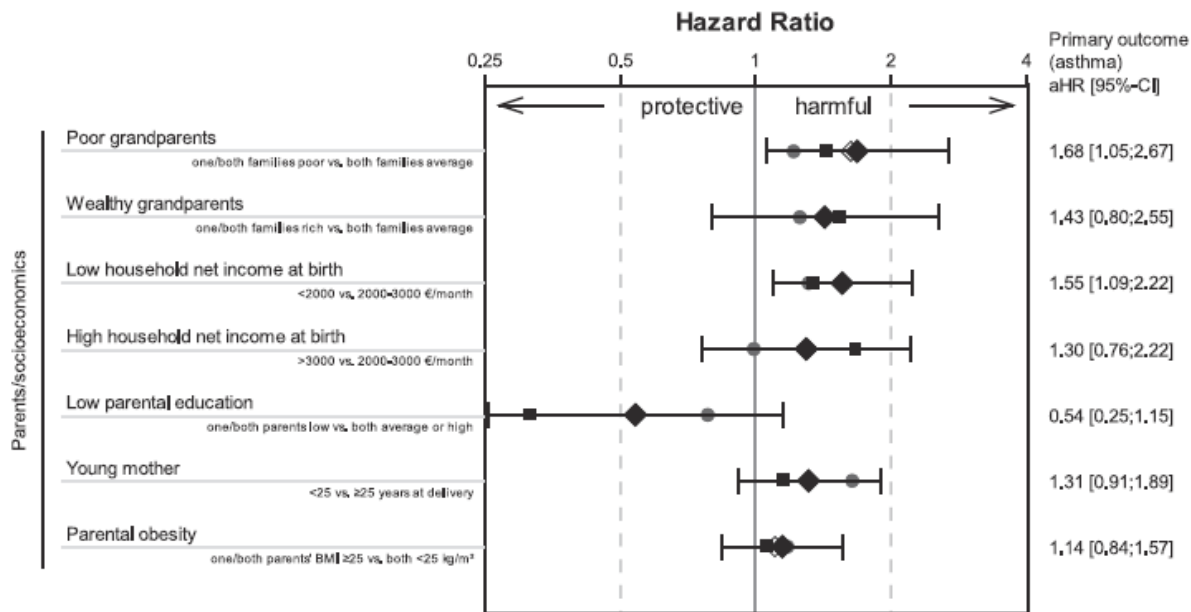
BHRQ = bronchial hyper-responsiveness quotient



***Bronchial hyper-responsiveness greatest in those with multi-morbidity vs asthma alone***

# Predictors of asthma in offspring

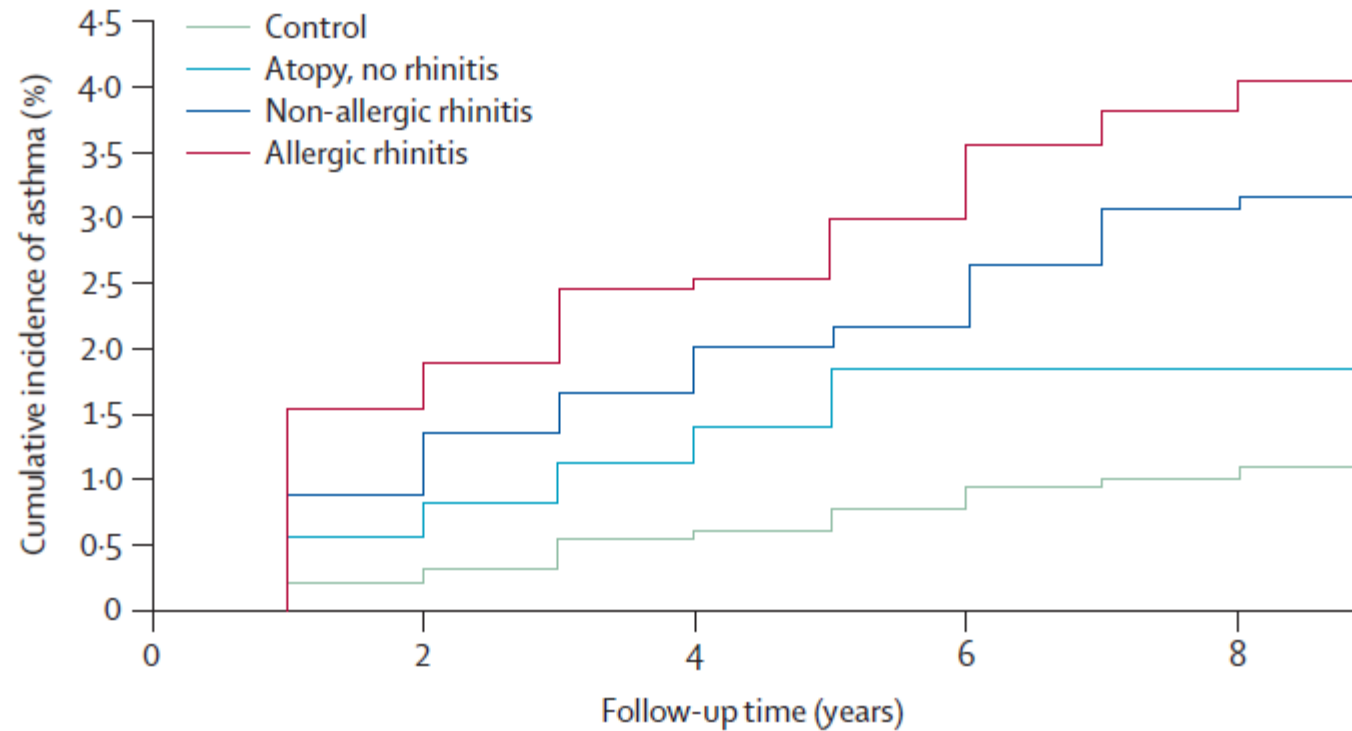
- Effect of socioeconomic factors and family history



