**Supplementary Table 1.** Qualitative assessment of the included case-control studies using Newcastle-Ottawa scale.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **References** | **Selection** | | | | **Comparability** | **Exposure** | | | **Total**  **quality score**  **(8/8)** |
| **Adequate case definition** | **Representative-ness of the cases** | **Selection of controls** | **Definition of controls** | **Comparability of case-controls (Age)** | **Ascertainment of exposure** | **Same ascertainment for cases and controls** | **Non-response rate** |
| H. Wengreen et al. | ★ | ★ | ★ | ★ | ★ | 0 | ★ | ★ | 7/8 |
| J. Aerssens et al. | ★ | ★ | ★ | ★ | ★ | 0 | ★ | 0 | 6/8 |
| Ercan Dincel et al. | ★ | 0 | 0 | ★ | ★ | 0 | ★ | 0 | 4/8 |
| Stiina Valimakia et al. | ★ | 0 | 0 | ★ | ★ | 0 | ★ | ★ | 5/8 |
| Diane Feskanich et al. | ★ | ★ | ★ | ★ | ★ | ★ | ★ | 0 | 7/8 |
| A.C. Ramalho et al. | ★ | ★ | ★ | ★ | ★ | 0 | ★ | 0 | 6/8 |

★: Indication that the study has met the criteria for a domain, 0: Indication that the criteria were not met

**Supplementary Table 2.** Meta-regression results

**BB vs bb (Random effect model)**

Random effects (MM), Z-Distribution, Log odds ratio

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Covariate | Coefficient | Standard error | 95% lower | 95% upper | Z-value | 2-sided p-value |
| Intercept | 0.9204 | 0.5209 | -0.1005 | 1.9413 | 1.77 | 0.0772 |
| Age : 75 over | -0.746 | 0.5682 | -1.8595 | 0.3676 | -1.31 | 0.1892 |
| **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 1.72, df = 1, p = 0.1892  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0912, Tau = 0.3020, I2 = 39.51%, Q = 6.61, df = 4, p = 0.1578  **Total between-study variance (intercept only)**  Tau2 = 0.1072, Tau = 0.3275, I2 = 43.25%, Q = 8.81, df = 5, p = 0.1168 | | | | | | |
|  | | | |  | Analysis of variance |  |
|  | | | | Q | df | p |
| Model | | | | 1.723835 | 1 | 0.189200139 |
| Residual | | | | 3.568875 | 4 | 0.467483359 |
| Total | | | | 5.29271 | 5 | 0.381211422 |
| Ratio of true (between studies) to total variance  **Statistics for Model 1**  **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 1.72, df = 1, p = 0.1892  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0912, Tau = 0.3020, I2 = 39.51%, Q = 6.61, df = 4, p = 0.1578  **Comparison of Model 1 with the null model**  **Total between-study variance (intercept only)**  Tau2 = 0.1072, Tau = 0.3275, I2 = 43.25%, Q = 8.81, df = 5, p = 0.1168  **Proportion of total between-study variance explained by Model 1**  R2 analog = 0.15 | | | |  |  |  |

**Supplementary Table 2.** Continued

**BB vs bb (Fixed effect model)**

Fixed effect, Z-Distribution, Log odds ratio

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Covariate | Coefficient | Standard error | 95% lower | 95% upper | Z-value | 2-sided p-value |
| Intercept | 0.897 | 0.4408 | 0.0331 | 1.761 | 2.03 | 0.0419 |
| Age : 75 over | -0.6784 | 0.4575 | -1.5752 | 0.2183 | -1.48 | 0.1381 |
|  |  | Analysis of variance |  |  |  |  |
|  | Q | df | p |  |  |  |
| Model | 2.198651 | 1 | 0.138132 |  |  |  |
| Residual | 6.612651 | 4 | 0.157829 |  |  |  |
| Total | 8.811302 | 5 | 0.116832 |  |  |  |
|  |  |  |  | Analysis of variance | | |
|  |  |  |  | Q | df | p |
| Model |  |  |  | 2.198651 | 1 | 0.138131553 |
| Residual |  |  |  | 6.612651 | 4 | 0.157829409 |
| Total |  |  |  | 8.811302 | 5 | 0.116831548 |
| Ratio of true (between studies) to total variance  **Statistics for Model 1**  **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 2.20, df = 1, p = 0.1381  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0000, Tau = 0.0000, I2 = 39.51%, Q = 6.61, df = 4, p = 0.1578  **Comparison of Model 1 with the null model**  **Total between-study variance (intercept only)**  Tau2 = 0.0000, Tau = 0.0000, I2 = 43.25%, Q = 8.81, df = 5, p = 0.1168  **Proportion of total between-study variance explained by Model 1**  This is not defined under the fixed effect model | | | |  |  |  |

