**Table 1: Frequency tables to summarise data source, outcome and exposure definitions for 46 studies. \*Studies may have multiple outcomes therefore column percentages will not sum to 1. \*\*Based on whether clear description given in methods.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Case Control N (%) | Cohort N (%) | Total N (%) |
| **Data Source** | | | |
| Clinical Trial | 0 (0) | 1 (4) | 1 (2) |
| Diabetes Registry | 2 (9) | 4 (17) | 6 (13) |
| Insurance database | 2 (9) | 9 (38) | 11 (24) |
| CPRD (or GPRD) | 8 (36) | 6 (25) | 14 (30) |
| Other primary/secondary care database | 1 (5) | 4 (17) | 5 (11) |
| Recruited from Hospital/Clinic | 9 (41) | 0 (0) | 9 (20) |
| **Outcome definition\*** | | | |
| All cancer | 5 (23) | 16 (67) | 21 (46) |
| Colorectal/Bowel | 2 (9) | 12 (50) | 14 (3) |
| HCC/ICC | 5 (23) | 2 (8) | 7 (15) |
| Ovarian/Endometrial | 2 (9) | 1 (4) | 3 (7) |
| Bladder | 0 (0) | 3 (13) | 3 (7) |
| Breast | 3 (14) | 10 (42) | 13 (28) |
| Oesophagus | 0 (0) | 4 (17) | 4 (9) |
| Kidney | 0 (0) | 2 (8) | 2 (4) |
| Liver | 0 (0) | 5 (21) | 5 (11) |
| Leukaemia | 0 (0) | 1 (4.2) | 1 (2) |
| Lung | 4 (18) | 8 (33) | 12 (26) |
| Melanoma | 0 (0) | 2 (8) | 2 (4) |
| Pancreas | 3 (14) | 10 (42) | 13 (28) |
| Prostate | 3 (14) | 8 (33) | 11 (24) |
| Stomach | 1 (5) | 4 (17) | 5 (11) |
| **Definition of exposure to metformin for primary estimate** | | | |
| Any Exposure | 14 (64) | 8 (33) | 22 (48) |
| Any exposure but minimum time/number of prescriptions needed | 1 (5) | 2 (8) | 3 (7) |
| Total Exposure (Number of prescriptions/time on metformin) | 6 (27) | 4 (17) | 10 (22) |
| Monotherapy | 1 (5) | 8 (33) | 9 (20) |
| Randomisation | 0 (0) | 1 (4) | 1 (2) |
| Combination therapy with sulfonylurea | 0 (0) | 1 (4) | 1 (2) |
| **Timing of Exposure measurement** | | | |
| Current use (at time of cancer/matched date) | 3 (14) | 0 (0) | 3 (7) |
| Time updated (current/ever/cumulative) | 0 (0) | 8 (33) | 8 (17) |
| Fixed from start of follow up, with exposure occurring in a baseline period or follow up starting from first exposure (Intention to treat (ITT)). | 0 (0) | 8 (33) | 8 (17) |
| Single summary measure of exposure over entire follow up. | 19 (86) | 8 (33) | 27 (59) |
| **Comparator group for primary estimate** | | | |
| Less exposure (i.e. continuous exposure variable) | 0 (0) | 2 (8) | 2 (4) |
| Diet Only | 0 (0) | 1 (4) | 1 (2) |
| Rosiglitazone | 0 (0) | 1 (4) | 1 (2) |
| Sulfonylurea | 2 (9) | 9 (38) | 11 (24) |
| Any other OAD | 3 (14) | 4 (17) | 7 (15) |
| No metformin (combination of diet and other OADs) | 17 (77) | 7 (29) | 24 (52) |
| **\*\* New users of Oral Antidiabetic Drugs (OADs)** | | | |
| Yes | 3 (14) | 7 (29) | 10 (22) |
| No | 17 (77) | 12 (50) | 29 (63) |
| Unsure | 2 (9) | 5 (21) | 7 (15) |