NB: Hazard Ratio of maternal smoking during pregnancy = 1.79

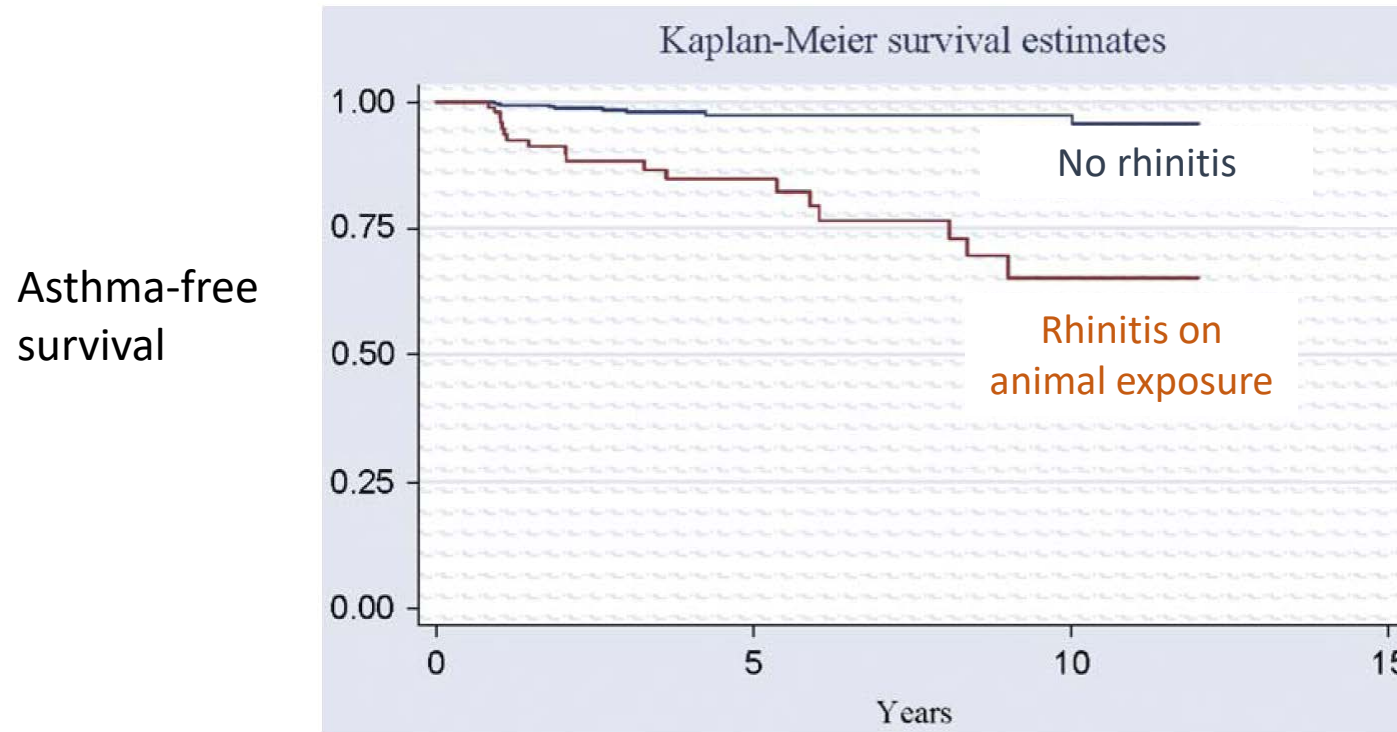


# AR predicts onset of asthma in adulthood



20-44 year olds, asthma free at baseline  
RR new onset asthma in AR 3.53 (2.11 – 5.91)

# Occupational rhinitis is a risk factor for occupational asthma: *lab animal workers*



Hazard ratio = 7.39 (3.29-16.60)

# Impact of rhinitis on asthma control

- Increase physician visits
- Increase risk of hospitalisation
- Increase SABA use
- Increase oral steroid use
- Higher ACQ scores

Thomas M et al Pediatrics 2005;115;129  
Clatworthy et al Prim Resp Care J 2009  
Sasonov et al Allergy 2005

# Clinical effects of treating concurrent allergic rhinitis

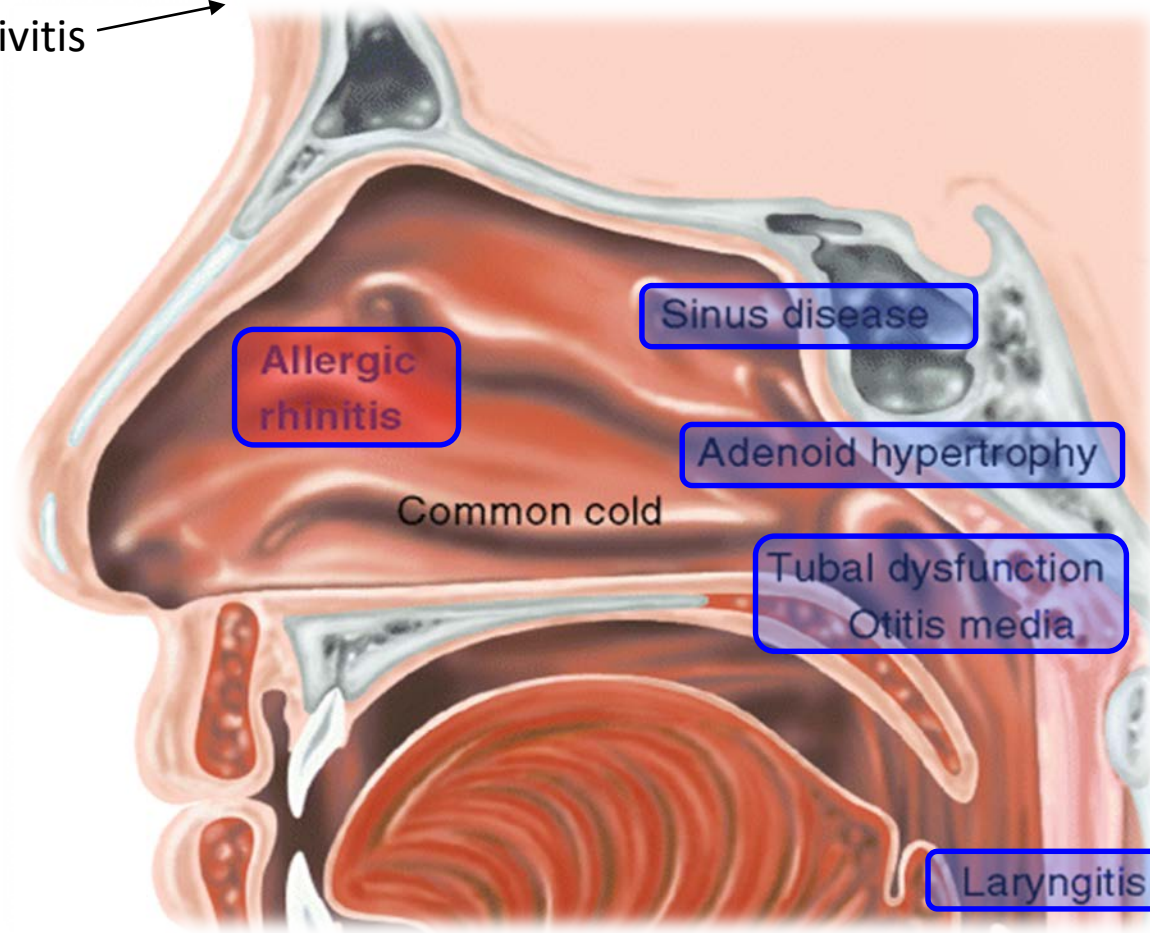
- Risk of asthma-related A&E attendance and hospitalisation:
  - Intranasal corticosteroid:  
RR 0.51 (0.34-0.7) and RR 0.34 (0.18-0.62)
  - Intranasal steroid + anti-histamine:  
• RR 0.37 (0.19-0.73) and 0.22 (0.07-0.63)
  - Adjusted for degree of asthma medication use

