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

<table>
<thead>
<tr>
<th>CRP</th>
<th>n</th>
<th>Annual change (multivariable adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>3430</td>
<td>-17.16</td>
</tr>
<tr>
<td>1.1 – 3</td>
<td>3012</td>
<td>-18.53</td>
</tr>
<tr>
<td>3.1 – 10</td>
<td>1620</td>
<td>=17.15</td>
</tr>
</tbody>
</table>

Mean FEV1 change = \( \frac{(3430 \times 17.16) + (3012 \times 18.53) + (1620 \times 17.15)}{3430 + 3012 + 1620} \)

= - 17.7 ml / year

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

<table>
<thead>
<tr>
<th>CRP</th>
<th>n</th>
<th>Annual change (multivariable adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>3430</td>
<td>-31.57</td>
</tr>
<tr>
<td>1.2 – 3</td>
<td>3012</td>
<td>-30.57</td>
</tr>
<tr>
<td>3.1 – 10</td>
<td>1620</td>
<td>-30.87</td>
</tr>
</tbody>
</table>

Mean FEV1 change = \( \frac{(3430 \times 31.57) + (3012 \times 30.57) + (1620 \times 30.87)}{3430 + 3012 + 1620} \)

= - 31.1 ml / year

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

\[
SD = \sqrt{n} \times \frac{upper \ limit \ - \ lower \ limit}{3.92}
\]

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

\[
SD = \sqrt{3430} \times \frac{19.9 \ - \ 14.41}{3.92}
\]

= \( \sqrt{3430} \times 1.4 \)

= 81.99

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

<table>
<thead>
<tr>
<th>CRP</th>
<th>n</th>
<th>Annual FEV1 change (multivariable adjusted)</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>3430</td>
<td>-17.16</td>
<td>81.99</td>
</tr>
<tr>
<td>1.3 – 3</td>
<td>3012</td>
<td>-18.53</td>
<td>79.36</td>
</tr>
<tr>
<td>3.1 – 10</td>
<td>1620</td>
<td>-17.15</td>
<td>69.23</td>
</tr>
</tbody>
</table>
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\textsuperscript{1} (where only two groups are combined at a time).

\[
\text{Combined } SD_{\text{Group } 1,2} = \sqrt{\frac{(n_1 - 1) \cdot SD_1^2 + (n_2 - 1) \cdot SD_2^2 + \frac{n_1 n_2}{n_1 + n_2} \cdot (m_1^2 + m_2^2) - 2(m_1 m_2)}{(n_1 + n_2 - 1)}}
\]

\[
= \sqrt{\frac{(3430 - 1) \cdot 81.99^2 + (3012 - 1) \cdot 79.36^2 + \frac{3430 \times 3012}{3430 + 3012} \cdot (-17.16^2 + -18.53^2 - 2(-17.16 \times -18.53))}{(3430 + 3012 - 1)}}
\]

\[
= \sqrt{\frac{(23050972.78 + 18963306.91 + 1603.72(637.83 - 635.95))}{6441}}
\]

\[
= 80.77
\]

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 \(n_2\)

\[
\text{Combined } SD_{\text{Group } 1,2,3} = \sqrt{\frac{(n_1 - 1) \cdot SD_1^2 + (n_2 - 1) \cdot SD_2^2 + \frac{n_1 n_2}{n_1 + n_2} \cdot (m_1^2 + m_2^2) - 2(m_1 m_2)}{(n_1 + n_2 - 1)}}
\]

\[
= \sqrt{\frac{(6442 - 1) \cdot 80.77^2 + (1620 - 1) \cdot 69.23^2 + \frac{6442 \times 1620}{6442 + 1620} \cdot (-17.80^2 + -17.15^2 - 2(-17.80 \times -17.15))}{6442 + 1620 - 1}}
\]

\[
= \sqrt{\frac{(42019750.07 + 7759531.71 + 129447(610.96 - 610.54))}{8061}}
\]

\[
= 78.58
\]

