# Spirometry, COPD and lung cancer

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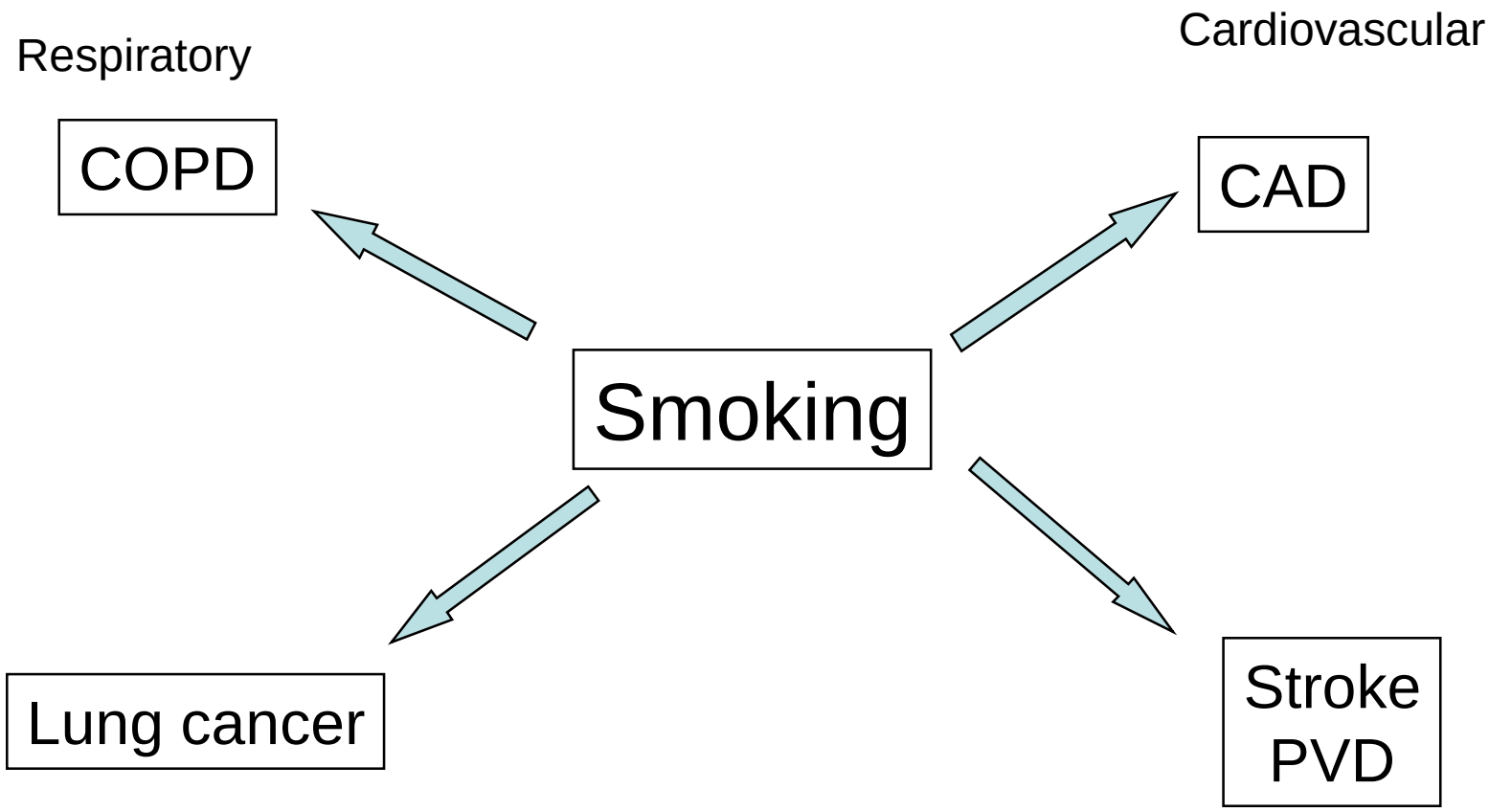
# Spirometry for those with smoking and dust exposures

| **Risk assessment** | **Disease** | **Outcome** |
|---|---|---|
| Blood pressure | Hypertension | Stroke |
| Lipids | Hypercholesterolaemia | Heart attack |
| Glucose | Hyperglycaemia | Diabetes |
| Bone density | Osteoporosis# | Fracture (low impact) |
| Spirometry | Airways obstruction# | COPD<br>Heart attack<br>Lung cancer |
| # Diagnose end organ damage (coronary angiogram or CT chest) | | |

# Smoking and lung disease

# Smoking and its complications

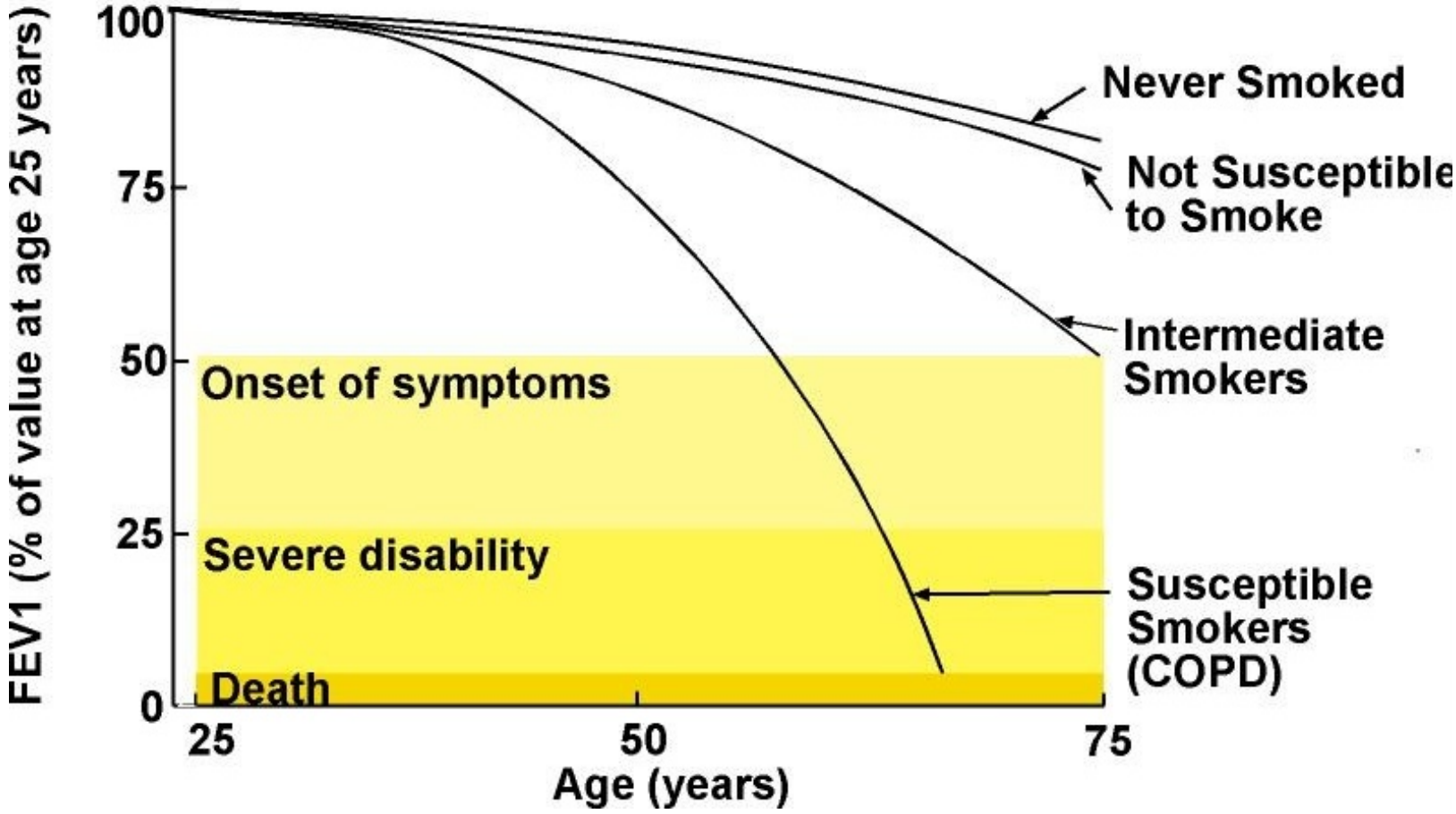


# Epidemiology of lung cancer

- Smoking (90%)
  - Duration over 30 years or over 30 pk years
- Age (over 50 yo)
- Other factors
  - Exposure to asbestos, radon, radiation and cooking fuels
  - Low consumption of fruit and vegetables (antioxidants)
  - Lower risk in atopics
- Lung function
- Family history

