

### Supplementary File 3. Sample calculations of decline rates for each study

#### Ahmadi-Abhari 2014

Mean FEV1 decline of people with baseline CRP ≤ 10mg/L who are never smokers

CRP	n	Annual change (multivariable adjusted)
≤ 1	3430	-17.16
1.1 – 3	3012	-18.53
3.1 – 10	1620	=17.15

$$\begin{aligned} \text{Mean FEV1 change} &= \frac{(3430 \times 17.16) + (3012 \times 18.53) + (1620 \times 17.15)}{(3430 + 3012 + 1620)} \\ &= -17.7 \text{ ml / year} \end{aligned}$$

Mean FVC decline of people with baseline CRP ≤ 10mg/L who are never smokers

CRP	n	Annual change (multivariable adjusted)
≤ 1	3430	-31.57
1.2 – 3	3012	-30.57
3.1 – 10	1620	-30.87

$$\begin{aligned} \text{Mean FEV1 change} &= \frac{(3430 \times 31.57) + (3012 \times 30.57) + (1620 \times 30.87)}{(3430 + 3012 + 1620)} \\ &= -31.1 \text{ ml / year} \end{aligned}$$

To calculate the standard deviations each group from the given 95% confidence intervals the following formula was used:

$$SD = \sqrt{n} \times \frac{\text{upper limit} - \text{lower limit}}{3.92}$$

E.g. The standard deviation of FEV1 decline in the CRP ≤ 1 category was calculated as follows:

$$\begin{aligned} SD &= \sqrt{3430} \times \frac{19.9 - 14.41}{3.92} \\ &= \sqrt{3430} \times 1.4 \\ &= 81.99 \end{aligned}$$

In this way standard deviations for all of the 3 included groups were calculated for both outcomes

CRP	n	Annual FEV1 change (multivariable adjusted)	Standard deviation
≤ 1	3430	-17.16	81.99
1.3 – 3	3012	-18.53	79.36
3.1 – 10	1620	-17.15	69.23

CRP	n	Annual FVC change (multivariable adjusted)	Standard deviation
≤ 1	3430	-31.57	122.99
1.4 – 3	3012	-30.57	119.42
3.1 – 10	1620	-30.87	104.00

The combined standard deviation was calculated using the following formula, available from the Cochrane handbook<sup>1</sup> (where only two groups are combined at a time).

$$\begin{aligned}
 \text{Combined } SD_{\text{Group } 1,2} &= \sqrt{\frac{(n_1 - 1) SD_1^2 + (n_2 - 1) SD_2^2 + \frac{n_1 n_2}{n_1 + n_2} (m_1^2 + m_2^2 - 2(m_1 m_2))}{(n_1 + n_2 - 1)}} \\
 &= \sqrt{\frac{(3430-1) 81.99^2 + (3012-1) 79.36^2 + \frac{3430 \times 3012}{3430+3012} (-17.16^2 + -18.53^2 - 2(-17.16 \times -18.53))}{(3430+3012-1)}} \\
 &= \frac{(23050972.78 + 18963306.91 + 1603.72(637.83 - 635.95))}{6441} \\
 &= 80.77
 \end{aligned}$$

Then the combined values of Group 1 and 2 are treated as one group as follows

$$SD_1 = 80.77, m_1 = -17.80, n_1 = 6442$$

Group 3 will be assigned to the values of  $SD_2, m_2$  and  $n_2$

$$\begin{aligned}
 \text{Combined } SD_{\text{Group } 1,2,3} &= \sqrt{\frac{(n_1 - 1) SD_1^2 + (n_2 - 1) SD_2^2 + \frac{n_1 n_2}{n_1 + n_2} (m_1^2 + m_2^2 - 2(m_1 m_2))}{(n_1 + n_2 - 1)}} \\
 &= \sqrt{\frac{(6442-1) 80.77^2 + (1620-1) 69.23^2 + \frac{6442 \times 1620}{6442+1620} (-17.80^2 + -17.15^2 - 2(-17.80 \times -17.15))}{(6442+1620-1)}} \\
 &= \frac{(42019750.07 + 7759531.71 + 1294.47(610.96 - 610.54))}{8061} \\
 &= 78.58
 \end{aligned}$$

The same calculations were carried out for the combined standard deviations of the FVC readings across the 3 CRP groups

### Bartholomew 1998

See Table 3 – Female never smokers

$$\text{FEV1 6 year change from baseline (all ages)} = -0.178$$

$$\text{Mean FEV1 annual decline} = \frac{0.178}{6}$$

$$= -30.5 \text{ ml/year}$$

$$\text{FVC 6 year change from baseline (all ages)} = -0.218$$

$$= \frac{0.218}{6}$$

$$= -36.3\text{ml/year}$$

See Table 3 – Male never smokers

$$\text{FEV1 6 year change from baseline (all ages)} = -0.261$$

$$\text{Mean FEV1 annual decline} = \frac{-0.261}{6}$$

$$= -43.5\text{ml/year}$$

$$\text{FVC 6 year change from baseline (all ages)} = -0.283$$

$$= \frac{-0.283}{6}$$

$$= 47.2\text{ml/year}$$

### Burchfiel 1995

Annual FEV1 decline (ml/year) extracted from Table 2

Male never smokers change from Exam 1-3 = -21.6ml/year

### Burrows 1986

Values of FEV1 decline extracted from Figure 3 for both males and females, where in males, height was assumed to be 1.75m and females 1.6m.