Corren et al JACI 2004;113:415-9

- Similar results in 2 retrospective studies
  - Crystal Peters et al JACI 2002;109:57-62
  - Adams et al JACI 2002;109:636-642

# Possible co-morbidities of (allergic) rhinitis - local

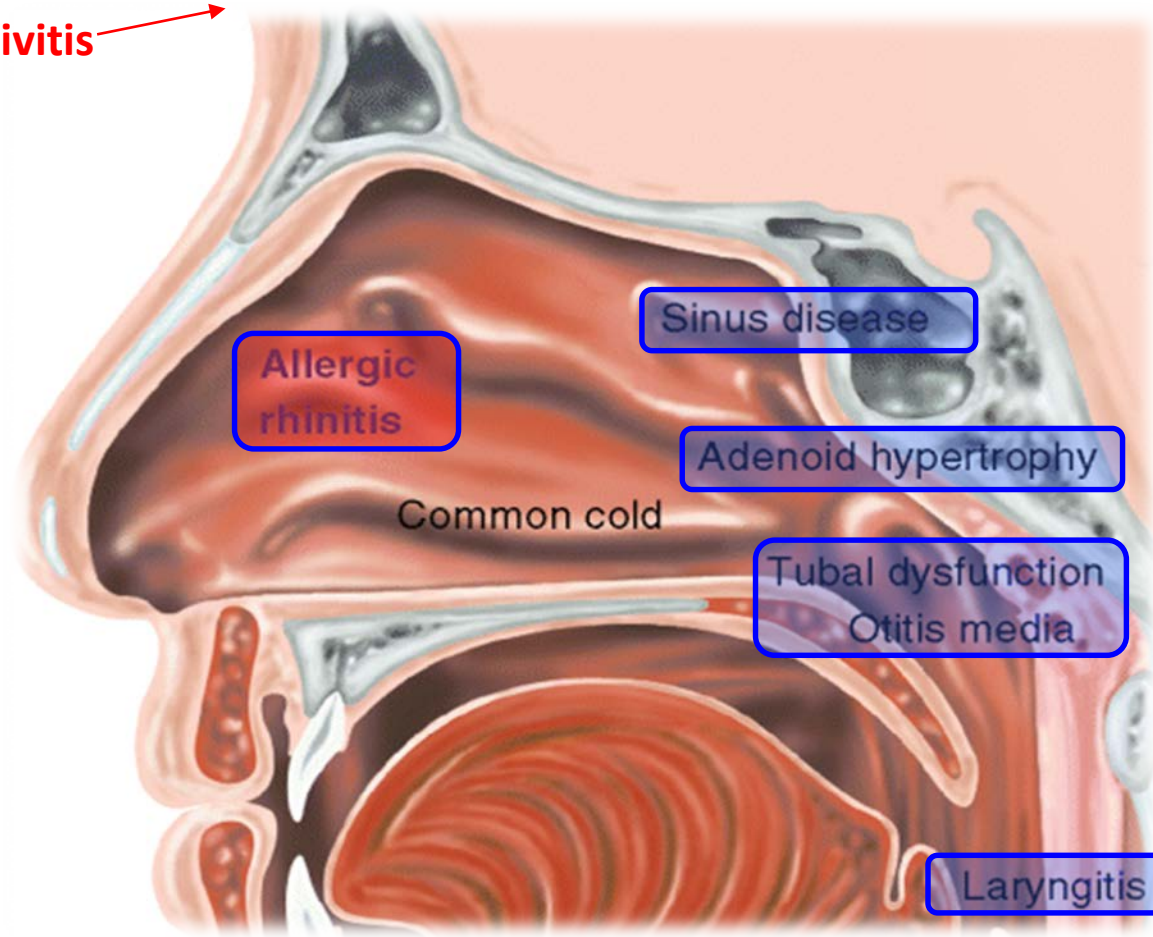
+ Conjunctivitis →



+ *Sleep disturbance/impairment.... Frank OSA?*  
+ *Pollen-food syndrome*

# Possible co-morbidities of (allergic) rhinitis - local

+ Conjunctivitis →



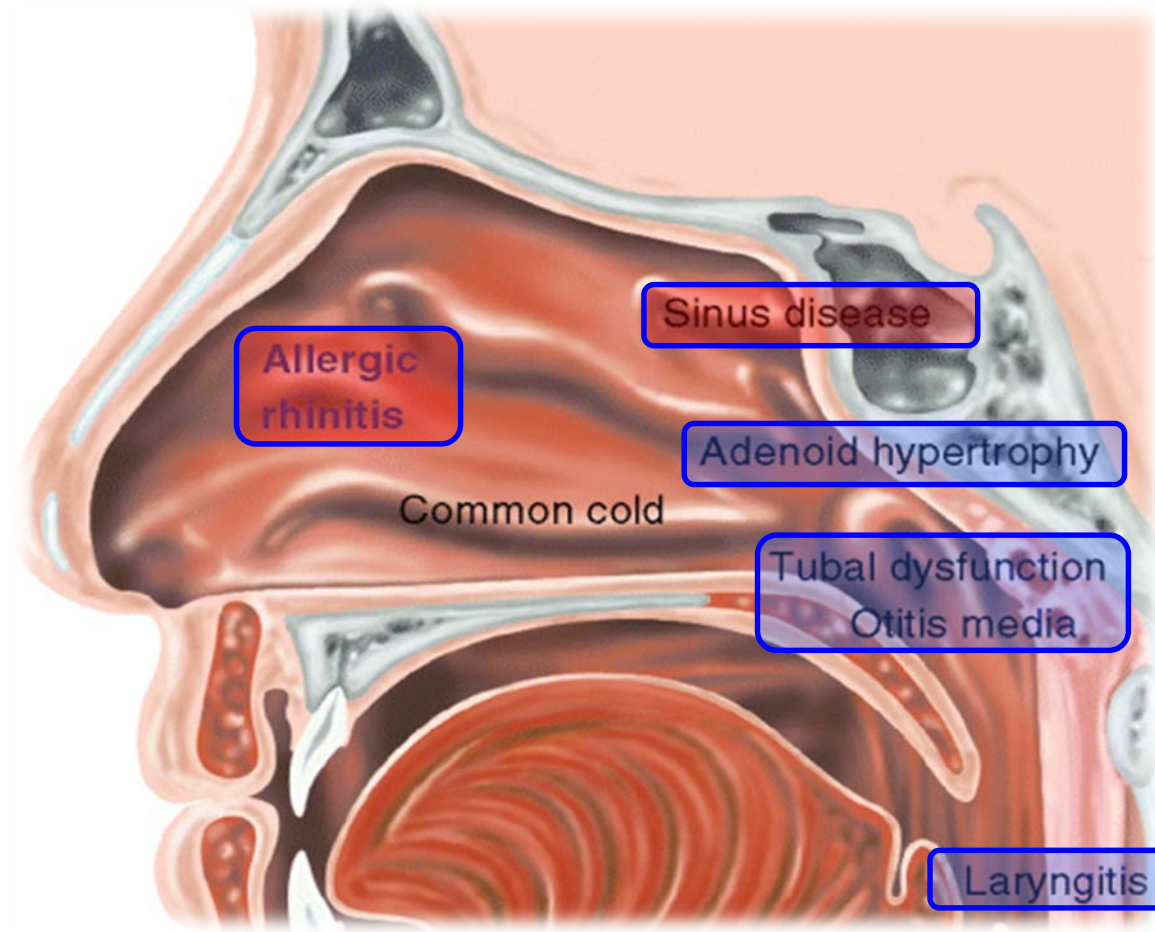
+ Sleep disturbance/impairment.... Frank OSA?  
+ Pollen-food syndrome

# Allergic rhinitis and conjunctivitis

- Ocular symptoms occur in 50–70% of patients with rhinitis
- more common with seasonal, outdoor allergens
- Distinct multi-morbidity or part of same condition?
- *NB: VKC, AKC are linked to atopy, but are probably more closely linked to eczema than to AR*



# Possible co-morbidities of (allergic) rhinitis - local



+ *Sleep disturbance/impairment.... Frank OSA?*  
+ *Pollen-food syndrome*



# Atopic disease increases risk of URTIs (and LRTIs)

- Finland: cross-sectional study of 1008 atopic and non-atopic adults 21–63 years old
- Information on atopic diseases and respiratory infections collected by questionnaire
- Specific IgE antibodies to common aeroallergens
- Adults with atopic disease: increased risk of URTI (**including common cold, sinusitis**, tonsillitis, and otitis media) with an adjusted RR 1.55 (1.14, 2.10)
- But even greater risk of LRTIs (are these simply asthma exacerbations?)
- Risk increased as IgE sensitization level increased
- *But when AR looked at separately, the effect was not significant*

**Table 4.** Risk of lower respiratory tract infections and upper respiratory tract infections during the past 12 months among subjects having atopic disease and high specific IgE level or positive allergy tests, The Finnish Environment and Asthma Study (FEAS).

Atopic manifestation	N	Lower respiratory tract infections		Upper respiratory tract infections	