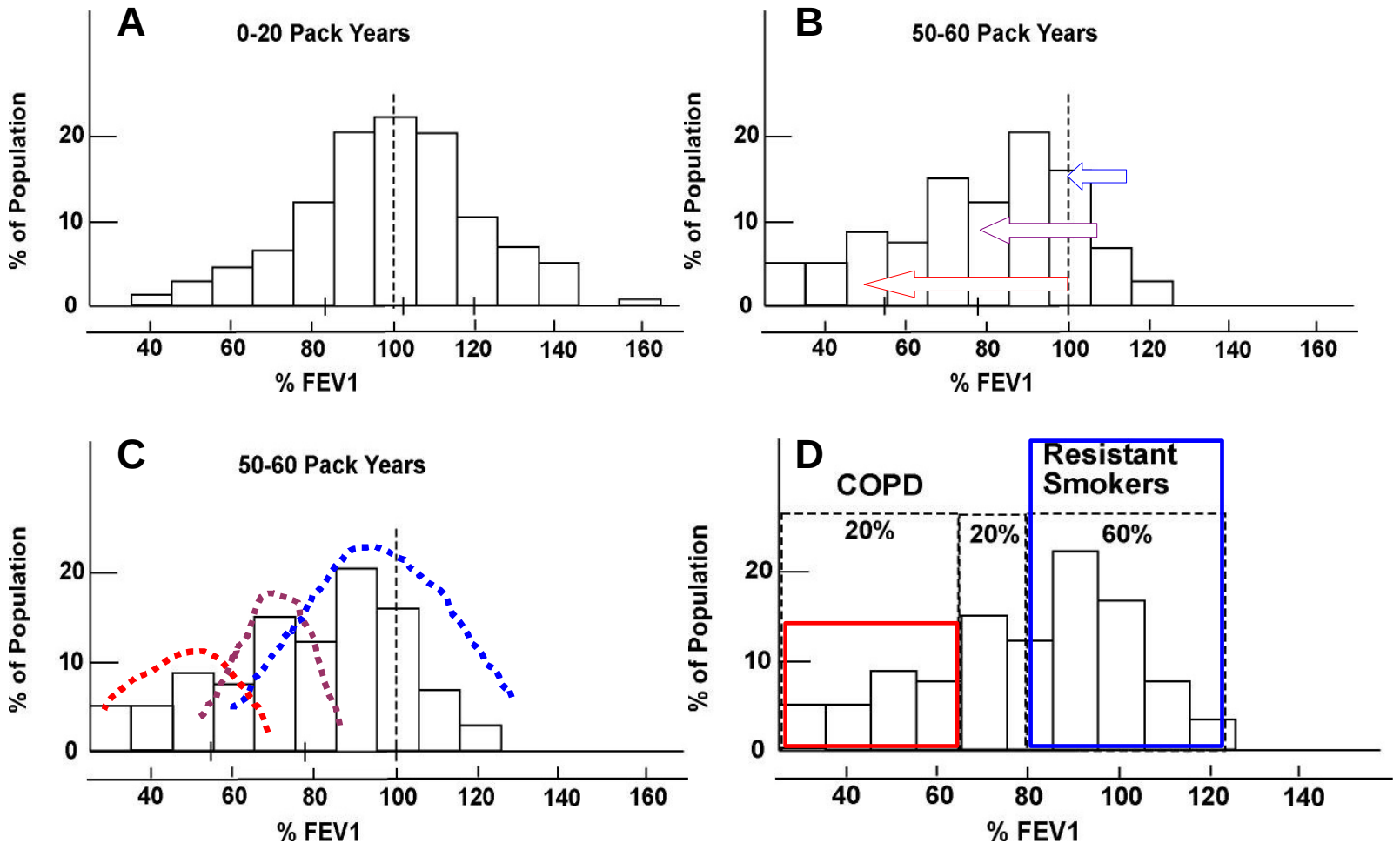
**Genetic factors**

# Decline of Lung Function: Not Homogeneous

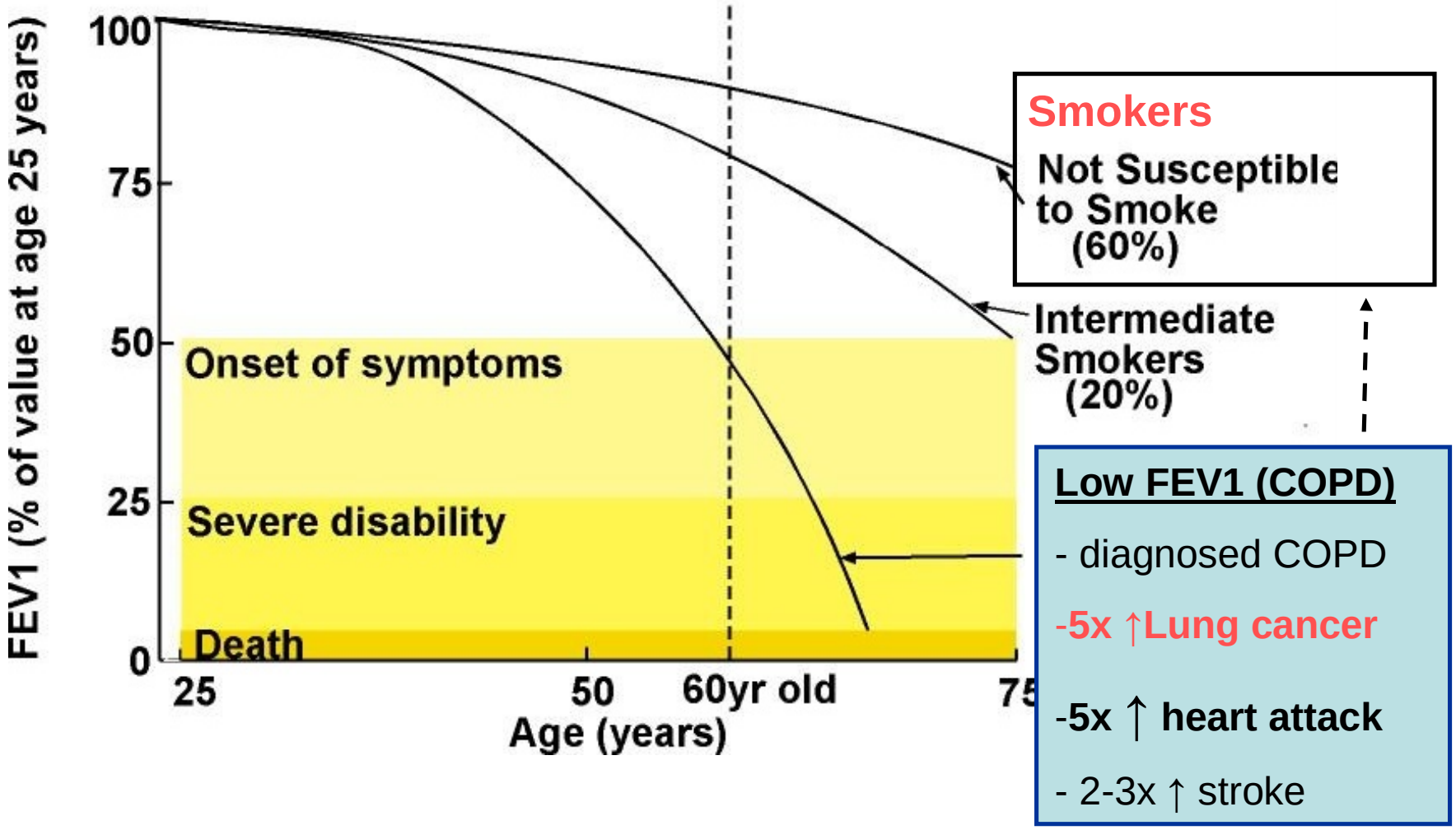



Lung function in smokers who get COPD

# Segmentation of Lung Function Decline



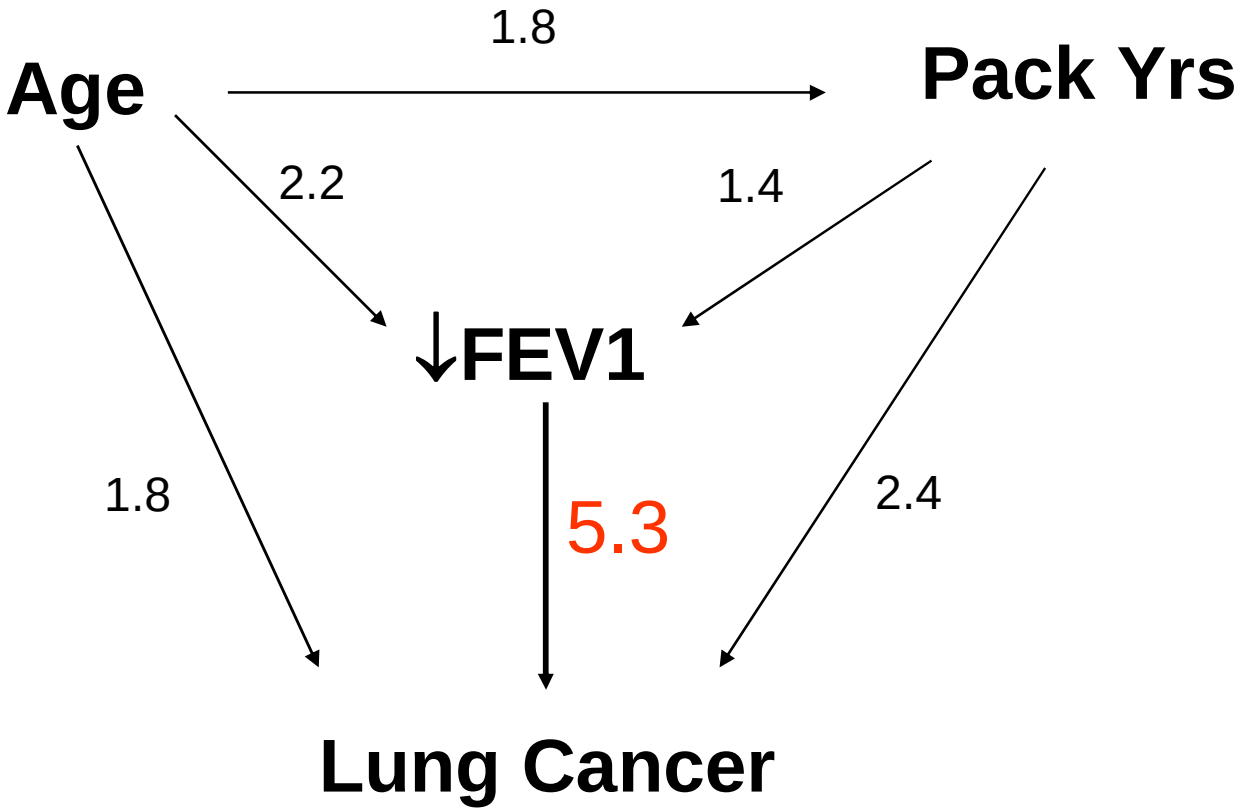
# Reduced $FEV_1$: linked to all cause mortality



# Lung Function and Lung Cancer

Consistently reported risk of 3-6x for lung cancer in smokers with impaired lung function

| **Lung cancer** | |
|---|---|
| **Age** | **RR 2.8** |
| **↓FEV1** | **RR 6.4** |
| **Pk yrs** | **RR 3.1** |