Using the formulae provided by the authors to predict  $\Delta\text{FEV1}$ :

$$\text{Males: } \Delta\text{FEV1} = 21.82 - 0.109\text{Age} \times \text{Height}^3$$

$$\text{Females: } \Delta\text{FEV1} = 19.79 - 0.205\text{Age} \times \text{Height}^2$$

The relevant values were then derived from the graph and then input into the formulae to produce the following values.

Male

Age	Height (cubed = 5.36)	FEV1 change
25	1.75	7.216*
30	1.75	4.295*
35	1.75	1.374*
40	1.75	-1.547
45	1.75	-4.468
50	1.75	-7.389
55	1.75	-10.309
60	1.75	-13.23
65	1.75	-16.151
70	1.75	-19.072

Mean decline rate: -10.309ml/yr (SD 6.31), where the \*figures were not used in the overall decline calculation.

Female

Age	Height (cubed = 5.36)	FEV1 change
25	1.6	6.67*
30	1.6	4.046*

35	1.6	1.422*
40	1.6	-1.202
45	1.6	-3.826
50	1.6	-6.45
55	1.6	-9.074
60	1.6	-11.698
65	1.6	-14.322
70	1.6	-16.946

Mean decline rate: -9.074 ml/yr (SD 5.668), where the \*figures were not used in the overall decline calculation.

### Griffith 2001

*Rates extracted from Table 4 (random effects model) for FEV1*

Females

Mean -0.047L/year (SE 0.0028)

Males

Mean = -0.047 + (-0.0053)  
= -0.0523L/year

SE =  $\sqrt{(0.0028)^2 + (0.0013)^2}$   
= 0.0031

*Table 5 for FVC*

Females

Mean -0.0656L/year (SE 0.0038)

Males

Mean = -0.0656 + (-0.0128)  
= -0.0784L/year

SE =  $\sqrt{(0.0038)^2 + (0.0019)^2}$   
= 0.0042

### Lange 1998

Combined mean (m) of all groups: =  $\frac{(m_1 \times n_1) + (m_2 \times n_2) + (m_3 \times n_3)}{n_1 + n_2 + n_3}$

Using values from Table 3 for non-asthmatic non-smoking women and men. The means, no. of subjects and standard deviations were combined for the 20-39 age group, 40-59 group and 60-79 group.

Females

Combined mean =  $\frac{(433 \times 5.0) + (1471 \times (-17.7)) + (809 \times (-31.7))}{2713}$   
= -18.25ml/year

Group 1 and 2 combined standard deviation

$$\begin{aligned}
 \text{Combined } SD_{\text{Group 1,2}} &= \sqrt{\frac{(n_1-1)SD_1^2 + (n_2-1)SD_2^2 + \frac{n_1n_2}{n_1+n_2}(m_1^2 + m_2^2 - 2m_1m_2)}{(n_1+n_2-1)}} \\
 &= \sqrt{\frac{(433-1)2.7^2 + (1471-1)1.4^2 + \frac{433 \times 1471}{433+1471}(5^2 + (-17.7)^2 - 2(5 \times -17.7))}{(433+1471-1)}} \\
 &= \sqrt{\frac{(432)2.7^2 + (1470)1.4^2 + \frac{636943}{1904}(5^2 + 313.29 - 2(-88.5))}{1903}} \\
 &= \sqrt{\frac{3149.28 + 2881.2 + 334.529(338.29 - 177)}{1903}} \\
 &= \sqrt{\frac{6030.48 + 334.529(338.29 - 177)}{1903}} \\
 &= \sqrt{\frac{6030.48 + 53956.18}{1903}} \\
 &= \sqrt{\frac{59986.66}{1903}} \\
 &= 5.6144 \text{ (combined SD of Group 1,2)}
 \end{aligned}$$

