Subtypes of childhood asthma and allergies and developmental patterns of lung function

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There is more to a low FEV$_1$ than asthma & COPD

Early life events are absolutely crucial for the development of COPD and the lifelong lung health

Can we potentially intervene during or after the crucial pre-school years?

Should we measure FEV$_1$ and if so, when?; What should we do about it?’

How can we identify children at risk
  – Multiple early allergic sensitization
  – Severe wheeze exacerbations and immune responses to viruses
Survival curves for cardiopulmonary mortality by tertiles of FEV$_1$ at baseline
Low lung function in early adulthood may identify individuals at risk of early comorbidities and mortality

- **FEV₁ < 80%**: higher prevalence of respiratory, cardiovascular, and metabolic abnormalities in early adulthood; higher and earlier (about a decade) incidence of comorbidities during follow-up (39 years vs 47 years in FOC; 30 years vs 37 years in CARDIA)

- Higher all-cause mortality than individuals with normal lung function in early adulthood
  - FOC, hazard ratio 2·3 [95% CI 1·4-3·7], p=0·001

- Independent of, but additive with, cumulative smoking exposure

‘Many common human diseases (*asthma and COPD*) are still diagnosed as if they are homogeneous entities, using criteria that have hardly changed in a century …… the treatment for diseases that are diagnosed in this way is generic, with empiricism as its cornerstone’

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COPD: A systemic disease

- **GOLD**: FEV$_1$/FVC ratio <70%

1. **Pulmonary**: Chronic airway inflammation, infection, remodelling
2. **Pulmonary**: Alveolar destruction and emphysema
3. **Extrapulmonary co-morbidities**: metabolic syndrome; heart disease; steatohepatitis & liver fibrosis; pro-inflammatory fatty deposits; etc.
“Crucial changes in lung function that define COPD are the results of changes taking place slowly over several decades”

Low FEV$_1$ in early adulthood as important in the genesis of COPD as accelerated decline.

“COPD is thought to result from an accelerated decline in FEV$_1$ over time.”

- Participants in 3 cohorts (the Framingham Offspring Cohort, the Copenhagen City Heart Study, and the Lovelace Smokers Cohort) according to lung function
- Trajectory 3 (Fast decline): FEV$_1$ $\geq$80% at baseline, 158/2207 (7%) got COPD
- Trajectory 4 (Normal decline): FEV$_1$ at $<$80% baseline, 174/657 (26%) got COPD
- Both trajectories contributed equally to COPD; different rates of decline unexplained

Suboptimal lung growth in childhood may be a precursor to adult COPD

Melbourne birth cohort at age 50, 76% retention
Age 50: non-asthmatics, current asthma, remitted asthma, COPD (FEV$_1$/FVC<0.70)
Lung function tracked back to age 10 years
OR for COPD with severe asthma 32 (3.4-269); stronger than smoking

Tai et al, Thorax 2014; 69: 805-10
CAMP: Possible lung-function trajectories during the first three decades of life

Airflow obstruction is an early phenomenon!

411 high-risk babies

403 (98%): raised volume rapid thoracoabdominal compression (RVRTC) and $BHR_{meth} (TcPO_2)$

Follow-up age 7 n=317 (77%), spirometry, questionnaire

Neonatal airflow obstruction predictive of asthma

Obstruction age 7 years: 40% antenatal, 60% postnatal

Bisgaard et al, Am J Respir Crit Care Med 2012; 185: 1183-9
Persistently low lung function trajectory may be partly established at birth and predisposes to COPD

N=599, unselected population
2,142 spirometry age 11-32

LCA: two trajectory model best fit, N=56 (9.3%) low trajectory – what will be long term consequences?

Associates of the low trajectory:
Maternal asthma, early life LRTI RSV, physician-diagnosed active asthma at age 32, and lower lung function infancy and at age 6 years

Trajectories of lung function (FEV$_1$ z-score) from 7 to 53 years of age

Up to three-quarters of COPD begins with poor lung function pathways in childhood

Childhood characteristics

Early below average, accelerated decline:
- Childhood asthma ($p<0.0001$), bronchitis ($p=0.0080$), allergic rhinitis, pneumonia or pleurisy, and a heavy-smoking mother

Persistently low:
- Ever asthma, eczema and food allergy, parental asthma

Conclusion: Important to pay attention to early life events

Lung function trajectories from pre-school age to physiological plateau in early adulthood

Most children in the low $V'_{\text{maxFRC}}$ trajectory in infancy did not progress to the low FEV$_1$ trajectory.

Persistently low FEV$_1$ predicted by:
- Multiple early sensitisation
- Recurrent wheezing with severe exacerbations (first 3 years of life)

Loss of lung function during childhood in children with wheeze exacerbations & multiple early sensitisation

Boys with multiple early atopy, persistent wheeze and severe exacerbations have the highest risk of progressively diminished lung function during childhood
Later onset and greater peak velocity of height growth in puberty: Increased FEV$_1$ and FVC

- An association of later pubertal age and rapid pubertal growth with increased FEV$_1$ & FVC
- Target modifiable childhood factors, such as obesity and overweight, that may contribute to pubertal growth patterns.