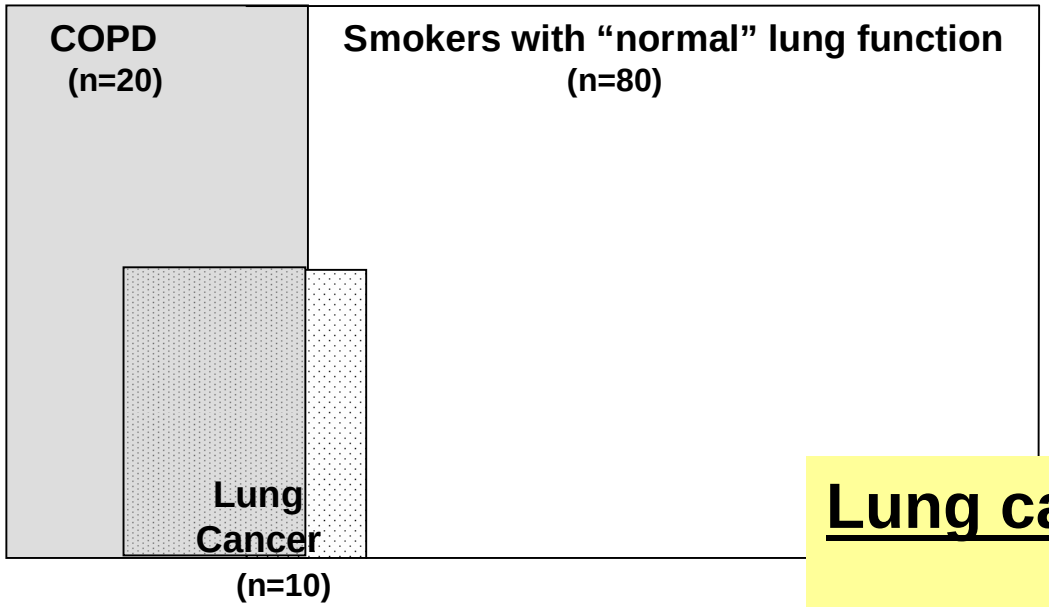


Eur Respir J 2009; 34: 1–7
DOI: 10.1183/09031936.00144208


# COPD prevalence is increased in lung cancer independent of age, sex and smoking history

**R.P. Young*, R.J. Hopkins*, T. Christmas#, P.N. Black¶, P. Metcalf+ and G.D. Gamble***

# Lifetime risk: COPD and lung cancer




Young RP, et al.
ERJ, On line Feb 5th, 2009

**Lung cancer develops in**

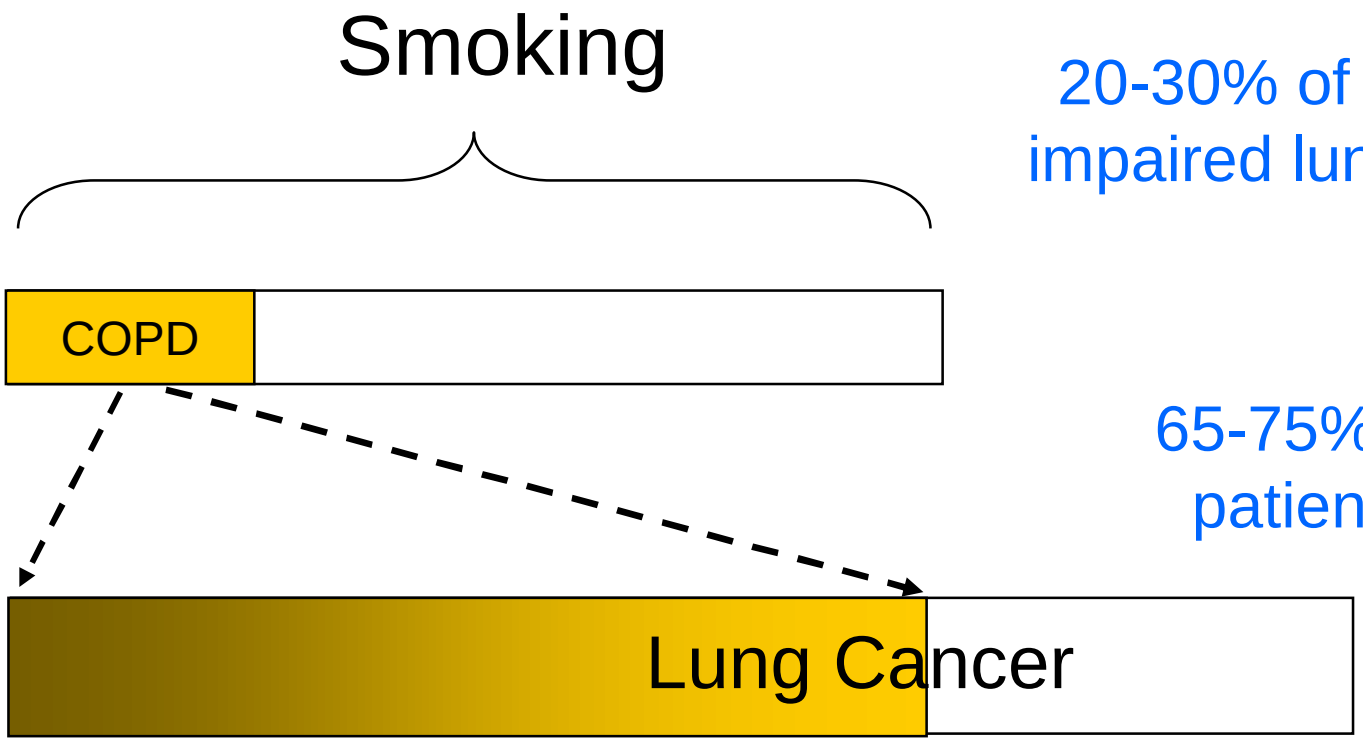
6/20 with COPD (30%)

4/80 with normal lung function (5%)

Lung cancer cases

-50% have GOLD 2+ COPD
-67% have GOLD 1+ COPD
-87% have COPD ± emphysema

# Smoking, lung function and lung cancer

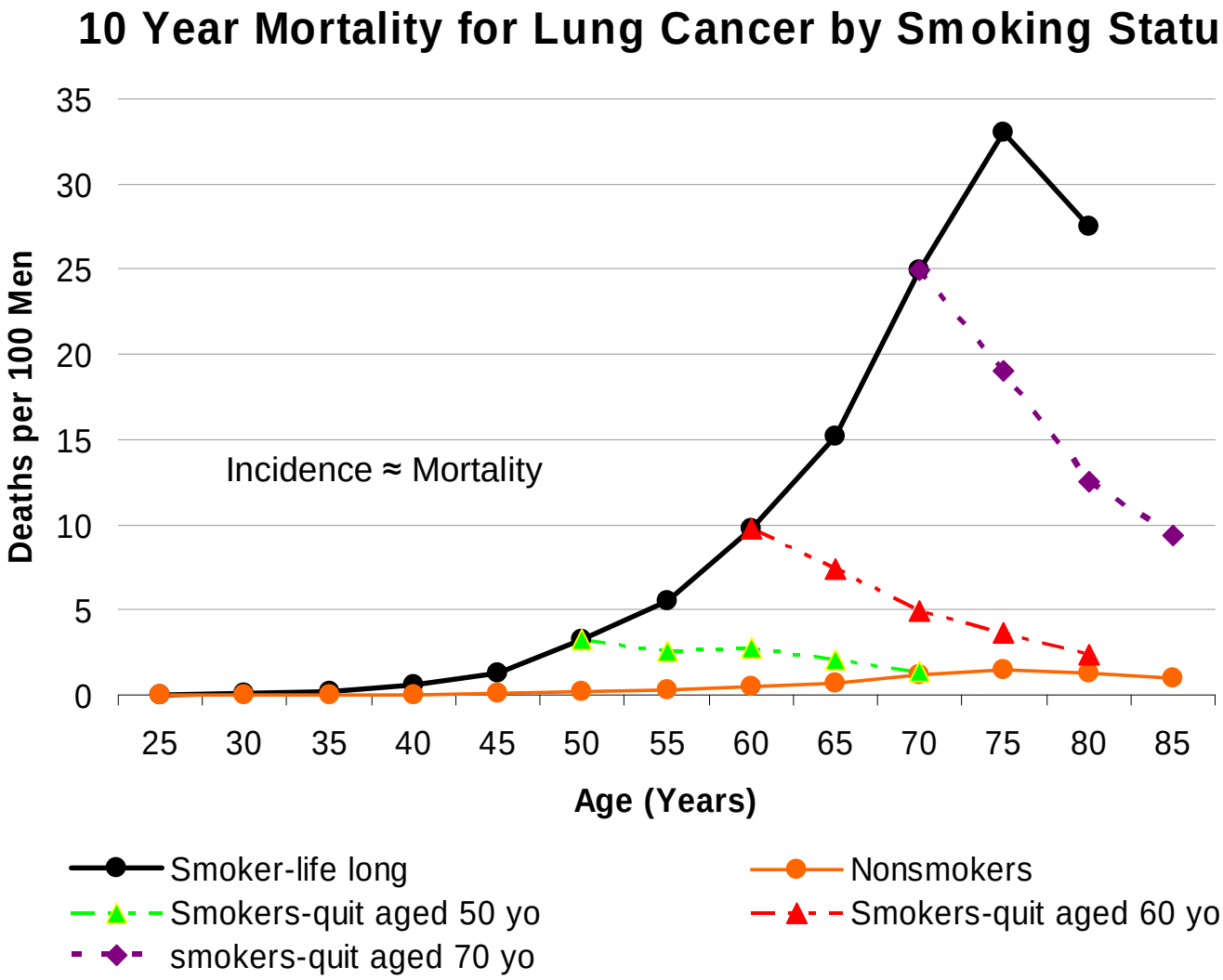



20-30% of smokers develop impaired lung function (COPD)

