Risk factors and early origins of chronic obstructive pulmonary disease

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COI statement

• None relevant to this presentation
Aims of the Presentation

• To show that premature airflow obstruction is a description not a disease – I don’t understand ‘COPD’

• To demonstrate the crucial importance of childhood events in the development of premature airflow obstruction

• To remind us that there is more to lung development than just the airway

• To show that childhood life events are not evanescent phenomena but have profound long term significance
‘COPD’, birth cohorts and early life

• Five fundamental preliminary observations
1. How spirometry evolves

- GLI data
  [www.lungfunction.org](http://www.lungfunction.org)

- 97,759 records, healthy non-smokers from 72 centres in 33 countries age 2.5-95 years

- Constructed predictive equations for spirometry

*Eur Respir J* 2012; 40: 1324-43
2. Barkerology:
If you can’t measure it well, measure it often!

MALES
3. Early Childhood Disadvantage

Effect of Childhood Disadvantage = Effect of Heavy Smoking

Early childhood disadvantage:
- Lower lung function
- No catch-up
- Faster rate of decline
- More COPD

Thorax 2010; 65: 14-20
4. Melbourne: the longest show in time
COPD: Childhood

- FU of Melbourne birth cohort at age 50, 76% retention
- Age 50: non-asthmatics, current asthma, remitted asthma, COPD (FEV₁/FVC<0.70)
- Lung function tracked back to age 10 years
- OR for COPD with severe asthma 32(3.4-269); stronger than smoking

Thorax 2014; 68: 805-10
5. Downhill all the way

- Three cohorts: Framingham Offspring, Copenhagen City Heart Study, Lovelace Smokers Cohort
- Mean age at enrolment 40 years
- 174/657 (26%) with FEV$_1$ <80% at enrolment had COPD after 22 years vs. 158/2207 (7%) with FEV$_1$ >80% (p<0.001)
- c50% COPD had normal FEV1, declined rapidly vs. low FEV$_1$ and normal decline, *unrelated to smoking*

*NEJM 2015; 373: 111-22*
Normals

COPD despite normal ΔFEV₁

No COPD because supranormal ΔFEV₁

COPD 'rapid decliners'
Lessons-1

• Any view of premature airflow obstruction which does not take account of early life factors is wrong

• If you reach a peak of normal airway function, you are MUCH less likely to develop premature airflow obstruction

• Accelerated decline is not a prerequisite for premature airflow obstruction

• Smoking does not appear to account for different rates of decline
‘COPD’, birth cohorts and early life

- Some fundamental preliminary observations
- ‘COPD’ vs. premature airflow obstruction
1. Variable airflow obstruction

2. Inflammation

3. Fixed airflow obstruction

4. Infection

5. Secretory function

Extramural - loss of alveolar guy ropes
Airway wall - reduction in airway calibre

Extramural – alveolar guy ropes
Airway wall – ASM, other
Intramural - mucus

Bacterial
Viral
Fungal

Too dry
Too wet

Present or absent?
Beneficial or harmful?
Cell type?
Neural?
Pathway based?
Normal or Diseased?

- Women aged 30, FEV$_1$/FVC ratio of 75% is wildly abnormal
- Above age 50, increasing numbers of normal people will have FEV$_1$/FVC ratio <70%
- Above age 70, >15% of normal people will have FEV$_1$/FVC ratio <70%

Is somebody weighing 50 kg underweight whatever their age?
Lessons-2

• COPD is not a disease, it is an imprecise description

• We need to describe airway disease in 21\textsuperscript{st} century terms!
‘COPD’, birth cohorts and early life

- Some fundamental preliminary observations
- ‘COPD’ vs. premature airflow obstruction
- Safe in the womb?
Cigarettes: structure

Antenatal collagen deposition
RedJ 2002; 26: 31-4

MUC5AC expression
RedJ 2011; 44: 222-9

Alveolar tethering points
BlueJ 2003; 163: 140-4
Cigarettes: more on structure

- Increased ASM thickness *BlueJ 2003; 163: 140-4*
- Airway lengthening and reduced calibre
- AHR independent of allergen exposure *RedJ 2012; 46: 695-72*

**READOUT IN THE BABY**

- Airway obstruction and AHR at birth
- Long term signalling from both AHR and obstruction
COPSAC Data

- 411 high-risk babies
- 403 (98%) RVRTC and BHR$_{\text{meth}}$ (TcPO$_2$)
- Follow-up age 7 n=317 (77%) , spirometry, questionnaire
- Neonatal airflow obstruction predictive of asthma
- Obstruction age 7: 40% antenatal, 60% postnatal

Neonatal BHR

- OR for later asthma 1.59 (1.11-2.28, p=0.001)
- Stronger predictor for later asthma than neonatal lung function

Am J Respir Crit Care Med 2012; 185: 1183-9
Cigarettes: Function

Increased cord blood MNC allergen response
**CEA 2002; 32: 43-50**

Reduced cytokine & TLR function
**Eur Respir J 2006; 28: 721-9**

Abnormal cytokine responses and increased viral infections
**BlueJ 2004; 170: 175-80**
More on cigarettes!