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

FEV1 6 year change from baseline (all ages) –0.178

Mean FEV1 annual decline = 0.178/6 = -0.305 ml/year

FVC 6 year change from baseline (all ages) = -0.218
See Table 3 – Male never smokers

FEV1 6 year change from baseline (all ages) = -0.261
Mean FEV1 annual decline = \( \frac{-0.261}{6} \)
= - 36.3ml/year

FVC 6 year change from baseline (all ages) = -0.283
Mean FEV1 annual decline = \( \frac{-0.283}{6} \)
= -43.5ml/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 \( \Delta \text{FEV1} \):

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

Females: \( \Delta \text{FEV1} = 19.79 - 0.205 \times \text{Height}^3 \)

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

**Male**

<table>
<thead>
<tr>
<th>Age</th>
<th>Height (cubed = 5.36)</th>
<th>FEV1 change</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>1.75</td>
<td>7.216*</td>
</tr>
<tr>
<td>30</td>
<td>1.75</td>
<td>4.295*</td>
</tr>
<tr>
<td>35</td>
<td>1.75</td>
<td>1.374*</td>
</tr>
<tr>
<td>40</td>
<td>1.75</td>
<td>-1.547</td>
</tr>
<tr>
<td>45</td>
<td>1.75</td>
<td>-4.468</td>
</tr>
<tr>
<td>50</td>
<td>1.75</td>
<td>-7.389</td>
</tr>
<tr>
<td>55</td>
<td>1.75</td>
<td>-10.309</td>
</tr>
<tr>
<td>60</td>
<td>1.75</td>
<td>-13.23</td>
</tr>
<tr>
<td>65</td>
<td>1.75</td>
<td>-16.151</td>
</tr>
<tr>
<td>70</td>
<td>1.75</td>
<td>-19.072</td>
</tr>
</tbody>
</table>

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

**Female**

<table>
<thead>
<tr>
<th>Age</th>
<th>Height (cubed = 5.36)</th>
<th>FEV1 change</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>1.6</td>
<td>6.67*</td>
</tr>
<tr>
<td>30</td>
<td>1.6</td>
<td>4.046*</td>
</tr>
</tbody>
</table>
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: $m = \frac{(m_1 \times n_1) + (m_2 \times n_2) + (m_3 \times n_3)}{n_1 + n_2 + n_3}$

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

\[
\text{Combined SD}_{\text{Group1,2}} = \sqrt{\frac{(n_1-1)SD_1^2+(n_2-1)SD_2^2+\frac{n_1n_2}{n_1+n_2}(m_1^2+m_2^2)-2(m_1m_2)}{(n_1+n_2-1)}}
\]

\[
= \sqrt{\frac{(433-1)2.7^2+(1471-1)1.4^2+\frac{433\times4471}{433+1471}(52^2+(-17.7)^2)-2(5\times-17.7)}{433+1471-1}}
\]

\[
= \sqrt{\frac{(432)2.7^2+(1470)1.4^2+\frac{636943}{1904}(52^2+313.29)-2(-88.5))}{1903}}
\]

= \frac{3149.28+2881.12+334.529(338.29-177)}{1903}

= \frac{6030.48+334.529(338.29-177)}{1903}

= \frac{6030.48+5395.18}{1903}

= \frac{5998.66}{1903}

= 5.6144 \text{ (combined SD of Group 1,2)}

Group 1 and 2 \quad n_1 \quad 1904 \quad m_1 \quad -12.538 \quad SD \quad 5.6144

Group 3 \quad n_2 \quad 809 \quad m_2 \quad -31.7 \quad SD \quad 2.1

\[
\text{Combined SD}_{\text{Group1,2 and 3}} = \sqrt{\frac{(n_1-1)SD_1^2+(n_2-1)SD_2^2+\frac{n_1n_2}{n_1+n_2}(m_1^2+m_2^2)-2(m_1m_2)}{(n_1+n_2-1)}}
\]

\[
= \sqrt{\frac{(1904-1)5.614^2+(809-1)2.1^2+\frac{1904\times809}{1904+809}((-12.538)^2+(-31.7)^2)-2(397.45))}{1904+809-1}}
\]

\[
= \frac{\sqrt{(59976.84)+(3563.28)+567.76(367.19)}}{2712}
\]

