Appendix S1 – Details of Meta-Analysis

In the meta-analysis there are \( k \) chromosomes and for each chromosome a parameter \( \mu \) is estimated.

The value of \( \mu \) may vary between chromosomes so that the \( i \)th chromosome true value is \( \mu_i \), and this is estimated as \( \hat{\mu}_i \), with sampling error \( \text{var}(\hat{\mu}_i - \mu_i) = s_i^2 \). Let \( \Delta^2 = \text{var}(\mu_i - \mu) \) be the variance between chromosome parameter estimates, where \( \mu \) is now the mean value over chromosomes.

Each estimate \( \hat{\mu}_i \) is then an independent estimate of \( \mu \) with sampling error \( \Delta^2 + s_i^2 \). The best estimate of \( \mu \) is then \( \hat{\mu} = \sum_i w_i \hat{\mu}_i \), where \( w_i^* = \left( \Delta^2 + s_i^2 \right)^{-1} \), with \( s.e.(\hat{\mu}) = \left( \sum w_i^* \right)^{-\frac{1}{2}} \). This requires an estimate of \( \Delta^2 \) to use in the weighting. Following DerSimonian and Laird (1986), the statistic \( Q_w = \sum_i w_i (\hat{\mu}_i - \bar{\mu}_w)^2 \) is used, where \( \bar{\mu}_w = \sum_i w_i \hat{\mu}_i / \sum w_i \) and \( w_i = s_i^2 \) (note that \( \bar{\mu}_w \) is also an estimate of \( \mu \) but using sub-optimum weighting \( w_i \), not \( w_i^* \). Since \( E(Q_w) = (k-1) + m\Delta^2 \), where

\[
m = \frac{\sum_i w_i^2}{\sum_i w_i^*},
\]

equating the observed \( Q_w \) with its expectation provides an estimate of \( \Delta^2 \),

\[
\hat{\Delta}_w^2 = \max \left\{ 0, \frac{Q_w - (k-1)}{\left[ \sum_i w_i - \left( \frac{\sum_i w_i^2}{\sum_i w_i^*} \right) \right] \} \right\}, \tag{S1}
\]

The maximisation step in (S1) provides an estimate of \( \Delta^2 \) with lower mean square error should \( \hat{\Delta}_w^2 < 0 \). This value is then used to calculate \( w_i^* \), \( \hat{\mu} \) and \( s.e.(\hat{\mu}) \) as described above.