**Table 2: Adjustment method for key time dependent confounders affected by prior treatment: Case control Studies.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Name** | **HbA1c** | | | **BMI** | | | **Other Diabetic Medication** | | |
| Adjusted for value prior to first exposure | Adjusted for value between exposure and index date a | Adjusted for value at index date a | Adjusted for value prior to first exposure | Adjusted for value between exposure and index date a | Adjusted for value at index datea | Adjusted for value prior to first exposure | Adjusted for value between exposure and index date a | Adjusted for value at index date a |
| **Azoulay et al. (2011) [24]** |  | ✔ |  |  | ✔ |  |  | ✔ |  |
| **Becker et al. (2013) [25]** |  |  |  |  | ✔ |  |  | ✔ |  |
| **Bodmer et al. (2011) [29]** |  | ✔ |  |  | ✔ |  |  | ✔ |  |
| **Bodmer et al. (2010) [30]** |  | ✔ |  |  | ✔ |  |  | ✔ |  |
| **Bodmer et al. (2012) (Lung) [26]** |  |  |  |  | ✔ |  |  | ✔ |  |
| **Bodmer et al. (2012) (Pancreatic) [28]** |  |  |  |  | ✔ |  |  | ✔ |  |
| **Bodmer et al. (2012) (Colorectal) [27]** |  |  |  |  | ✔ |  |  | ✔ |  |
| **Bosco et al. (2011) [31]** |  |  |  |  |  |  |  |  |  |
| **Chaiteerakij et al. (2013) [32]** |  |  |  |  |  |  |  |  |  |
| **Dabrowski et al. (2013) [34]** |  |  |  |  |  |  |  | ✔ |  |
| **Donadon et al. (2010) [35]** |  |  | ✔ |  |  | ✔ |  |  |  |
| **Li et al. (2009) [37]** |  |  |  |  | ✔ |  |  | ✔ |  |
| **Evans et al. (2005) [7]** |  |  |  |  | ✔ |  |  |  |  |
| **Hassan et al. (2012) [38]** |  |  |  |  |  |  |  |  |  |
| **Margel et al. (2013) [39]** |  |  |  |  |  |  |  | ✔ |  |
| **Mazzone et al. (2012) [40]** |  | ✔ |  |  | ✔ |  |  |  |  |
| **Monami et al. (2009) [42]** |  |  | ✔ |  |  | ✔ |  | ✔ |  |
| **Monami et al. (2011) [41]** |  |  |  | ✔ |  |  |  | ✔ |  |
| **Smiechowski et al. (2013) [43]** | ✔b | ✔ |  | ✔b | ✔ |  | ✔b | ✔ |  |
| **Wang et al. (2013) [44]** |  |  |  |  |  |  |  |  |  |
| **Chen et al. (2013) [33]** |  |  |  |  |  |  |  | ✔ |  |
| **Donadon et al. (2010) - 2 [36]** |  |  |  |  |  | ✔ |  |  |  |

a Index date = time of cancer diagnosis/matched date for control.

b Sensitivity analysis assessed whether there was a difference between adjusting for covariates measured before exposure or anytime between 1 year prior to exposure and index date.

**Table 3: Adjustment method for key time dependent confounders affected by prior treatment: Cohort Studies**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study name** | **HbA1c** | | | **BMI** | | | **Other Diabetic Medication** | | |
| Adjusted for value at cohort entry (at time of or prior to first exposure) | Adjusted as a time updated variable | Measured as an average of values/ at any point after exposure | Adjusted for value at cohort entry (at time of or prior to first exposure) | Adjusted as a time updated variable | Measured as an average of values/ at any point after exposure | Adjusted for value at cohort entry (at time of or prior to first exposure) | Adjusted as a time updated variable | Measured as an average of values/ at any point after exposure |
| **Currie et al. (2009) [3]** |  |  |  |  |  |  |  |  |  |
| **Currie et al. (2013) [47]** | ✔ |  |  | ✔ |  |  |  |  |  |
| **Geraldine et al. (2012) [49]** | ✔ |  |  | ✔a |  |  |  |  |  |
| **Home et al. (2010) [51]** |  |  |  |  |  |  |  |  |  |
| **Hsieh et al. (2012) [8]** |  |  |  |  |  |  |  |  |  |
| **Lai et al. (2012) (HCC) [52]** |  |  |  |  |  |  |  |  |  |
| **Lai et al. (2012) (LUNG) [53]** |  |  |  |  |  |  |  |  |  |
| **Lee et al. (2011) [54]** |  |  |  |  |  |  |  |  | ✔ |
| **Libby et al. (2009) [5]** |  |  | ✔ |  |  | ✔ | ✔b |  |  |
| **Qiu et al. (2013) [59]** |  |  |  |  |  |  |  |  |  |
| **Redaniel et al. (2012) [60]** |  |  | ✔ | ✔ |  |  |  |  |  |
| **Ruiter et al. (2012) [9]** |  |  |  |  |  |  |  |  |  |
| **Tsilidis et al. (2014) [61]** |  |  |  | ✔ |  |  |  |  |  |
| **Yang et al. (2011) [63]** | ✔ |  |  | ✔ |  |  |  |  | ✔ |
| **Buchs & Silverman (2011) [45]** |  |  |  |  |  |  |  |  | ✔ |
| **Oliviera et al. (2008) [58]** |  |  |  |  |  |  |  |  |  |
| **Hense et al. (2011) [50]** |  |  |  | ✔ |  |  | ✔ |  |  |
| **Chiu et al. (2013) [46]** |  |  |  |  |  |  |  |  |  |
| **Ferrara et al. (2011) [48]** | ✔ |  |  |  |  |  |  | ✔ |  |
| **Lehman et al. (2012) [55]** |  |  | ✔ |  |  |  |  |  |  |
| **Morden et al. (2011) [56]** | ✔c |  |  | ✔\* |  |  |  |  |  |
| **Neumann et al. (2011) [57]** |  |  |  |  |  |  |  | ✔ |  |
| **Van Staa et al. (2012) [62]** |  |  |  | ✔ |  |  |  | ✔ |  |
| **Morgan et al. (2012) [64]** | ✔ |  |  | ✔ |  |  |  |  |  |

aweight used instead of BMI

bmeasured within 3 months/1 year of cohort entry (either side of first exposure)

cdiabetes complications used as proxy measures for severity

Grey boxes indicate that adjustment not necessary. For HbA1c and BMI, this was due to randomised treatment allocation. For use of other OADs, adjustment was not necessary if the study looked at incident users of diabetes medications and censored at change in medication.