		RR (95% CI)	RR <sup>a</sup> (95% CI)	RR (95% CI)	RR <sup>a</sup> (95% CI)
Atopic disease with positive allergy tests	199	2.56 (1.55, 4.23)	2.79 (1.66, 4.70)	1.77 (1.23, 2.57)	1.42 (0.97, 2.07)
Atopic disease with high specific IgE level <sup>b</sup>	119	2.14 (1.15, 3.96)	2.23 (1.19, 4.18)	1.52 (0.95, 2.41)	1.28 (0.80, 2.05)

**Table 5.** Risk of respiratory infections in the past 12 months according to different atopic diseases, The Finnish Environment and Asthma Study (FEAS).

	N	Lower respiratory tract infections		Upper respiratory tract infections	
		RR (95% CI)	RR <sup>a</sup> (95% CI)	RR (95% CI)	RR <sup>a</sup> (95% CI)
Total <sup>b</sup>	967				
Non-atopic	526	1	1	1	1
Asthma	73	4.66 (2.65, 8.20)	4.69 (2.64, 8.35)	1.85 (1.10, 3.11)	1.62 (0.96, 2.74)
Rhinitis	210	1.12 (0.43, 2.88)	1.24 (0.48, 3.23)	1.38 (0.78, 2.46)	1.21 (0.68, 2.17)
Dermatitis	337	1.69 (1.01, 2.81)	1.82 (1.08, 3.07)	1.93 (1.39, 2.67)	1.62 (1.16, 2.26)

# Allergic rhinitis and CRS

- Large questionnaire survey (>52,000 adults)
- Investigating association of CRS with asthma...
- ...but also enquiring about 'hay fever or nasal allergies'
- 56.7% with CRS also reported AR
- *'Parallel' evidence for association of AR and CRS?*
- But proportion of people with AR who also have nasal polyps is similar to general population

Jarvis et al Allergy 2012; 67:91-98  
Georgalas et al Allergy 2014; 69:828-833  
Fokkens et al Rhinol Suppl. 2012;23:3

# Allergic rhinitis and CRS

- Association is unclear
- No firm evidence to conclude AR is a risk factor for CRS
- (Whilst IgE may be relevant to the pathology of CRSwNP, this is distinct from atopy)
- (Possible exception is AFRS where sensitisation is a prerequisite)
- Summary of studies in favour of and against allergy being a predisposing factor for CRS in adults and children...