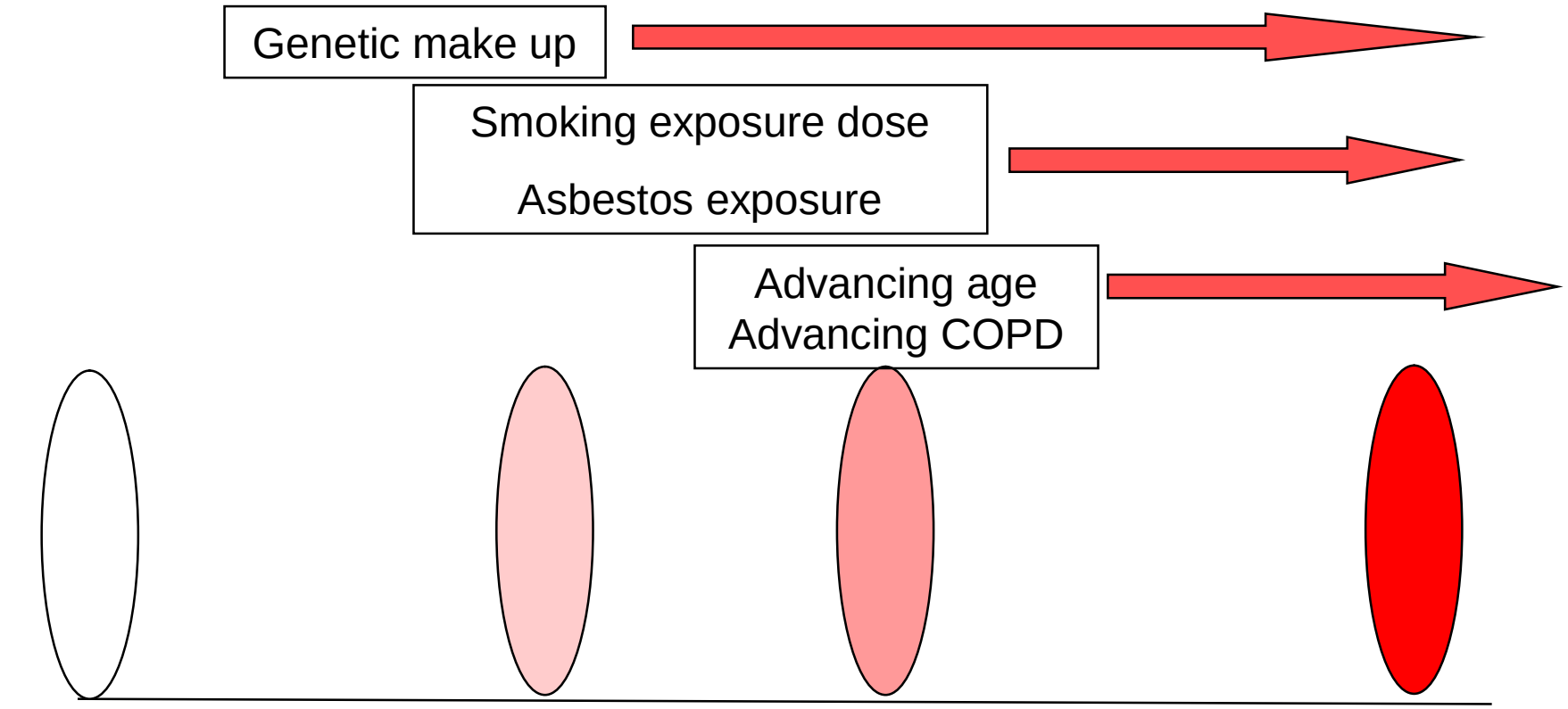
65-75% of lung cancer patients have COPD

Parallel:
Obesity predisposes to diabetes

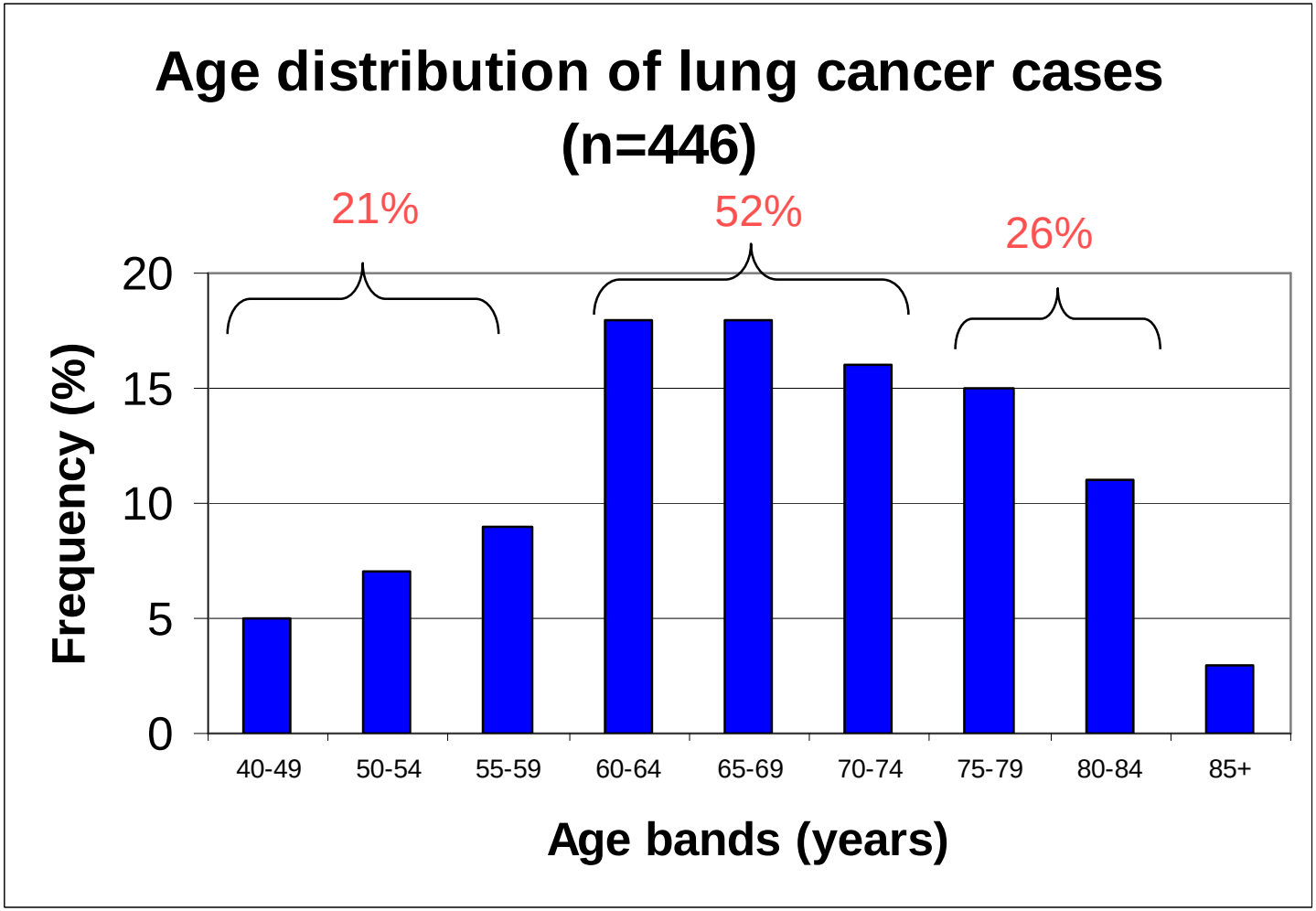
# Lung Cancer Risk climbs steeply with age