Group 1 and 2  $n_1$  1904  $m_1$  -12.538  $SD$  5.6144

Group 3  $n_2$  809  $m_2$  -31.7  $SD$  2.1

$$\begin{aligned}
 \text{Combined } SD_{\text{Group 1,2 and 3}} &= \sqrt{\frac{(n_1-1)SD_1^2 + (n_2-1)SD_2^2 + \frac{n_1n_2}{n_1+n_2}(m_1^2 + m_2^2 - 2m_1m_2)}{(n_1+n_2-1)}} \\
 &= \sqrt{\frac{(1904-1)5.614^2 + (809-1)2.1^2 + \frac{1904 \times 809}{1904+809}((-12.538)^2 + (-31.7)^2 - 2(397.45))}{(1904+809-1)}} \\
 &= \sqrt{\frac{(59976.84) + (3563.28) + 567.76(367.19)}{2712}} \\
 &= \sqrt{\frac{63540.12 + 208475.79}{2712}}
 \end{aligned}$$

Combined SD females = 10.015

Males

$$\begin{aligned}
 \text{Combined mean} &= \frac{(357 \times (-4.6)) + (780 \times (-24.2)) + (455 \times (-37.1))}{1592} \\
 &= -23.49 \text{ ml/year}
 \end{aligned}$$

$$\begin{aligned}
 \text{Combined } SD_{\text{Group 1,2}} &= \sqrt{\frac{(n_1-1)SD_1^2 + (n_2-1)SD_2^2 + \frac{n_1n_2}{n_1+n_2}(m_1^2 + m_2^2 - 2m_1m_2)}{(n_1+n_2-1)}} \\
 &= \sqrt{\frac{(357-1)4.2^2 + (780-1)2.6^2 + \frac{357 \times 780}{357+780}((-4.6)^2 + (-24.2)^2 - 2(-4.6 \times -24.2))}{(357+780-1)}}
 \end{aligned}$$

$$= \sqrt{\frac{(356) 4.2^2 + (779) 2.6^2 + 244.91(21.16 + 585.64 - 2(111.32))}{(1136)}}$$

$$= \sqrt{\frac{6279.84 + 5266.04 + 244.91(384.16)}{1136}}$$

$$= \sqrt{\frac{105630.51}{1136}}$$

$$= 9.643 \text{ (combined SD of Group 1,2)}$$

Group 1 and 2	$n_1$ 1137	$m_1$ -18.046	SD 9.643
Group 3	$n_2$ 455	$m_2$ -31.7	SD 3.7

$$\text{Combined SD}_{\text{Group1,2,3}} = \sqrt{\frac{(n_1-1) SD_1^2 + (n_2-1) SD_2^2 + \frac{n_1 n_2}{n_1 + n_2} (m_1^2 + m_2^2 - 2(m_1 m_2))}{(n_1 + n_2 - 1)}}$$

$$= \sqrt{\frac{(1137-1) 9.643^2 + (455-1) 3.7^2 + \frac{1137 \times 455}{1137 + 455} ((-18.046)^2 + (-31.7)^2 - 2(572.06))}{(1137 + 455 - 1)}}$$

$$= \sqrt{\frac{(105633.74) + (6215.26) + 324.96(186.43)}{1591}}$$

$$= \sqrt{\frac{111849 + 60582.29}{1591}}$$

Combined SD males = 10.41

### Liao 2015

FEV1 and FEV1/FVC decline were extracted from Table III (Linear Mixed Model)

Time dependent estimates (SE)

Years after baseline

FEV1 = 25.8 (0.6)

FEV1/FVC = -0.0029 (0.0001)

### Luoto 2018

Value for absolute FEV<sub>1</sub> decline for never smokers was extracted from Table 3 (Basic model adjusted for age, sex and smoking status)

FEV<sub>1</sub> absolute decline = -46.4

SD calculated from 95% CI using formula:

$$SD = \sqrt{n} \times \frac{\text{upper limit} - \text{lower limit}}{3.92}$$

$$SD = \sqrt{387} \times \frac{-41.7 - -51.2}{3.92}$$

$$SD = 47.7$$

Relative FEV<sub>1</sub> decline was extracted from Table 4 (basic model, non-smoker) = -2.23%/year

SD was calculated using the 95% CI as done for absolute decline values

$$SD = \sqrt{387} \times \frac{-2.00 - -2.46}{3.92}$$

$$SD = 2.3$$

Value for absolute FVC decline for never smokers was extracted from Table 5 (Basic model adjusted for age, sex and smoking status)

FVC absolute decline = -43.7

SD calculated from 95% CI using formula:

$$SD = \sqrt{n} \times \frac{\text{upper limit} - \text{lower limit}}{3.92}$$

$$SD = \sqrt{387} \times \frac{-37.0 - -50.4}{3.92}$$

$$SD = 67.2$$

Relative FVC decline was extracted from Table 6 (basic model, non-smoker) = -1.68%/year