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## Studies in favor

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### Adult literature

Simultaneous increase of prevalence of AR and CRS (53)  
Increased percentage of positive allergic test in patients with CRS (27, 54–57)  
Increased incidence of allergy in nasal polyposis patients (58, 59)  
Strong correlation between the extent of disease on CT evaluation and the amount of eosinophils within the sinus tissue, as well as the presence of specific IgE antibodies (60)  
CT changes in patients with ragweed allergy (61)  
Increased percentage of NP in allergic patients (62)  
Immunotherapy increases success of surgery (31, 63) especially in AFRS (64)  
Experimental study where nasal challenge with allergen has resulted in secondary maxillary sinus inflammation (26)

### Pediatric literature

Increased incidence of atopic predisposition in pediatric patients with sinusitis (70, 71)  
Correlation of allergy and severity of sinus disease (70, 72)  
ESS in children with AR does not have a poorer outcome.  
Treatment for the allergy before surgery may improve the success of ESS (73)

## Studies against

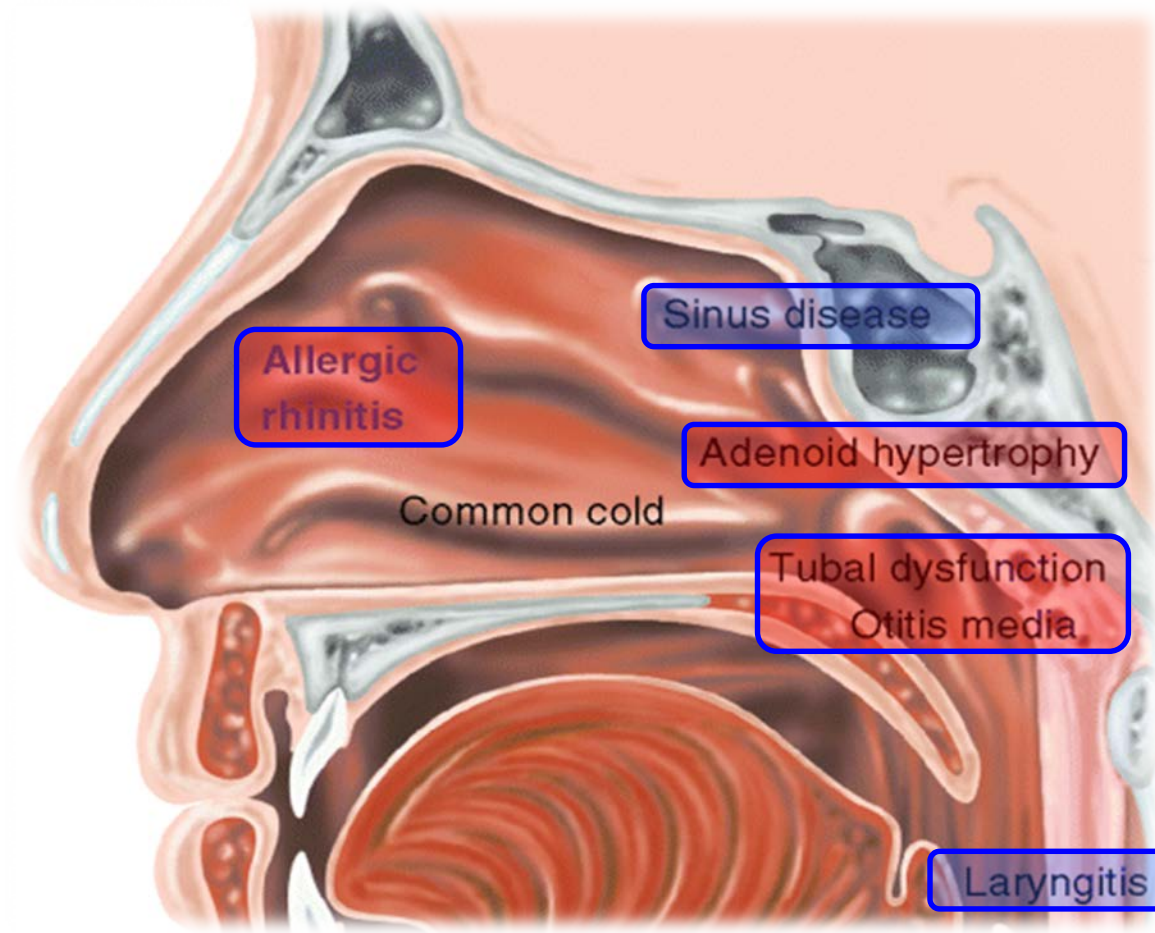
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### Possible selection or referral bias (19–23)

No increased percentage of allergy in NP patients (59, 65–69)  
Allergic rhinitis was less prevalent in those with worse disease on sinus CT scans (56)  
No increase of CRS during pollen season (27)  
The presence of allergy does not affect symptom severity, surgery likelihood, extent of disease on CT (33–35)  
  
Same percentage of positive allergy test in CRS and normal children (74)  
  
Same prevalence of CRS in atopic and nonatopic children (75)  
Percentage of opacification the same between allergic and nonallergic adults and children (76)

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# Possible co-morbidities of (allergic) rhinitis - local



+ *Sleep disturbance/impairment.... Frank OSA?*  
+ *Pollen-food syndrome*



# AR and otitis media with effusion

**Table 1** Predisposing factors of Otitis Media with Effusion (OME)

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- Age
  - Male Sex
  - Craniofacial abnormalities (e.g. cleft palate)
  - Day-care school and attendance
  - Adenoid hypertrophy
  - Atopy
  - Tobacco smoke exposure
  - Upper airway infection (acute otitis, chronic rhinosinusitis, infective rhinitis)
  - Extreme pre-term
-

# AR and otitis media with effusion

- 291 children aged 5
- Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) cohort
- OME diagnosed based on tympanometric and objective evaluation
- Asthma, eczema, allergic- and non-allergic rhinitis were diagnosed prospectively by pre-defined algorithms
- Allergic sensitization by ImmunoCAP
- OME diagnosed in 39% of the cohort
- Associated with allergic rhinitis (aOR = 3.36, CI = 1.26–8.96, P = 0.02)
- not with non-allergic rhinitis, asthma or eczema
- (but only 10% of cohort diagnosed as having AR)