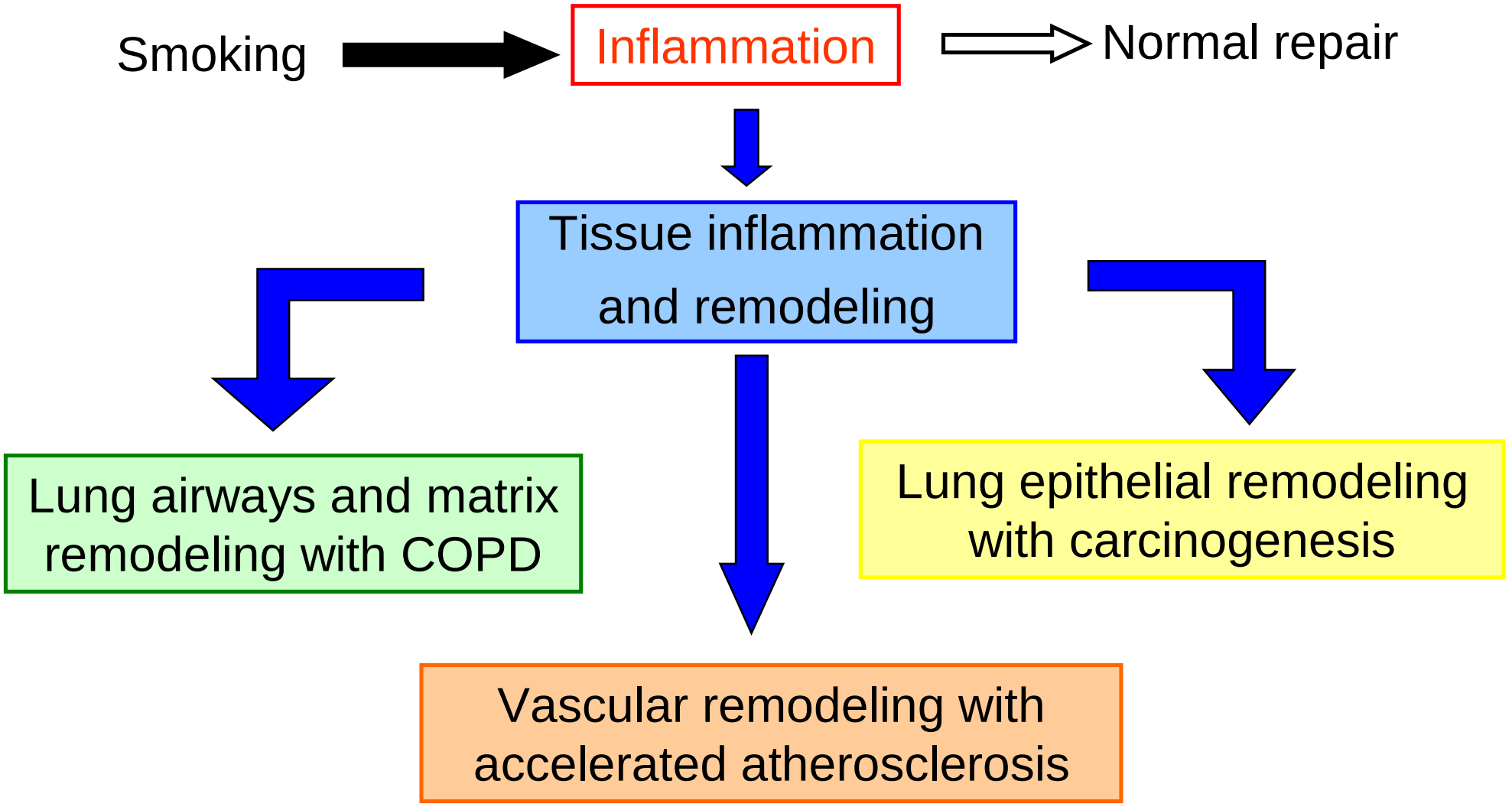
# Risk spectrum for lung cancer risk

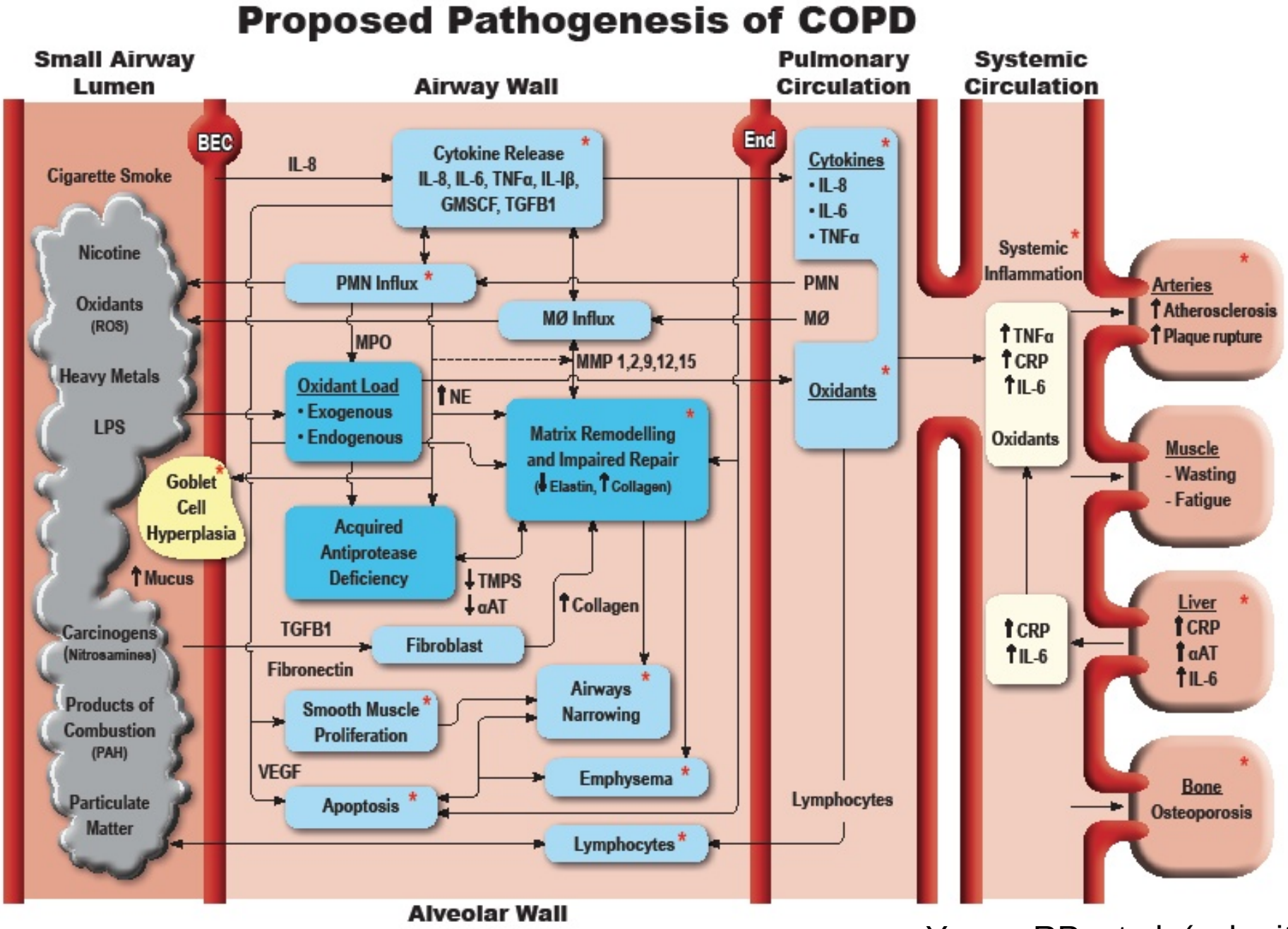


# Lung cancer and age distribution



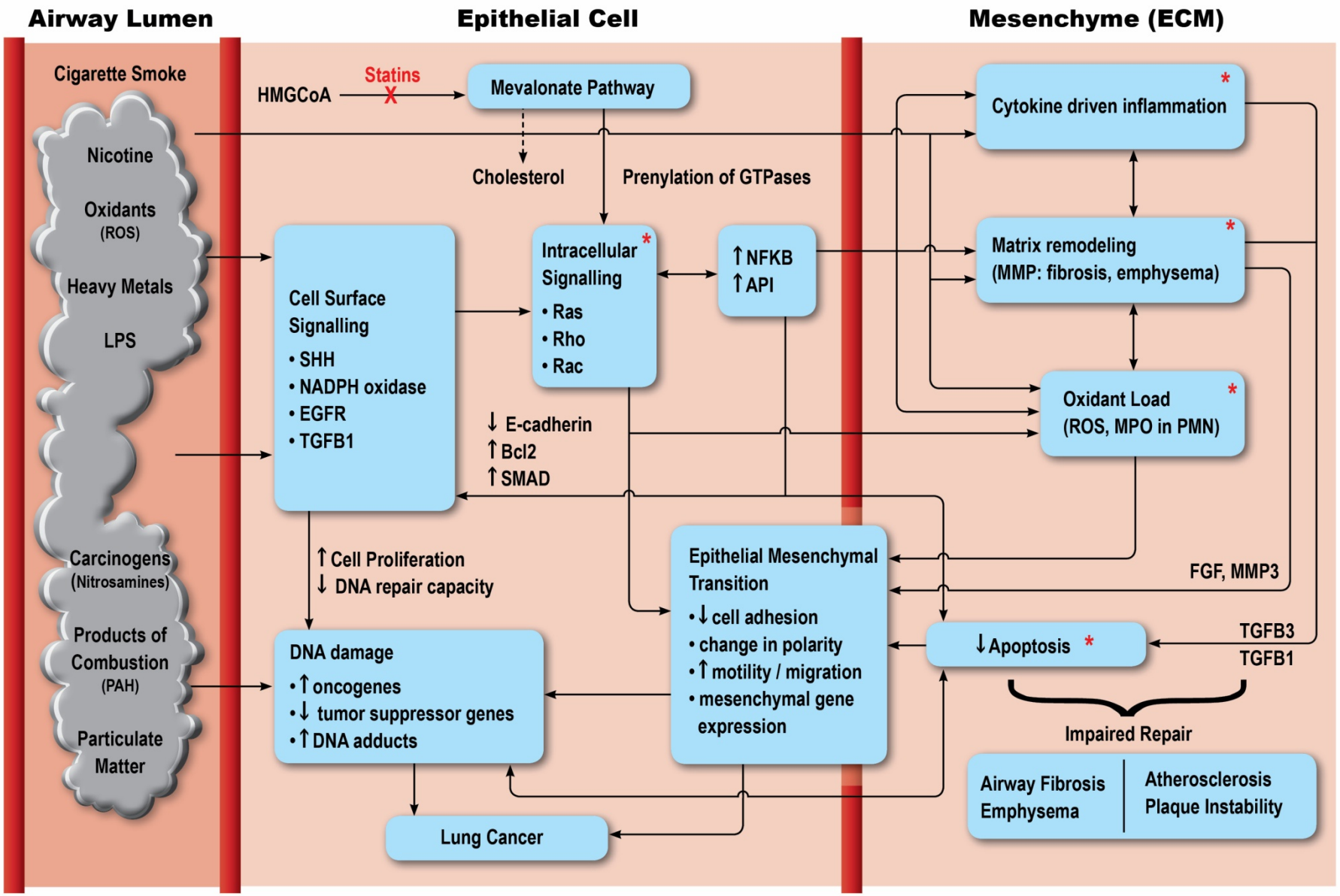
# Inflammation and cardio-pulmonary disease






Young RP, et al. (submitted)

