**Appendices Online Content**

Supplementary Figures

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**Supplementary Figure 1**. Forest plot with hazard ratios for baseline sulphonylurea of site-specific obesity-related cancer among non-gliclazide sulphonylureas compared with gliclazide

*Abbreviations: CI, confidence interval; HR, Hazard ratio; ITT, intention to treat.*

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**Supplementary Figure 2.** Forest plot with hazard ratios for cumulative exposure of site-specific obesity-related cancer among non-gliclazide sulphonylureas compared with gliclazide

*Abbreviations: CI, confidence interval; HR, Hazard ratio; ITT, intention to treat.*

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| **Supplementary Table 1. Incidence and relative risk of obesity-related cancer for sulphonylurea users: new user subgroup analysis** | | | | | | | |
| **SUs** | **Cancers (n)** | **PYS** | **IR (95% CI) (per 100,000 PYS)** | **Unadjusted** | | **Adjusted§** | |
|
| **Baseline sulphonylurea** | **Cumulative exposure** | **Baseline sulphonylurea** | **Cumulative exposure** |
| **HR (95%CI)** | **HR (95%CI)** | **HR (95%CI)** | **HR (95%CI)** |
| **Male** |  |  |  |  |  |  |  |
| Gliclazide\* | 65 | 10103.4 | 643.4 (504.9–819.8) | 1.00 | 1.00 | 1.00 | 1.00 |
| Glibenclamide | 7 | 696.2 | 1005.5 (481.1–2101.2) | 0.80 (0.08–7.74) | 0.86 (0.43–1.71) | 1.30 (0.09–18.17) | 0.47 (0.08–2.51) |
| Glimepiride | 59 | 9692.8 | 608.7 (472.0–785.0) | 1.82 (0.91–3.66) | **0.85 (0.74–0.99)** | 1.75 (0.79–3.90) | 0.85 (0.73–1.00) |
| Tolbutamide | 87 | 14250.9 | 610.5 (495.1–752.8) | 1.03 (0.54–1.99) | 0.98 (0.87–1.10) | 1.19 (0.57–2.44) | 0.94 (0.82–1.07) |
| **Female** |  |  |  |  |  |  |  |
| Gliclazide\* | 63 | 8890.6 | 708.6 (554.1–906.3) | 1.00 | 1.00 | 1.00 | 1.00 |
| Glibenclamide | 5 | 809.9 | 617.4 (257.7–1479.2) | 3.66 (0.79–17.0) | 0.48 (0.21–1.11) | 6.42 (0.89–46.06) | 0.25 (0.06–1.12) |
| Glimepiride | 51 | 8859.0 | 575.7 (437.9–756.9) | 0.87 (0.45–1.70) | 0.98 (0.84–1.15) | 0.77 (0.36–1.63) | 1.00 (0.84–1.19) |
| Tolbutamide | 110 | 13240.0 | 830.8 (689.7–1000.8) | 0.90 (0.52–1.57) | 1.07 (0.95–1.20) | 0.97 (0.53–1.77) | 1.04 (0.92–1.19) |
| **Site-specific cancers** | | | | | | | |
| ***Advanced prostate cancer*** | | | | | | | |
| Gliclazide\* | 18 | 10103 | 178.2 (175.6–180.8) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 38 | 24640 | 154.2 (152.7–155.8) | 1.04 (0.36–3.00) | 0.94 (0.77–1.14) | 1.75 (0.52–5.81) | 0.84 (0.68–1.06) |
| Other sulphonylureas (Glibenclamide excluded) | 38 | 23944 | 158.7 (157.1–160.3) | 1.11 (0.38–3.20) | 0.93 (0.76–1.14) | 1.82 (0.55–6.11) | 0.84 (0.68–1.05) |
| ***Breast cancer*** | | | | | | | |
| Gliclazide\* | 22 | 8890.6 | 247.5 (244.2–250.8) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 67 | 22908.9 | 292.5 (290.2–294.7) | 1.14 (0.48–2.71) | 1.03 (0.86–1.25) | 0.86 (0.32–2.34) | 1.07 (0.86–1.34) |
| Other sulphonylureas (Glibenclamide excluded) | 64 | 22099.0 | 289.6 (287.4–291.9) | 1.06 (0.44–2.55) | 1.05 (0.87–1.27) | 0.84 (0.31–2.29) | 1.08 (0.86–1.34) |
| ***Colorectal cancer*** | | | | | | | |
| Gliclazide\* | 40 | 18994.0 | 210.6 (154.5–287.0) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 90 | 47548.8 | 189.3 (154.0–232.7) | 0.91 (0.46–1.81) | 0.99 (0.86–1.13) | 0.94 (0.44–1.99) | 0.98 (0.85–1.13) |
| Other sulphonylureas (Glibenclamide excluded) | 90 | 46042.7 | 195.5 (159.0–240.3) | 0.95 (0.48–1.89) | 0.99 (0.86–1.13) | 0.98 (0.46–2.08) | 0.98 (0.85–1.13) |
| *For all the models, age was used as the timescale and baseline year was used as a stratification variable. Abbreviations: SU, Sulphonylurea; PYS, person-years; IR, incidence rate; CI, confidence interval; HR, hazard ratio. § Adjusted for baseline covariates: smoking (yes/no, not known), diabetes duration, hemoglobin A1c level, body mass index, creatinine, and known metformin usage years. Site-specific analysis for colorectal cancer was also adjusted by gender. \* Reference. Number in bold means a significant difference at P<0.05 level.* | | | | | | | |