# AR and otitis media with effusion

- Meta-analysis of 24 studies
- Risk factors associated with chronic otitis media (COM) and recurrent otitis media (ROM)
- The presence of allergy or atopy increased the risk of COM/ROM (OR, 1.36; 95% CI, 1.13–1.64;  $P = 0.001$ )
- Other risk factors: URTI, snoring, previous history of AOM/ROM, second-hand smoke and low social status are risk factors for COM/ROM

# AR and adeno(tonsillar) hypertrophy (AH/ATH)

- 436 children, aged 4-9, with AR and/or A and/or AD...
- ...and HDM sensitisation
- 229 non-atopic controls
- Incidence of AH
- Association with allergic disease type
- And age, sex, infections, other allergic sensitizations
- *'The aim of the study was to estimate the incidence of adenoid hypertrophy (AH) in children hypersensitive to dust mites'*

# AR and adenotonsillar hypertrophy (ATH)

- AH in 176 (40.4%) study group vs 51 (22.3%) controls
- More AH in AR vs Asthma or AD
- But:
  - Unclear how the participating children were recruited
  - Detailed demographics are not given
  - Referral to a graph which isn't present

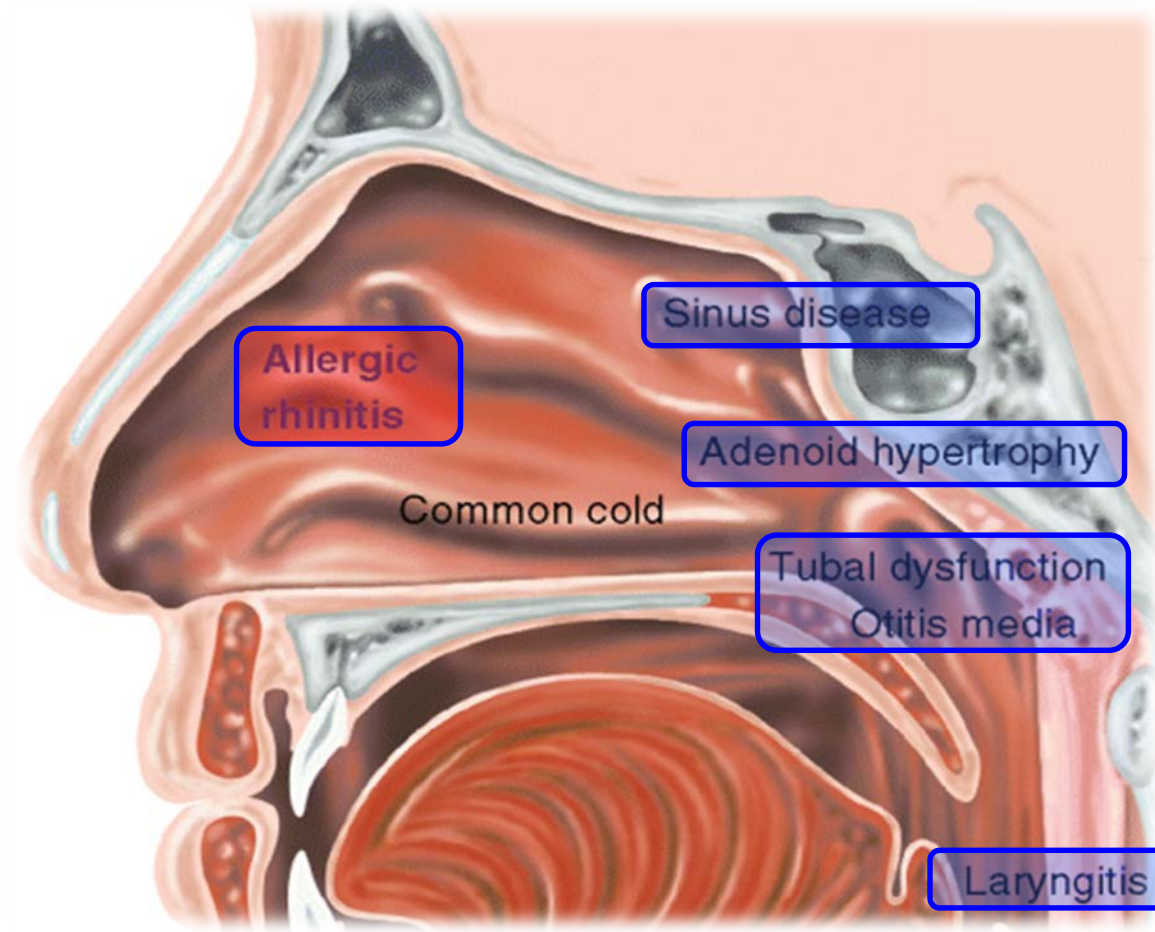
# AR and adenotonsillar hypertrophy (ATH)

- 117 children, 1-14 years, with ATH
- Control group, 100 children, other diagnoses
- 70.3% of ATH group SPT +ve vs 10% control group
- Increase atopy in ATH cases (though not necessarily AR)
- *Lack of detail concerning controls*

# AR and adenotonsillar hypertrophy (ATH)

- Study comparing children with AR + AH with those with AR alone
- Mould sensitisation associated with increased risk of AH
- Cochrane systematic review of INS in AH:  
*'...intranasal corticosteroids may significantly improve nasal obstruction symptoms in children with moderate to severe adenoidal hypertrophy, and this improvement may be associated with a reduction in adenoid size...'*