SD was calculated using the 95% CI as done for absolute decline values

$$SD = \sqrt{387} \times \frac{-1.46 - -1.93}{3.92}$$

$$SD = 2.4$$

### **Maselko 2006**

PEFR decline extracted from Table 3 (never smokers)

Yearly decline

Men

Time (L/min/year)      -8.61 (SE 2.3) P<0.01

Women

Time (L/min/year)      -8.58 (SE 1.8) P<0.01

### **Pearson 1998**

Figures of FEV1 decline extracted from Table 1 using the following calculation:

$$\text{Yearly decline} = \frac{FEV_{\text{last visit}} - FEV_{\text{first visit}}}{\text{mean follow up time (years)}}$$

Men

$$\begin{aligned} \text{Yearly decline} &= \frac{3.8L - 4.3L}{11.5 \text{ years}} \\ &= 0.0435L/\text{year} \end{aligned}$$

Women

$$\begin{aligned} \text{Yearly decline} &= \frac{2.6L - 2.8L}{5.7 \text{ years}} \\ &= 0.0351L/\text{year} \end{aligned}$$

### **Pelkonen 2001**

Figures of 15 year FEV1 decline extracted from Table 1 (Never smokers n=200) = -46.4ml/year (p<0.001)

Figures of 30 year FEV1 decline extracted from Table 1 (Never smokers n=100) = -34.8/year (p<0.001)

### **Proctor 2006**

**PEFR decline calculated from Table 1 using the follow calculation, where EFR is expiratory flow rate.**

$$\text{Yearly decline} = \frac{EFR_{\text{Year 8}} - EFR_{\text{Year 0}}}{8 \text{ years}}$$

Men

$$\begin{aligned}\text{Yearly decline} &= \frac{298.36 - 390.34}{8 \text{ years}} \\ &= -11.50\text{L/min/year}\end{aligned}$$

Women

$$\begin{aligned}\text{Yearly decline} &= \frac{224.62 - 277.20}{8 \text{ years}} \\ &= -6.57\text{L/min/year}\end{aligned}$$

### **Sherman 1992**

FEV1 Slopes extracted from Table 5, specifically never-smokers who experienced no symptoms (mean [SD] ml/year).

Men 32.8 (29.5) ml/year

Women 27.5 (20.4) ml/year

### **Triebner 2017**

Exact figures of FEV1 and FVC decline for both men and women (never smokers) were obtained by contacting the author.

Graphically represented in Figure 4.

Women

FEV1 decline -22.4ml/year (SD 36.4)

FVC decline -14.1ml/year (SD 42.8)

### **Wang 2004**

5-year FEV1 slope extracted from Table 1, looking at healthy males.

Mean -56ml/year (SD 45)



## Xu 1995

Estimates of height-adjusted FEV1 for different ages in both male and females and for different birth cohorts were obtained from the graph in Figure 2.

Time related FEV1 changes were calculated as follows:

### Birth after 1946

$$\text{Men} = \frac{3800\text{ml} - 4100\text{ml}}{40 - 25} = \frac{-300\text{ml}}{40 - 25} = -20\text{ml/year}$$

$$\text{Women} = \frac{2800\text{ml} - 3000\text{ml}}{40 - 25} = \frac{-200\text{ml}}{40 - 25} = -13.3\text{ml/year}$$

### Cohort 1935 – 1946

$$\text{Men} = \frac{3400\text{ml} - 4100\text{ml}}{50 - 25} = \frac{-600\text{ml}}{25} = -24\text{ml/year}$$

$$\text{Women} = \frac{2500\text{ml} - 2930\text{ml}}{50 - 25} = \frac{-430\text{ml}}{25} = -17.2\text{ml/year}$$

### Cohort 1923 – 1934

$$\text{Men} = \frac{2780\text{ml} - 3640\text{ml}}{65 - 35} = \frac{-860\text{ml}}{30} = -28.7\text{ml/year}$$

$$\text{Women} = \frac{2050\text{ml} - 2700\text{ml}}{65 - 35} = \frac{-650\text{ml}}{30} = -21.7\text{ml/year}$$

### Cohort before 1923

$$\text{Men} = \frac{2700\text{ml} - 3300\text{ml}}{65 - 45} = \frac{-600\text{ml}}{20} = -30\text{ml/year}$$

$$\text{Women} = \frac{1970\text{ml} - 2450\text{ml}}{65 - 45} = \frac{-480\text{ml}}{20} = -24\text{ml/year}$$

## Reference

1. The Cochrane Collaboration; 2011 [updated March 2011. Available from: [https://handbook-5-1.cochrane.org/chapter\\_7/table\\_7\\_7\\_a\\_formulae\\_for\\_combining\\_groups.htm](https://handbook-5-1.cochrane.org/chapter_7/table_7_7_a_formulae_for_combining_groups.htm) accessed August 3rd 2018.