= \frac{63540.12+208475.79}{2712}

= 10.015

Males

Combined mean = \frac{(357\times(-4.6)+(780\times(-24.2))+(455\times(-37.1))}{1592}

= -23.49ml/year

\[
\text{Combined SD}_{\text{Group1,2}} = \sqrt{\frac{(n_1-1)SD_1^2+(n_2-1)SD_2^2+\frac{n_1n_2}{n_1+n_2}(m_1^2+m_2^2)-2(m_1m_2)}{(n_1+n_2-1)}}
\]

\[
= \sqrt{\frac{(357-1)4.2^2+(780-1)2.6^2+\frac{357\times780}{357+780}((-4.6)^2+(-24.2)^2)-2(-4.6 \times-24.2)}{(357+780-1)}}
\]

= \text{Combined SD of Group 1,2 for Males}
\[
\sqrt{\left(356 \times 4.2^2 + (779 \times 2.6^2 + 244.91(21.16 + 585.64 - 2(111.32))) \right) / 1136}
\]

\[
\sqrt{\left(6279.84 + 5266.04 + 244.91(384.16) \right) / 1136}
\]

\[
\sqrt{105630.51 / 1136}
\]

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

Group 1 and 2

\[
\begin{aligned}
n_1 & = 1137 \\
m_1 & = -18.046 \\
SD & = 9.643
\end{aligned}
\]

Group 3

\[
\begin{aligned}
n_2 & = 455 \\
m_2 & = -31.7 \\
SD & = 3.7
\end{aligned}
\]

Combined SD

\[
\frac{(n_1 - 1) \times SD_1^2 + (n_2 - 1) \times SD_2^2 + n_1 n_2 (m_1^2 + m_2^2 - 2(m_1 m_2))}{(n_1 + n_2 - 1)}
\]

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

\[
= \sqrt{(105633.74 + 6215.26 + 324.96(186.43)) / 1591}
\]

\[
= \sqrt{111849 + 60582.29} / 1591
\]

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 FEV1 decline for never smokers was extracted from Table 3 (Basic model adjusted for age, sex and smoking status)

FEV1 absolute decline = -46.4

SD calculated from 95% CI using formula:

\[
SD = \sqrt{n} \times \frac{upper \ limit \ - \ lower \ limit}{3.92}
\]

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

SD = 47.7

Relative FEV1 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:
\[
SD = \sqrt{n} \times \frac{upper \ limit - lower \ limit}{3.92}
\]
\[
SD = \sqrt{387} \times \frac{-37.0 - -50.4}{3.92}
\]
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
\[
SD = \sqrt{n} \times \frac{-1.46 - -1.93}{3.92}
\]
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:

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

Men
Yearly decline = \[\frac{3.8L - 4.3L}{11.5\ years}\]
= 0.0435L/year

Women
Yearly decline = \[\frac{2.6L - 2.8L}{5.7\ years}\]
= 0.0351L/year
**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

\[
\text{Yearly decline} = \frac{298.36 - 390.34}{8 \text{ years}} = -11.50 \text{L/min/year}
\]

Women

\[
\text{Yearly decline} = \frac{224.62 - 277.20}{8 \text{ years}} = -6.57 \text{L/min/year}
\]

**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)
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**

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

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

**Cohort 1935 – 1946**

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

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

**Cohort 1923 – 1934**

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

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

**Cohort before 1923**

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

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

Reference