# Proposed Pathogenesis of Lung Cancer

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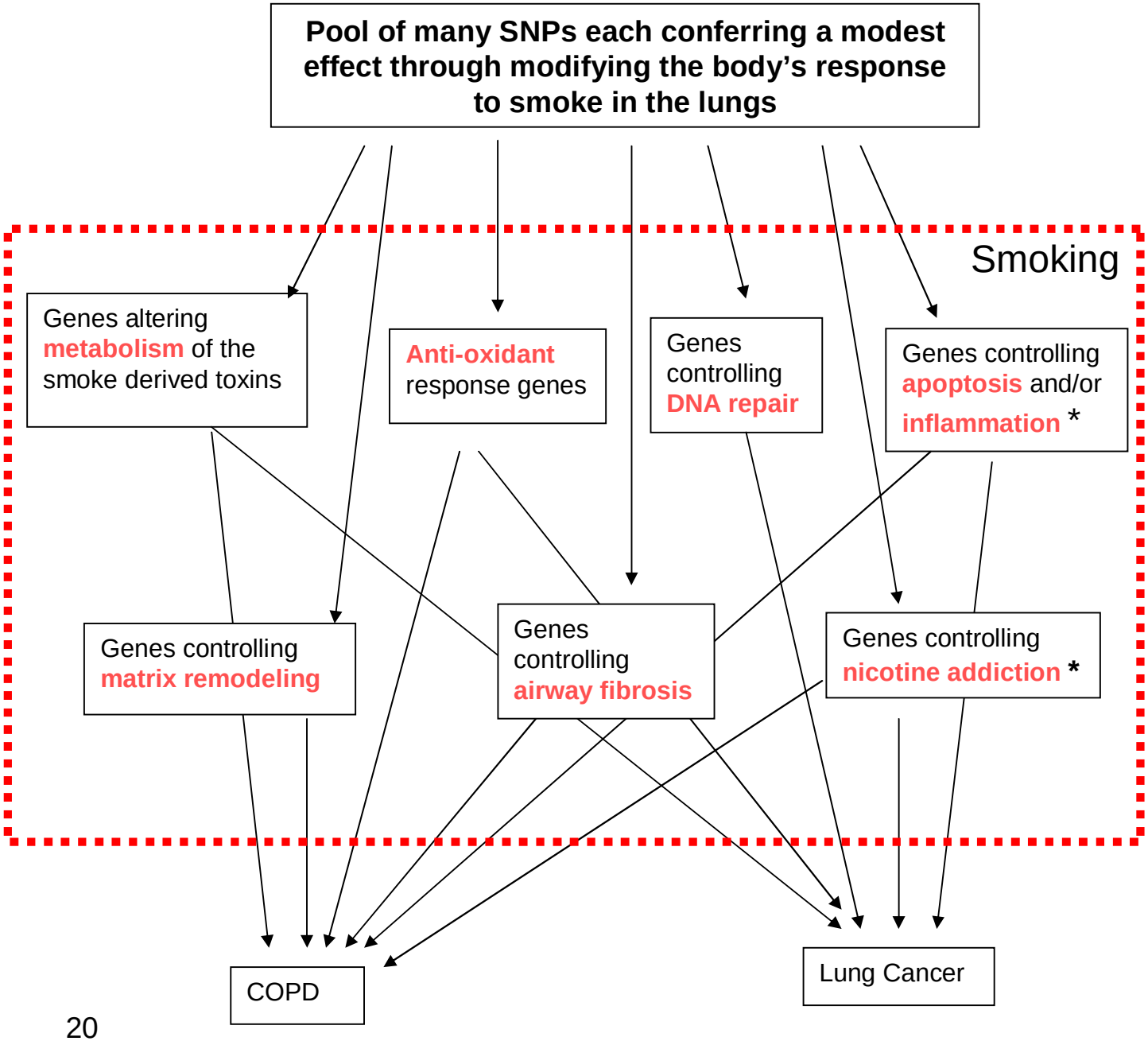



Genetic susceptibility to lung cancer

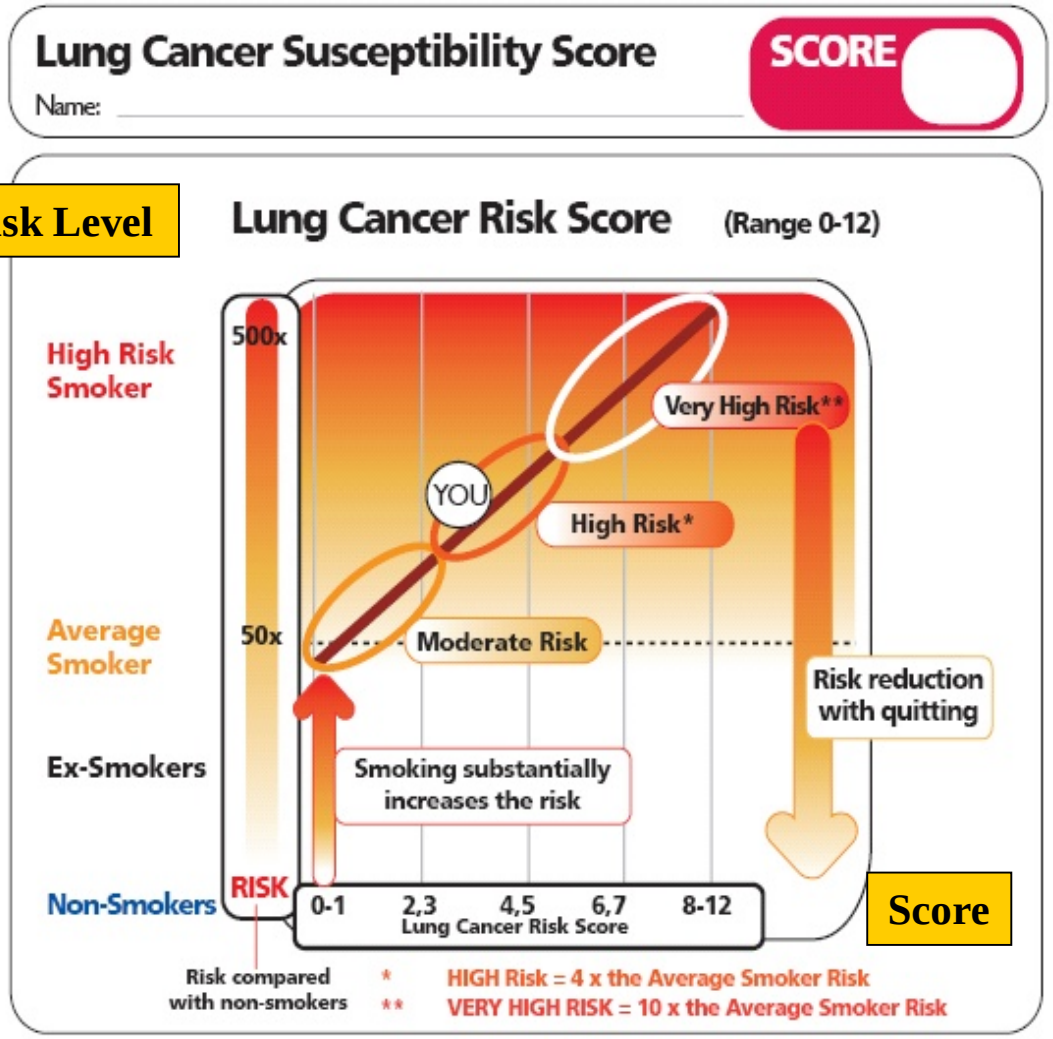
Many genetic variants

Interaction with smoking

Affect many different pathways

Overlap between genes conferring COPD and lung cancer

nAChR gene* locus associated with lung cancer, COPD and nicotine addiction




No one is lower than average risk for lung cancer

## Lung cancer susceptibility score

- Educational tool to personalise risk and raise awareness of lung cancer
- Refines existing risk derived from smoking exposure
- Based on age, FHx of lung cancer, COPD and SNP markers
- Target 40+ yr old who are smokers and ex-smokers (last 10 years)
- Aim to motivate smoker to quit or ex-smoker to avoid relapse
- Referenced against the “average” smoker’s risk
- Shows risk reduction with quitting

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# April 2008 – “Lung cancer” gene discovered

**Headlines**

- NY times
- Herald Tribune
- Financial Times
- NZ Herald

Vol 452|3 April 2008|doi:10.1038/nature06885 nature

LETTERS

## A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25

Rayjean J. Hung[1,2]*, James D. McKay[1]*, Valerie Gaborieau[1], Paolo Boffetta[1], Mia Hashibe[1], David Zaridze[3], Anush Mukeria[3], Neonilia Szeszenia-Dabrowska[4], Jolanta Lissowska[5], Peter Rudnai[6], Eleonora Fabianova[7], Dana Mates[8], Vladimir Bencko[9], Lenka Foretova[10], Vladimir Janout[11], Chu Chen[12], Gary Goodman[12], John K. Field[13], Triantafillos Liloglou[13], George Xinarianos[13], Adrian Cassidy[13], John McLaughlin[14], Geoffrey Liu[15], Steven Narod[16], Hans E. Krokan[17], Frank Skorpen[17], Maiken Bratt Elvestad[17], Kristian Hveem[17], Lars Vatten[17], Jakob Linseisen[18], Françoise Clavel-Chapelon[19], Paolo Vineis[20,21], H. Bas Bueno-de-Mesquita[22], Eiliv Lund[23], Carmen Martinez[24], Sheila Bingham[25], Torgny Rasmuson[26], Pierre Hainaut[1], Elio Riboli[20], Wolfgang Ahrens[27], Simone Benhamou[28,29], Pagona Lagiou[30], Dimitrios Trichopoulos[30], Ivana Holcátová[31], Franco Merletti[32], Kristina Kjaerheim[33], Antonio Agudo[34], Gary Macfarlane[35], Renato Talamini[36], Lorenzo Simonato[37], Ray Lowry[38], David I. Conway[39], Ariana Znaor[40], Claire Healy[41], Diana Zelenika[42], Anne Boland[42], Marc Delepine[42], Mario Foglio[42], Doris Lechner[42], Fumihiko Matsuda[42], Helene Blanche[43], Ivo Gut[42], Simon Heath[43], Mark Lathrop[42,43] & Paul Brennan[1]

nature Vol 452|3 April 2008|doi:10.1038/nature06846

LETTERS

## A variant associated with nicotine dependence, lung cancer and peripheral arterial disease

Thorgeir E. Thorgeirsson[1]*, Frank Geller[1]*, Patrick Sulem[1]*, Thorunn Rafnar[1]*, Anna Wiste[1,2], Kristinn P. Magnusson[1], Andrei Manolescu[1], Gudmar Thorleifsson[1], Hreinn Stefansson[1], Andres Ingason[1], Simon N. Stacey[1], Jon T. Bergthorsson[1], Steinunn Thorlacius[1], Julius Gudmundsson[1], Thorlakur Jonsson[1], Margret Jakobsdottir[1], Jona Saemundsdottir[1], Olof Olafsdottir[1], Larus J. Gudmundsson[1], Gyda Bjornsdottir[1], Kristleifur Kristjansson[1], Halla Skuladottir[3], Helgi J. Isaksson[4], Tomas Gudbjartsson[5], Gregory T. Jones[8], Thomas Mueller[9], Anders Gottsäter[10], Andrea Flex[11], Katja K. H. Aben[12,13], Femmie de Vegt[12], Peter F. A. Mulders[14], Dolores Isla[15], Maria J. Vidal[15], Laura Asin[16], Berta Saez[17], Laura Murillo[18], Thorsteinn Blondal[19], Halldor Kolbeinsson[6], Jon G. Stefansson[6], Ingunn Hansdottir[20], Valgerdur Runarsdottir[20], Roberto Pola[11,21], Bengt Lindblad[10], Andre M. van Rij[8], Benjamin Dieplinger[9], Meinhard Haltmayer[9], Jose I. Mayordomo[15,16,17], Lambertus A. Kiemeney[12,13,14], Stefan E. Matthiasson[22], Hogni Oskarsson[23], Thorarinn Tyrfingsson[20], Daniel F. Gudbjartsson[1], Jeffrey R. Gulcher[1], Steinn Jonsson[7], Unnur Thorsteinsdottir[1,22], Augustine Kong[1] & Kari Stefansson[1,22]