Mahmoud O et al, Am J Respir Crit Care Med. 2018;198(12):1539-48
Should we measure FEV₁ and if so, when?
Over to you – not an easy answer
How to reconcile these studies?

- There is no doubt that for the majority, lung function when you first go to school tracks to late middle age.
- Tracking may start from the pre-school years (e.g. Tucson, Perth, MAAS); PIAF findings need confirmation.
- There may be a first two decades catch up group if you are male and thin (<10% of the population), but needs confirming in another cohort.
- An early low FEV$_1$ is a sign of early all-cause mortality: BUT, what do we do now in terms of public health? Is it too late when children get to school?
- Early life smoke exposure, multiple early allergic sensitization and early-life recurrent acute severe wheeze are markers of trouble to come.
Hypothesising with data: Machine-learned subtypes of allergic sensitisation

1053 children

8 allergens

Machine learning patterns of allergic sensitisation

Allergic sensitisation ‘stratified’
Unanticipated risk group for asthma discovered

Four allergic sensitisation patterns ‘learned’ from data

- Ever atopic
- Atopic age 8

Two-class model – latent atopic vulnerability
- Non-dust mite
- Dust mite
- Multiple late
- Multiple early

Five-class model – latent atopic vulnerability
- N/A
- 77
- 11
- 24
- 24

Allergic sensitisation ‘stratified’
‘Pathologic’ and ‘benign’ subtypes of sensitisation

DRR, dose response ratio; FEV, forced expiratory volume; FVC, forced vital capacity; IoW, Isle of Wight; MAAS, Manchester Asthma and Allergy Study; NO, nitric oxide

Clustering 28 cytokine responses of PBMCs to RV-16: Six patterns of cytokine responses

Custovic et al, Am J Respir Crit Care Med. 2018;197(10):1265-1274
Trajectories of asthma and allergic sensitisation in rhinovirus-16 response clusters

- The IFN\text{\textsuperscript{lowest}}Inflam\text{\textsuperscript{high}}TH2-chem\text{\textsuperscript{low}}Reg\text{\textsuperscript{mod}} cluster: associated with early-onset asthma and sensitization, and the highest risk of exacerbations (1.37 [1.07–1.76], P=0.014) and LRTI hospitalizations (2.40 [1.26–4.58], P=0.008) throughout childhood.

- IFN\text{\textsuperscript{highest}}Inflam\text{\textsuperscript{mod}}TH2-chem\text{\textsuperscript{mod}}Reg\text{\textsuperscript{high}} cluster: low prevalence of asthma/sensitization in infancy, which increased sharply to become the highest among all clusters by adolescence (but with low risk of asthma exacerbations).

Custovic et al, Am J Respir Crit Care Med. 2018;197(10):1265-1274
TH2 cytokine responses to PHA differ in rhinovirus-16-response clusters

Custovic et al, Am J Respir Crit Care Med. 2018;197(10):1265-1274
Preterm LCSC
Low BW Immunology Lung structure ?Programming

ACUTE ATTACKS OF WHEEZE!!
An important, largely-unanswered question is how best to translate findings between RCTs, patient cohorts, & birth cohorts, i.e. between clinical and general populations, in order to inform better prevention and management strategies.
Multidisciplinary approach to discover interventions to prevent, modify and cure obstructive lung diseases

Conclusions
Towards mechanism-based treatments

• Asthma and COPD now: Diagnoses and symptoms without clearly defined mechanisms

• Patients with multiple disease subtypes are forced into a single group for empirical treatment

• A compelling case for reforming the taxonomy of obstructive airway diseases

• The future: Disaggregate these diagnoses to facilitate patient stratification – Life-course perspective is key

• Birth cohorts, patient studies, RCTs, and mechanistic studies (humans and animal models) together will generate invaluable “big data” assets to provide a foundation for a step change towards personalised medicine

Conclusions
Towards mechanism-based treatments

- Extend endotype discovery: Cross-disciplinary, cutting edge analytics based on large, complex datasets (including clinical and general populations, i.e. patient cohorts and birth cohorts)
- Key role for industry: Integrate clinical trials data in this discovery platform; test novel targets
- Generate hypotheses: Test using in vitro and in vivo experimental models
- Solution: An integrative approach whereby clinicians, statisticians, computer scientists, geneticists, physicists, basic scientist and epidemiologists work together to understand the heterogeneity of asthma
- Vision: “Team science” in place of “selfish science”

3. Belgrave, Custovic et al, JACI 2017;139(2):400-407
I would rather be a devil in alliance with truth, than an angel in alliance with falsehood.

(Ludwig Andreas Feuerbach)