# Possible co-morbidities of (allergic) rhinitis - local



+ *Sleep disturbance/impairment.... Frank OSA?*  
+ *Pollen-food syndrome*

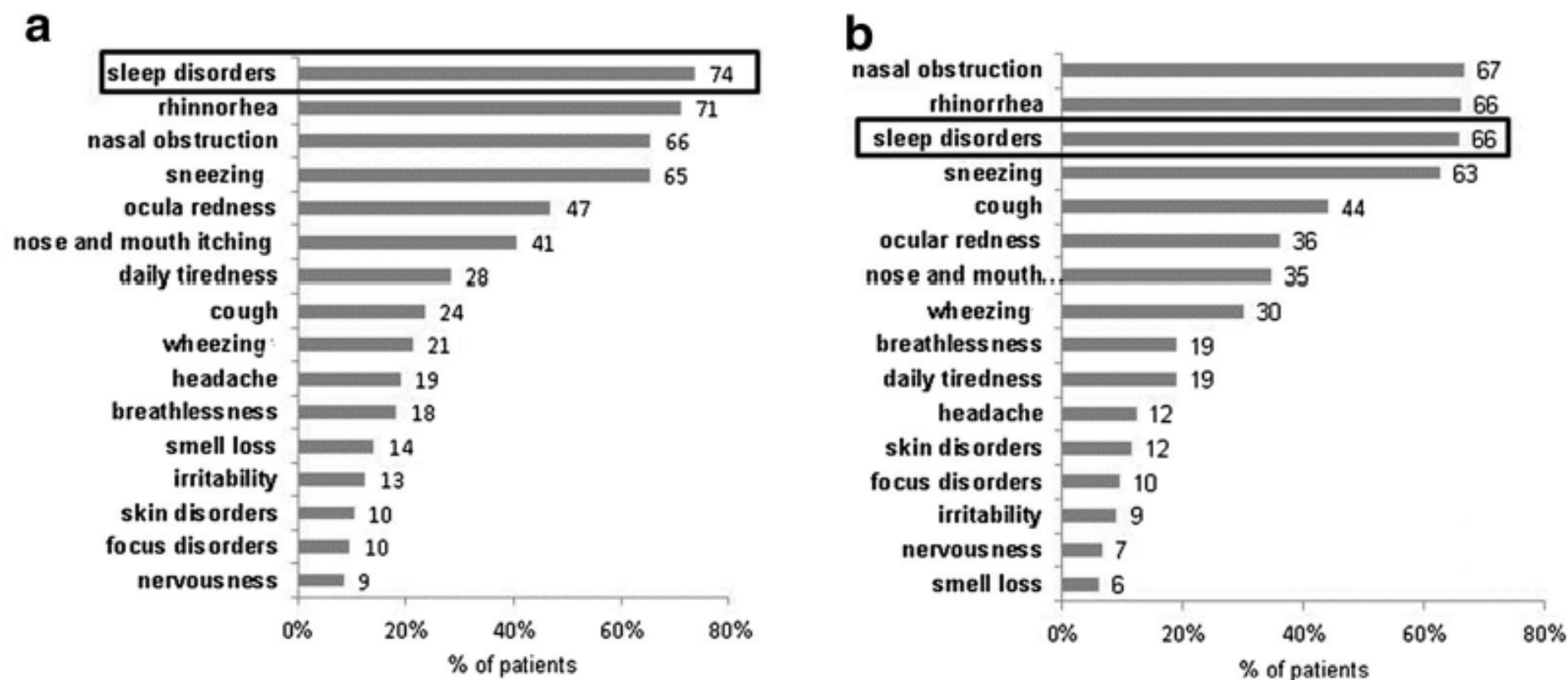
RESEARCH

Open Access



# Poor sleep is highly associated with house dust mite allergic rhinitis in adults and children

Damien Leger<sup>1\*</sup>, Bénédicte Bonnefoy<sup>2</sup>, Bernard Pigearias<sup>3</sup>, Bertrand de La Giclais<sup>4</sup> and Antoine Chartier<sup>5</sup>



**Fig. 1** Main symptoms leading to physician visit. The number of participants who mentioned each symptom as a reason for visiting the physician. *Graph a* presents data related to adults. *Graph b* presents data related to children



# AR and sleep

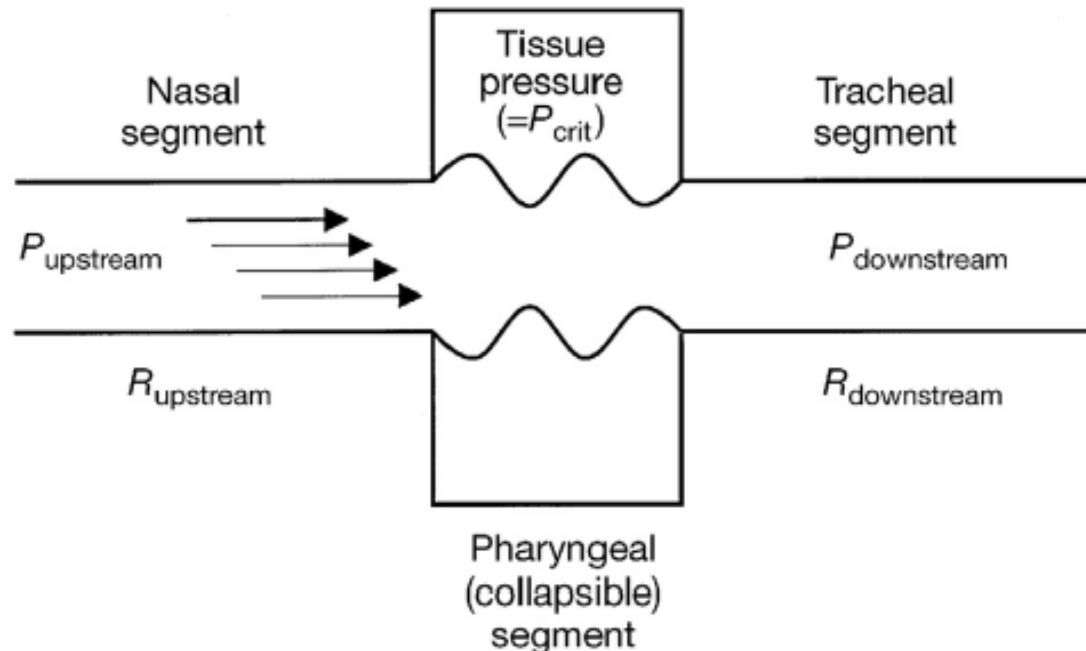
- AR has significant effect on sleep
- Treating AR (with INS) can improve subjective sleep quality and reduce fatigue

*Craig et al J Allergy Clin Immunol. 1998;101:633–7*

- But is AR associated with frank OSA?
- And does treatment of rhinitis have a benefit on OSA?