LETTERS

nature genetics

## Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1

Christopher I Amos[1], Xifeng Wu[1], Peter Broderick[2], Ivan P Gorlov[1], Jian Gu[1], Timothy Eisen[3], Qiong Dong[1], Qing Zhang[1], Xiangjun Gu[1], Jayaram Vijayakrishnan[2], Kate Sullivan[2], Athena Matakidou[2], Yufei Wang[2], Gordon Mills[4], Kimberly Doheny[5], Ya-Yu Tsai[5], Wei Vivien Chen[1], Sanjay Shete[1], Margaret R Spitz[1,6] & Richard S Houlston[2,6]

ww.nature.com/naturegenetics

**$P=10^{-17}$**

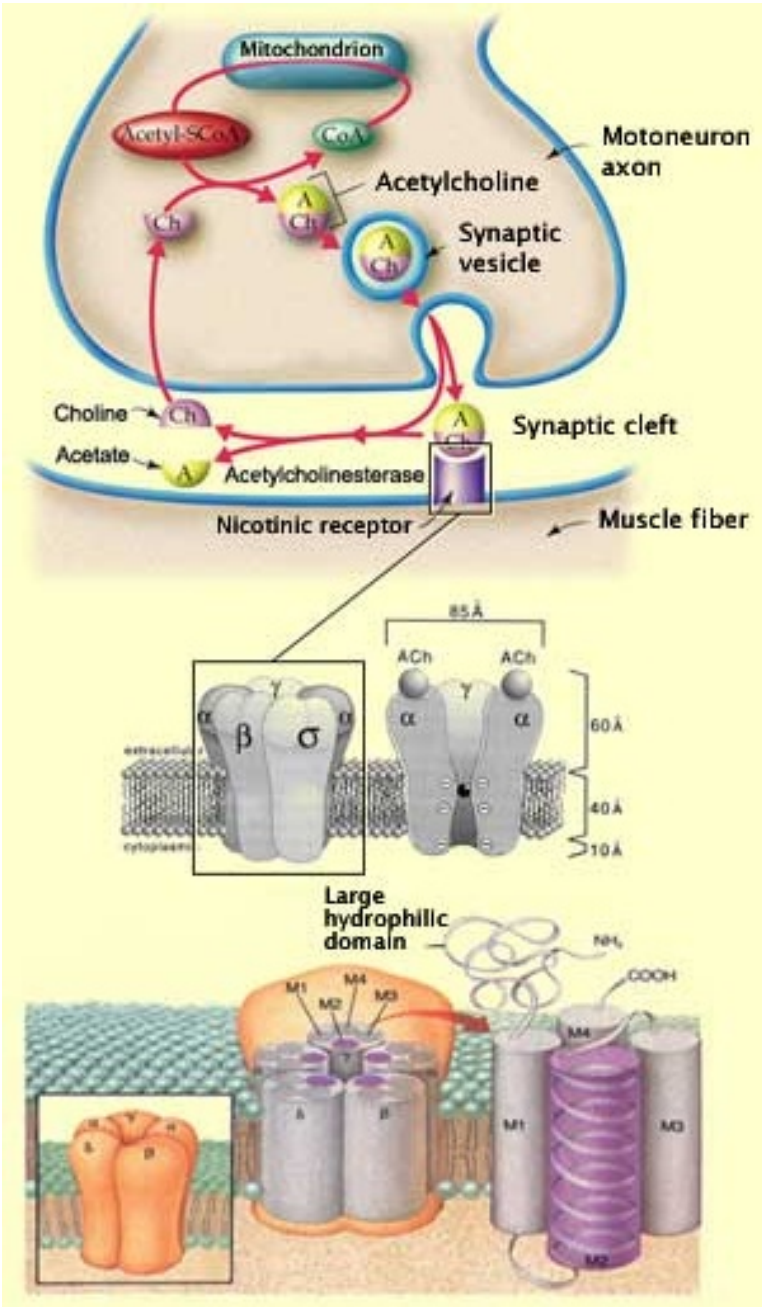
Eur Respir J 2008; 32: 1–7
DOI: 10.1183/09031936.00093908


# Lung cancer gene associated with COPD: triple whammy or possible confounding effect?

R.P. Young*,#, R.J. Hopkins*, B.A. Hay*, M.J. Epton¶, P.N. Black* and G.D. Gamble*

**Nicotinic acetylcholine receptor SNP**

-Chromosome 15q25 (GWAS)
-associated with lung cancer, COPD and nicotine addiction
-Nicotine up-regulates inflammation in the lung
-SNP appears to be involved in modifying this inflammatory effect
- SNPs associated with both diseases



# Lung cancer genetics: Auckland Study

Genotypes for the α5 subunit of the nAChR gene (Young RP, et al. ERJ Nov 2008)

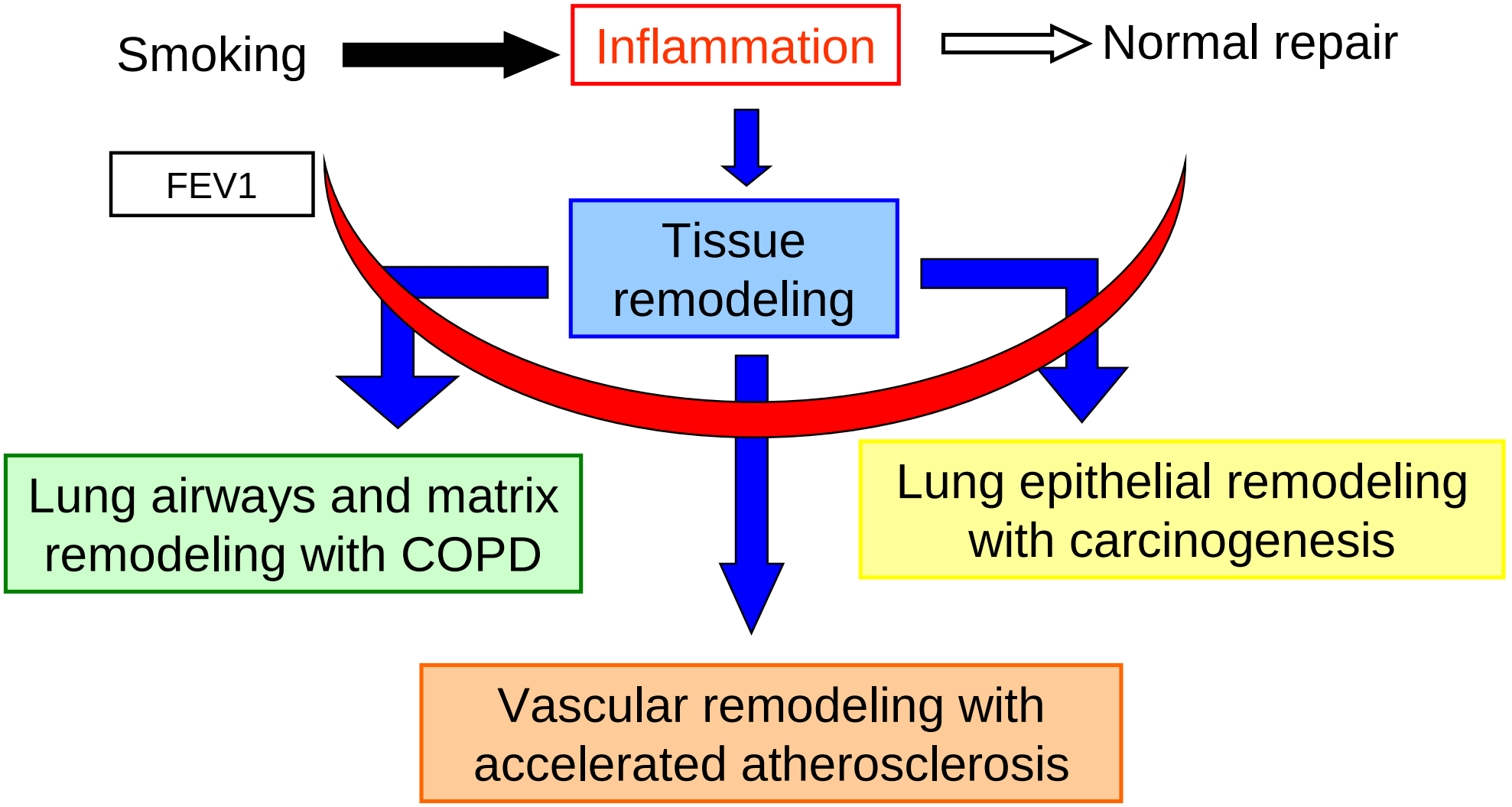
| ***Primay Cohorts*** (call rate %) | **GG** | **GA** | **AA** | **OR* (95% CI)** | **P value*** |
|---|---|---|---|---|---|
| **Controls N=475** (97%) | 225 (47%) | 205 (43%) | 45 (9%) | - | - |
| **COPD N=445** (97%) | 166 (37%) | 219 (49%) | 60 (14%) | 1.5 (1.0-2.3) | 0.06 |
| **Lung cancer N=437** (96%) | 170 (39%) | 199 (46%) | 68 (16%) | 1.8 (1.2-2.7) | 0.005 |
| ***Subgroup Analyses*** | | | | | |
| **COPD and LC+COPD, N=706** | 252 (36%) | 344 (49%) | 110 (16%) | 1.8 (1.2-2.6) | 0.002 |
| **LC + COPD#, N=261** | 86 (33%) | 125 (48%) | 50 (19%) | 2.3 (1.4-3.6) | 0.0002 |
| **LC only, N=168** | 81 (48%) | 69 (41%) | 18 (11%) | 1.2 (0.6-2.1.) | 0.64 |