**Table 4: Parameter estimates from meta regression models after backwards stepwise selection**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | All cancer | | Colorectal/Bowel | | | Lung | | Breast | | | Pancreatic | |
|  |  | **\*Estimate 95% CI for effect on log risk ratio** | **P value** | | **\*Estimate 95% CI for effect on log risk ratio** | **P value** | **\*Estimate 95% CI for effect on log risk ratio** | **P value** | | **\*Estimate 95% CI for effect on log risk ratio** | **P value** | **\*Estimate 95% CI for effect on log risk ratio** | **P value** |
| Comparator Group | No metformin | 0 (ref) |  | |  |  | 0 (ref) |  | | 0 (ref) |  | 0 (ref) |  |
|  | Diet only | -1.19 (-2.43 , 0.05) | 0.075 | |  |  |  |  | |  |  |  |  |
|  | Less Metformin | 0.18 (-0.27 , 0.63) |  |  | 0.05 (-0.34 , 0.44) | 0.107 | | -0.37 (-0.8 , 0.07) | 0.057 | -2.32 (-5.12 , 0.49) | 0.136 |
|  | Other OAD | 0.24 (-0.06 , 0.54) |  |  | -0.15 (-0.31 , 0.02) | -0.22 (-0.41 , -0.03) | -0.44 (-2.46 , 1.57) |
| Bias from Exposure Definition | Low Risk |  |  | |  |  | 0 (ref) |  | |  |  |  |  |
|  | High Risk |  |  | |  |  | -0.44 (-0.72 , -0.17) | 0.007 | |  |  |  |  |
| Bias from Outcome Definition | Low Risk |  |  | |  |  | 0 (ref) |  | |  |  | 0 (ref) |  |
|  | High Risk |  |  | |  |  | -0.17 (-0.48 , 0.14) | 0.234 | |  |  | 0.99 (-0.85 , 2.83) | 0.251 |
| Immortal Time bias | Low Risk |  |  | | 0 (ref) |  |  |  | |  |  |  |  |
|  | High Risk |  |  | | -0.39 (-0.85 , 0.08) | 0.097 |  |  | |  |  |  |  |
| Bias from Time dependent confounding | Low Risk |  |  | |  |  |  |  | | 0 (ref) |  |  |  |
|  | High Risk |  |  | |  |  |  |  | | 0.22 (0.01 , 0.44) | 0.043 |  |  |
| Bias from Baseline confounding | Low Risk |  |  | |  |  |  |  | | 0 (ref) |  |  |  |
|  | High Risk |  |  | |  |  |  |  | | -0.22 (-0.45 , 0.02) | 0.063 |  |  |
| Incident users | Yes |  |  | |  |  | 0 (ref) |  | | 0 (ref) |  | 0 (ref) |  |
|  | No |  |  | |  |  | 0.18 (-0.14 , 0.5) | 0.218 | | -0.25 (-0.49 , -0.02) | 0.039 | -1.12 (-3.54 , 1.3) | 0.317 |
| Constant |  | -0.28 (-0.51 , -0.05) | 0.019 | | -0.06 (-0.22 , 0.11) | 0.483 | 0.01 (-0.16 , 0.18) | 0.892 | | 0.17 (-0.08 , 0.41) | 0.151 | 0.11 (-2.19 , 2.4) | 0.916 |
|  |  |  |  | |  |  |  |  | |  |  |  |  |
| 1I squared |  | 88.60% |  | | 75.00% |  | 0% |  | | 1.9% |  | 75.4% |  |
| 2Adjusted R2 |  | 6.90% |  | | 30.40% |  | 100% |  | | 100% |  | 65.2% |  |
| 3Tau2 |  | 0.059 |  | | 0.036 |  | 0 |  | | 0 |  | 0.265 |  |

\*Estimate represents the expected change in the log risk ratio (either HR or OR depending on analysis method) for the effect of metformin on cancer, for each study level predictor. For example, a study of metformin and lung cancer, in which there is high risk of bias from exposure definition, is estimated to have a log risk ratio 0.44 lower than a study not at risk of bias from exposure definition.

1 I squared is the estimate of residual variation due to study heterogeneity

2 Adjusted R2 is the estimated proportion of between study variance explained by the covariates in the meta regression

3 Tau2 is the estimate of the remaining between study variance