# AR and OSA

- Main site of problem in OSA is the collapsible pharyngeal segment of airway
- But increased nasal resistance upstream may  $\uparrow$  risk of collapse

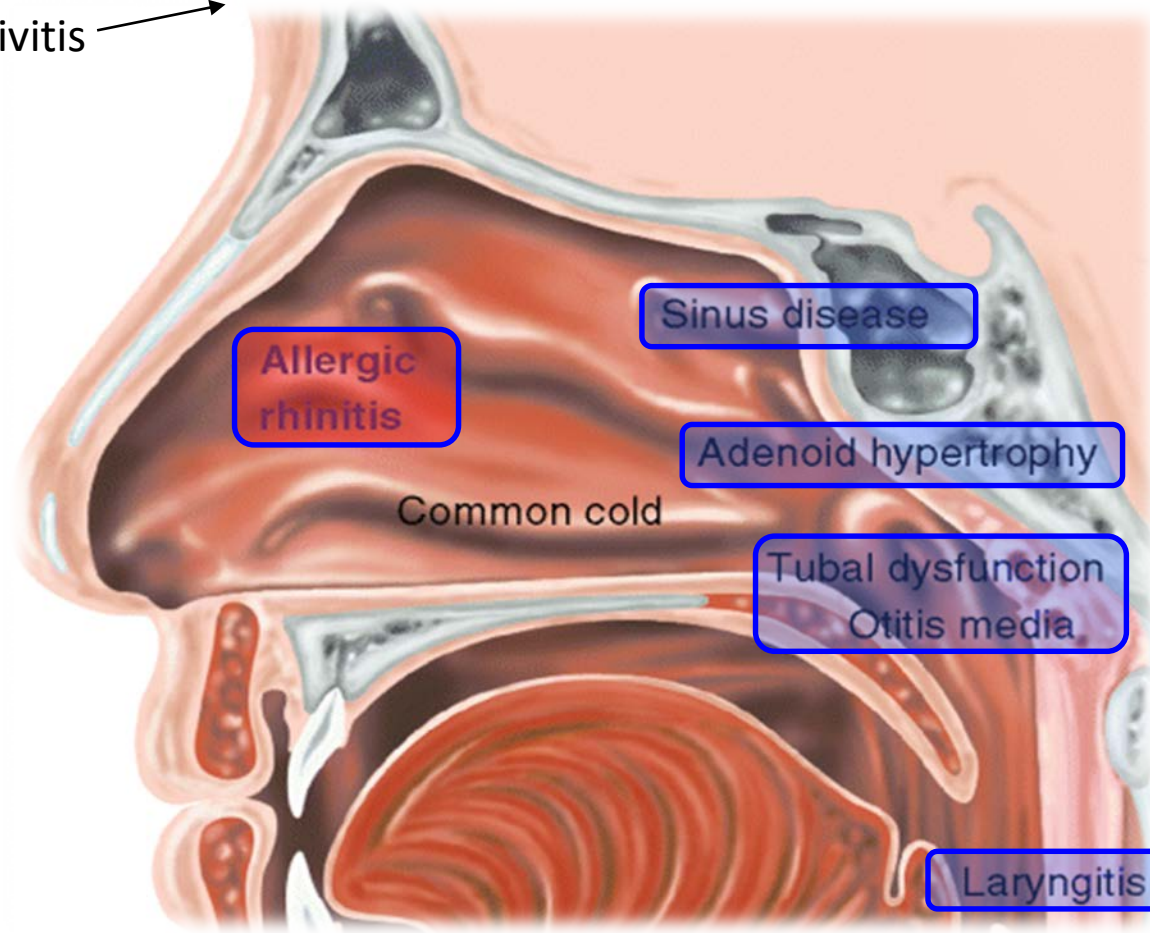


# AR and OSA

- Main site of problem is collapsible pharyngeal segment of airway
- But increased nasal resistance upstream may ↑ risk of collapse
- Adults: studies show subjective improvement on sleep quality with intra-nasal corticosteroids, but generally little effect on AHI
- Children: more evidence of beneficial effect of INS on AHI (but AR status not often included)
- Guidelines generally refer to INS as an adjunctive treatment

# Possible co-morbidities of (allergic) rhinitis - local

+ Conjunctivitis →



+ Sleep disturbance/impairment.... Frank OSA?  
**+ Pollen-food syndrome**

# AR and food allergy

- Food allergy is, with a few exceptions, IgE-mediated
- Primary food allergy is more common in individuals who are atopic (based on aeroallergen sensitisation)
- Though probably more closely related to eczema than AR
- That said, pollen-food syndrome only occurs in those with AR (or subclinical disease with relevant sensitisation)
- Tree (***birch***), grass, and mugwort pollen sensitisations most relevant
- Anecdotally, more common in adults than children
- Generally mild, oro-pharyngeal symptoms; occasionally more severe, e.g. consumption of soy milk

# AR and food allergy

- 1360 Italian children referred to allergy specialists with AR
- standardized questionnaires on atopic diseases
- skin-prick test (SPT) with airborne allergens and six food allergens
- 325 (23.9%) oral allergy syndrome (OAS)

*Dondi et al. Pediatr Allergy Immunol. 2013 Dec;24(8):742-51*

- BAMSE cohort in Sweden
- 25% 8-year-olds with allergic rhinitis also had OAS

*Westman et al. J Allergy Clin Immunol 2012;129:403-8*

# AR and food allergy

- Standardisation of a PFS diagnostic questionnaire
- 110 subjects reporting allergic rhinitis (AR) in the UK birch pollen season from March to May
- Fifty-two participants (47%) were diagnosed with PFS

*Skypala et al. Clin Exp Allergy. 2011 Jul;41(7):1001-11*

# Summary 1

- Multi-morbidity is common in allergic disease
- Epidemiological data concentrate on asthma, allergic rhinitis and eczema
- Multi-morbidity (2 or more of these) may be present in  $\geq 10\%$  young adults
- Shared genetic risk factors
- The majority of asthmatics have nasal disease
- Allergic rhinitis is a risk factor for new onset asthma and asthma in the next generation
- Treating AR may improve asthma control



## Summary 2

- Atopy is a risk factor for URTIs and LRTIs
- But no clear evidence that AR is a risk factor for CRS
- Allergic rhinitis and atopy are risk factors for OME and ROM
- Evidence that AR is a risk factor for adenoid hypertrophy is less convincing
- But treatment with INS may help nonetheless
- AR impairs sleep, but role in OSA unclear (particularly in adults)
- Pollen-food syndrome is common in adults and children