# Clinical utility of spirometry

Reduced $FEV_1$ (compared to normal lung function)

- Predicts increased risk of coronary artery disease
- Predicts increased risk of lung cancer
- Predicts increased risk of stroke
- Predicts increased risk of peripheral arterial disease

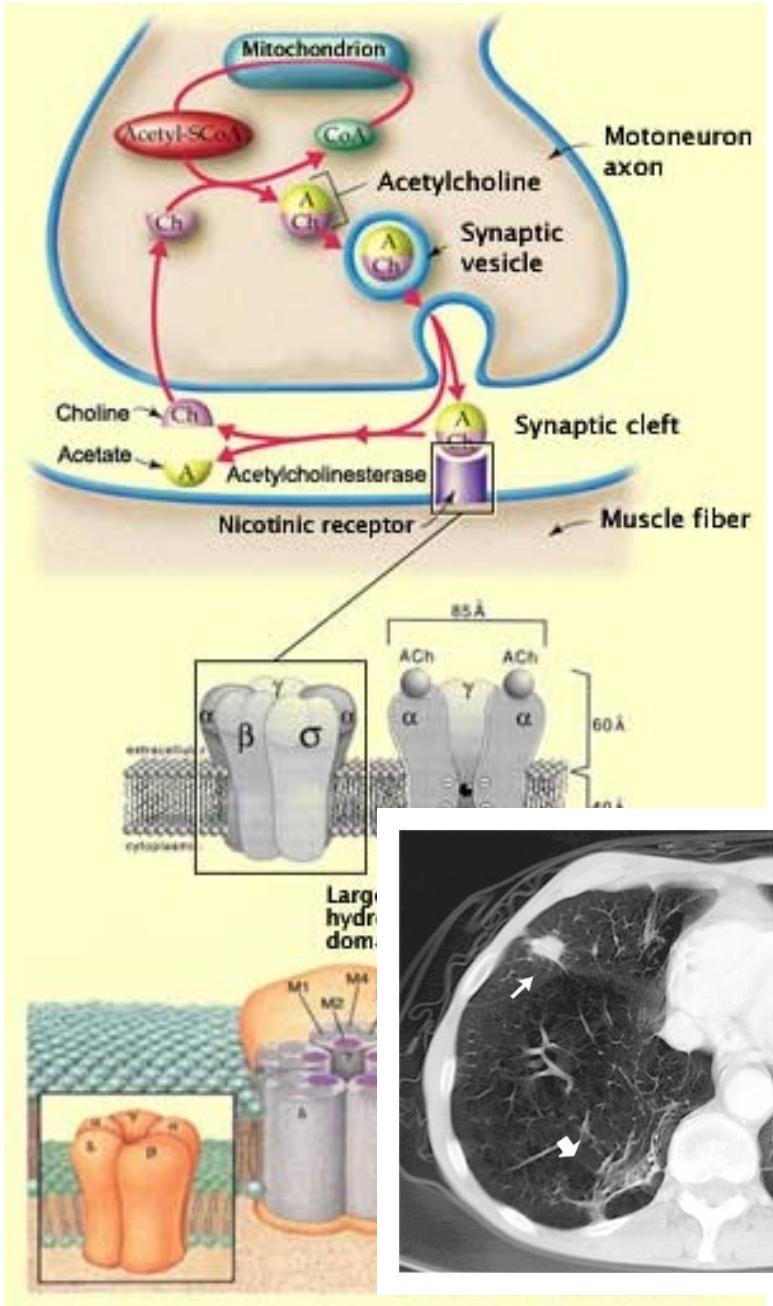
# Smoking, lung function and mortality



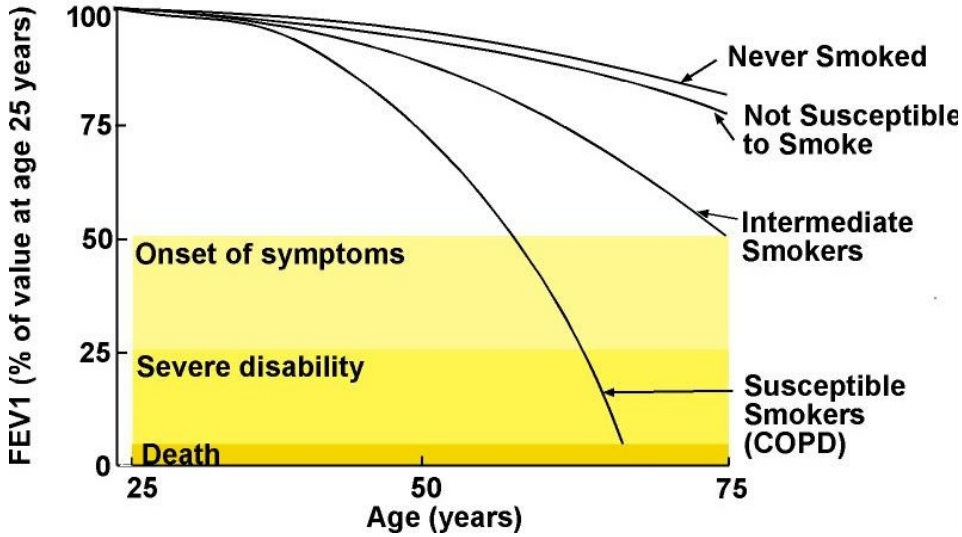
↓$FEV_1$ = “barometer” of a person’s tendency (or susceptibility) to exaggerated airway inflammation and adverse remodeling.

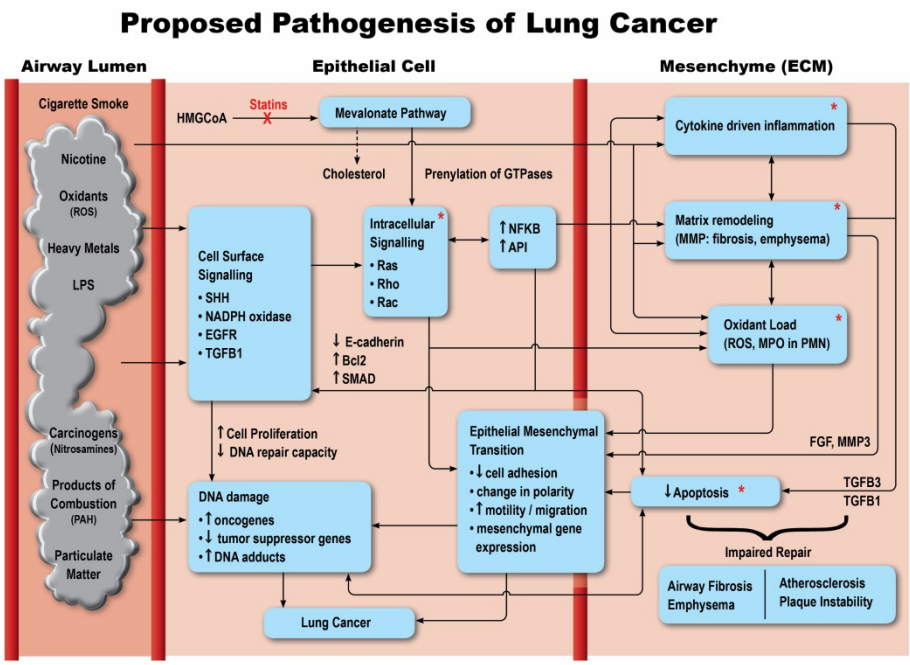
# Clinical implications of detecting COPD

- Increased cardiovascular and lung cancer risk and urgent need for aggressive smoking cessation
- Inclusion of COPD in lung cancer risk models
- Consideration of statin therapy in increased cardiovascular risk
- Initiation of usual inhaler therapy for symptom control


Mitochondrion
Acetyl-SCoA
CoA
Motoneuron axon
Acetylcholine
Synaptic vesicle
Choline
Acetate
Acetylcholinesterase
Synaptic cleft
Nicotinic receptor
Muscle fiber
85 Å
ACh
ACh
60 Å




FEV1 (% of value at age 25 years)
100
75
50
25
0
25
50
75
Age (years)
Never Smoked
Not Susceptible to Smoke
Intermediate Smokers
Onset of symptoms
Severe disability
Death
Susceptible Smokers (COPD)


Proposed Pathogenesis of Lung Cancer
Airway Lumen
Epithelial Cell
Mesenchyme (ECM)
Cigarette Smoke
Nicotine
Oxidants (ROS)
Heavy Metals
LPS
Carcinogens (Nitrosamines)
Products of Combustion (PAH)
Particulate Matter
HMGCoA
Statins
Mevalonate Pathway
Cholesterol
Prenylation of GTPases
Cell Surface Signalling
• SHH
• NADPH oxidase
• EGFR
• TGFB1
Intracellular Signalling
• Ras
• Rho
• Rac
↑ NFKB
↑ API
↓ E-cadherin
↑ Bcl2
↑ SMAD
↑ Cell Proliferation
↓ DNA repair capacity
DNA damage
• ↑ oncogenes
• ↓ tumor suppressor genes
• ↑ DNA adducts
Epithelial Mesenchymal Transition
• ↓ cell adhesion
• change in polarity
• ↑ motility / migration
• mesenchymal gene expression
Lung Cancer
Cytokine driven inflammation
Matrix remodeling (MMP: fibrosis, emphysema)
Oxidant Load (ROS, MPO in PMN)
FGF, MMP3
↓ Apoptosis
TGFB3
TGFB1
Impaired Repair
Airway Fibrosis Emphysema
Atherosclerosis Plaque Instability

# Smoking and its complications