Daughter more likely to smoke
Daughter more likely to have asthma
More likely to smoke
Synergistic effects if mother and child smoke

Grandchildren more likely to have asthma

Chest 2005; 127: 1232-41
Thorax 2015; 70: 237-43
Thorax. 2013; 68: 1021-8
Pollution!

• 624 children, spirometry age 4.5 years

• Developmental residential exposure to benzene, NO$_2$

• Effects for pregnancy, and no other time point, including recent and current

• Worse for allergic children, low SES

Thorax 2015; 70: 64-73.
Pollution!

- Childrens Health Study, Southern California
- Annual spirometry
- Air quality improved greatly over time with Government policies

NEJM 2015; 372: 905-13
Combining atopy and wheeze phenotypes

- Manchester birth cohort

- 4 (?) wheeze phenotypes
  - None
  - Transient
  - Late onset
  - Persistent

- 5 atopy phenotypes
  - None
  - Dust mite
  - Non-dust mite
  - Multiple early
  - Multiple late
Conclusions

• Persistent wheeze, multiple early atopy, and exacerbations predict a bad trajectory

• Risk progressive loss of lung function age 3-11

• More marked in boys

*Am J Respir Crit Care Med 2014; 189: 1101-9*
Lessons-3

- Cigarettes are the worst culprit before conception, before birth and in childhood

- At least some effects are mediated via nicotine (advocates of e-cigarettes take note!)

- Pollution is also important, both antenatally and postnataally
‘COPD’, birth cohorts and early life

• Some fundamental preliminary observations

• ‘COPD’ vs. premature airflow obstruction

• Safe in the womb?

• Birth right?
Preterm Birth: a new adult disease?

- Becoming MORE common
- Effects cannot be ameliorated by surfactant, etc.
- Airway obstruction even if no neonatal intensive care needed
AHR & Fixed obstruction

- BPD vs. non-BPD vs. term

- Acute BDR, diurnal variation, AHR
Airway Inflammation & BPD

- N=17 asthmatics, normals, BPD survivors

- Spirometry, & FeNO and exhaled breath temperature as measures of airway inflammation

- BPD results
  - Worse lung function
  - Lower FeNO
  - Exhaled breath temperature

- Conclusion: despite BHR, no evidence of ongoing inflammation in BPD
The Very Late Pre-termer

- 44,173 women delivering between 1989 and 2008
- N=2661 children had asthma meds reimbursed, 41512 controls
- Early term 108 extra cases, biggest burden
- Post-term seemed to be protective

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<th>mod pre-term</th>
<th>late pre-term</th>
<th>early term</th>
<th>Term</th>
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<td>≥32/40</td>
<td>3.9 (3.2-4.8)</td>
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<td>0.9 (0.8-1.0)</td>
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*J Pediatr 2014; 164: 295-9*
Lessons-4

• Even very late preterm birth has long term consequences

• These patients are, however, unlikely to have eosinophilic inflammation
‘COPD’, birth cohorts and early life

- Some fundamental preliminary observations
- ‘COPD’ vs. premature airflow obstruction
- Safe in the womb?
- Birth right?
- Think beyond the airway
Nicotine exposure and septation of developing alveoli

Control
Nicotine

*p<0.05

Cell Biology International 2014; 18: 747-767
Early Emphysema?

- Proof of concept studies:
  - Early postnatal hyperoxia and/or corticosteroid therapy

- Could nicotine also be implicated as a culprit?

*Int J Environ Res Public Health 2011; 8: 875-98*

- (Also He3 MRI data)
Lessons-5

• There may be premature emphysema as well as premature airflow obstruction determined early on – more studies are needed
‘COPD’, birth cohorts and early life

• Some fundamental preliminary observations

• ‘COPD’ vs. premature airflow obstruction

• Safe in the womb?

• Birth right?

• Think beyond the airway

• Summary and conclusions
So, what did we learn?

- COPD is as outmoded as ‘anaemia’ and ‘arthritis’ as a diagnostic label.
- The roots of premature airflow obstruction stretch back into childhood, antenatally and beyond.
- The big issues: smoking, asthma history, viral infections, pollution.
- You cannot understand adult airway disease without knowing about childhood events!
Thanks for listening;
Start your ‘COPD’ research in early life!