**Supplementary Table 2.** Continued

**B vs b (Random effect model)**

Random effects (MM), Z-Distribution, Log odds ratio

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Covariate | Coefficient | Standard error | 95% lower | 95% upper | Z-value | 2-sided p-value |
| Intercept | 0.361 | 0.2587 | -0.1459 | 0.868 | 1.4 | 0.1628 |
| Age : 75 over | -0.2554 | 0.2884 | -0.8207 | 0.3099 | -0.89 | 0.3759 |
| **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 0.78, df = 1, p = 0.3759  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0346, Tau = 0.1861, I2 = 51.64%, Q = 8.27, df = 4, p = 0.0821  **Total between-study variance (intercept only)**  Tau2 = 0.0299, Tau = 0.1729, I2 = 47.11%, Q = 9.45, df = 5, p = 0.0923 | | | | | | |
|  | | | |  | Analysis of variance |  |
|  | | | | Q | df | p |
| Model | | | | 1.723835 | 1 | 0.189200139 |
| Residual | | | | 3.568875 | 4 | 0.467483359 |
| Total | | | | 5.29271 | 5 | 0.381211422 |
| Ratio of true (between studies) to total variance  **Statistics for Model 1**  **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 1.72, df = 1, p = 0.1892  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0912, Tau = 0.3020, I2 = 39.51%, Q = 6.61, df = 4, p = 0.1578  **Comparison of Model 1 with the null model**  **Total between-study variance (intercept only)**  Tau2 = 0.1072, Tau = 0.3275, I2 = 43.25%, Q = 8.81, df = 5, p = 0.1168  **Proportion of total between-study variance explained by Model 1**  R2 analog = 0.15 | | | |  |  |  |

**Supplementary Table 2.** Continued

**B vs b (Fixed effect model)**

Fixed effect, Z-Distribution, Log odds ratio

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Covariate | Coefficient | Standard error | 95% lower | 95% upper | Z-value | 2-sided p-value |
| Intercept | 0.3687 | 0.2117 | -0.0461 | 0.7836 | 1.74 | 0.0815 |
| Age : 75 over | -0.2393 | 0.2202 | -0.6708 | 0.1922 | -1.09 | 0.2771 |
|  |  | Analysis of variance |  |  |  |  |
|  | Q | df | p |  |  |  |
| Model | 1.181354 | 1 | 0.277081 |  |  |  |
| Residual | 8.271975 | 4 | 0.082108 |  |  |  |
| Total | 9.453329 | 5 | 0.092292 |  |  |  |
|  |  |  |  | Analysis of variance | | |
|  |  |  |  | Q | df | p |
| Model |  |  |  | 2.198651 | 1 | 0.138131553 |
| Residual |  |  |  | 6.612651 | 4 | 0.157829409 |
| Total |  |  |  | 8.811302 | 5 | 0.116831548 |
| Ratio of true (between studies) to total variance  **Statistics for Model 1**  **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 2.20, df = 1, p = 0.1381  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0000, Tau = 0.0000, I2 = 39.51%, Q = 6.61, df = 4, p = 0.1578  **Comparison of Model 1 with the null model**  **Total between-study variance (intercept only)**  Tau2 = 0.0000, Tau = 0.0000, I2 = 43.25%, Q = 8.81, df = 5, p = 0.1168  **Proportion of total between-study variance explained by Model 1**  This is not defined under the fixed effect model | | | |  |  |  |

**Supplementary Table 2.** Continued

**BB + Bb vs bb (Random effect model)**

Random effects (MM), Z-Distribution, Log odds ratio

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Covariate | Coefficient | Standard error | 95% lower | 95% upper | Z-value | 2-sided p-value |
| Intercept | 0.1696 | 0.4111 | -0.6361 | 0.9753 | 0.41 | 0.6799 |
| Age : 75 over | -0.0272 | 0.4636 | -0.9359 | 0.8814 | -0.06 | 0.9531 |
| **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 0.00, df = 1, p = 0.9531  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.1139, Tau = 0.3375, I2 = 61.99%, Q = 10.52, df = 4, p = 0.0325  **Total between-study variance (intercept only)**  Tau2 = 0.0801, Tau = 0.2830, I2 = 52.49%, Q = 10.52, df = 5, p = 0.0617 | | | | | | |
|  | | | |  | Analysis of variance |  |
|  | | | | Q | df | p |
| Model | | | | 1.723835 | 1 | 0.189200139 |
| Residual | | | | 3.568875 | 4 | 0.467483359 |
| Total | | | | 5.29271 | 5 | 0.381211422 |
| Ratio of true (between studies) to total variance  **Statistics for Model 1**  **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 1.72, df = 1, p = 0.1892  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0912, Tau = 0.3020, I2 = 39.51%, Q = 6.61, df = 4, p = 0.1578  **Comparison of Model 1 with the null model**  **Total between-study variance (intercept only)**  Tau2 = 0.1072, Tau = 0.3275, I2 = 43.25%, Q = 8.81, df = 5, p = 0.1168  **Proportion of total between-study variance explained by Model 1**  R2 analog = 0.15 | | | |  |  |  |

**Supplementary Table 2.** Continued

**BB + Bb vs bb (Fixed effect model)**

Fixed effect, Z-Distribution, Log odds ratio

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Covariate | Coefficient | Standard error | 95% lower | 95% upper | Z-value | 2-sided p-value |
| Intercept | 0.1797 | 0.3143 | -0.4363 | 0.7958 | 0.57 | 0.5675 |
| Age : 75 over | 0.0086 | 0.3264 | -0.6312 | 0.6483 | 0.03 | 0.9791 |
|  |  | Analysis of variance |  |  |  |  |
|  | Q | df | p |  |  |  |
| Model | 0.000686 | 1 | 0.979103 |  |  |  |
| Residual | 10.52392 | 4 | 0.032469 |  |  |  |
| Total | 10.5246 | 5 | 0.061664 |  |  |  |
|  |  |  |  | Analysis of variance | | |
|  |  |  |  | Q | df | p |
| Model |  |  |  | 2.198651 | 1 | 0.138131553 |
| Residual |  |  |  | 6.612651 | 4 | 0.157829409 |
| Total |  |  |  | 8.811302 | 5 | 0.116831548 |
| Ratio of true (between studies) to total variance  **Statistics for Model 1**  **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 2.20, df = 1, p = 0.1381  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0000, Tau = 0.0000, I2 = 39.51%, Q = 6.61, df = 4, p = 0.1578  **Comparison of Model 1 with the null model**  **Total between-study variance (intercept only)**  Tau2 = 0.0000, Tau = 0.0000, I2 = 43.25%, Q = 8.81, df = 5, p = 0.1168  **Proportion of total between-study variance explained by Model 1**  This is not defined under the fixed effect model | | | |  |  |  |

**Supplementary Table 2.** Continued

**Bb vs BB + bb (Random effect model)**

Random effects (MM), Z-Distribution, Log odds ratio

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Covariate | Coefficient | Standard error | 95% lower | 95% upper | Z-value | 2-sided p-value |
| Intercept | -0.406 | 0.3143 | -1.022 | 0.2101 | -1.29 | 0.1965 |
| Age : 75 over | 0.4813 | 0.3345 | -0.1744 | 1.137 | 1.44 | 0.1503 |
| **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 2.07, df = 1, p = 0.1503  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0122, Tau = 0.1106, I2 = 16.07%, Q = 4.77, df = 4, p = 0.3122  **Total between-study variance (intercept only)**  Tau2 = 0.0316, Tau = 0.1777, I2 = 32.26%, Q = 7.38, df = 5, p = 0.1938 | | | | | | |
|  | | | |  | Analysis of variance |  |
|  | | | | Q | df | p |
| Model | | | | 1.723835 | 1 | 0.189200139 |
| Residual | | | | 3.568875 | 4 | 0.467483359 |
| Total | | | | 5.29271 | 5 | 0.381211422 |
| Ratio of true (between studies) to total variance  **Statistics for Model 1**  **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 1.72, df = 1, p = 0.1892  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0912, Tau = 0.3020, I2 = 39.51%, Q = 6.61, df = 4, p = 0.1578  **Comparison of Model 1 with the null model**  **Total between-study variance (intercept only)**  Tau2 = 0.1072, Tau = 0.3275, I2 = 43.25%, Q = 8.81, df = 5, p = 0.1168  **Proportion of total between-study variance explained by Model 1**  R2 analog = 0.15 | | | |  |  |  |

**Supplementary Table 2.** Continued

**Bb vs BB + bb (Fixed effect model)**

Fixed effect, Z-Distribution, Log odds ratio

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Covariate | Coefficient | Standard error | 95% lower | 95% upper | Z-value | 2-sided p-value |
| Intercept | -0.4065 | 0.3012 | -0.9968 | 0.1839 | -1.35 | 0.1772 |
| Age : 75 over | 0.5059 | 0.3128 | -0.1073 | 1.119 | 1.62 | 0.1059 |
|  |  | Analysis of variance |  |  |  |  |
|  | Q | df | p |  |  |  |
| Model | 2.61477 | 1 | 0.105873 |  |  |  |
| Residual | 4.766023 | 4 | 0.312158 |  |  |  |
| Total | 7.380793 | 5 | 0.193825 |  |  |  |
|  |  |  |  | Analysis of variance | | |
|  |  |  |  | Q | df | p |
| Model |  |  |  | 2.198651 | 1 | 0.138131553 |
| Residual |  |  |  | 6.612651 | 4 | 0.157829409 |
| Total |  |  |  | 8.811302 | 5 | 0.116831548 |
| Ratio of true (between studies) to total variance  **Statistics for Model 1**  **Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero**  Q = 2.20, df = 1, p = 0.1381  **Goodness of fit: Test that unexplained variance is zero**  Tau2 = 0.0000, Tau = 0.0000, I2 = 39.51%, Q = 6.61, df = 4, p = 0.1578  **Comparison of Model 1 with the null model**  **Total between-study variance (intercept only)**  Tau2 = 0.0000, Tau = 0.0000, I2 = 43.25%, Q = 8.81, df = 5, p = 0.1168  **Proportion of total between-study variance explained by Model 1**  This is not defined under the fixed effect model | | | |  |  |  |