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| **Supplementary Table 2. Incidence and relative risk of obesity-related cancer for sulphonylurea users: analysis based on a 2-year lag period** | | | | | | | | |  |
| **SUs** | **Cancers (n)** | **PYS** | **IR (95% CI) (per 100,000 PYS)** | **Unadjusted** | | | **Adjusted§** | |  |
|  |
| **Baseline sulphonylurea** | | **Cumulative exposure** | **Baseline sulphonylurea** | **Cumulative exposure** |  |
| **HR (95%CI)** | | **HR (95%CI)** | **HR (95%CI)** | **HR (95%CI)** |  |
| **Male** |  |  |  |  | |  |  |  |  |
| Gliclazide\* | 121 | 20939.0 | 577.9 (483.8–690.2) | 1.00 | | 1.00 | 1.00 | 1.00 |  |
| Glibenclamide | 26 | 4766.1 | 545.5 (371.8–800.4) | 0.84 (0.35–2.06) | | 0.98 (0.80–1.20) | 1.21 (0.44–3.28) | 0.90 (0.70–1.15) |  |
| Glimepiride | 149 | 25984.0 | 573.4 (488.6–673.0) | 0.98 (0.59–1.61) | | 0.99 (0.91–1.09) | 0.92 (0.52–1.63) | 1.00 (0.90–1.11) |  |
| Tolbutamide | 211 | 34061.1 | 619.5 (541.5–708.7) | 0.84 (0.53–1.32) | | 1.03 (0.96–1.11) | 0.94 (0.56–1.58) | 1.01 (0.92–1.09) |  |
| **Female** |  |  |  |  | |  |  |  |  |
| Gliclazide\* | 98 | 18748.0 | 522.7 (429.1–636.8) | 1.00 | | 1.00 | 1.00 | 1.00 |  |
| Glibenclamide | 41 | 4995.5 | 820.7 (605.1–1113.3) | **1.93 (1.02–3.65)** | | 0.94 (0.81–1.09) | 1.95 (0.88–4.35) | 0.90 (0.74–1.09) |  |
| Glimepiride | 129 | 23760.9 | 542.9 (457.1–644.9) | 1.08 (0.67–1.76) | | 0.99 (0.90–1.09) | 1.17 (0.68–1.99) | 0.97 (0.87–1.07) |  |
| Tolbutamide | 215 | 34437.6 | 624.3 (546.4–713.3) | 1.03 (0.67–1.60) | | 1.02 (0.94–1.11) | 0.92 (0.57–1.49) | 1.03 (0.94–1.12) |  |
| **Site-specific cancers** | | | | | | | | |  |
| ***Advanced prostate cancer*** | | | | | | | | | |
| Gliclazide\* | 37 | 20939.0 | 176.7 (174.9–178.5) | 1.00 | 1.00 | | 1.00 | 1.00 |  |
| Other sulphonylureas | 97 | 64811 | 149.7 (148.7–150.6) | 0.71 (0.33–1.53) | 1.02 (0.90–1.16) | | 0.92 (0.38–2.25) | 0.98 (0.85–1.14) |  |
| Other sulphonylureas (Glibenclamide excluded) | 92 | 60045 | 153.2 (152.2–154.2) | 0.71 (0.33–1.52) | 1.03 (0.91–1.16) | | 0.89 (0.36–2.18) | 0.99 (0.86–1.15) |  |
| ***Breast cancer*** | | | | | | | | | |
| Gliclazide\* | 35 | 18748.0 | 186.7 (184.7–188.7) | 1.00 | 1.00 | | 1.00 | 1.00 |  |
| Other sulphonylureas | 153 | 63194.0 | 242.1 (240.9–243.3) | 1.55 (0.77–3.11) | 0.97 (0.86–1.10) | | 1.62 (0.72–3.67) | 0.95 (0.83–1.09) |  |
| Other sulphonylureas (Glibenclamide excluded) | 135 | 58199 | 232.0 (230.7–233.2) | 1.38 (0.67–2.80) | 0.98 (0.87–1.11) | | 1.46 (0.64–3.35) | 0.96 (0.84–1.11) |  |
| ***Colorectal cancer*** | | | | | | | | | |
| Gliclazide\* | 62 | 39687.0 | 156.2 (121.8–200.3) | 1.00 | 1.00 | | 1.00 | 1.00 |  |
| Other sulphonylureas | 245 | 128005.1 | 191.4 (168.9–216.9) | 0.95 (0.57–1.58) | 1.04 (0.95–1.14) | | 0.97 (0.55–1.70) | 1.02 (0.93–1.13) |  |
| Other sulphonylureas (Glibenclamide excluded) | 228 | 118243.5 | 192.8 (169.4–219.5) | 0.97 (0.58–1.63) | 1.04 (0.95–1.14) | | 0.98 (0.55–1.73) | 1.02 (0.93–1.13) |  |
| *For all the models, age was used as the timescale and baseline year was used as a stratification variable. Abbreviations: SU, Sulphonylurea; PYS, person-years; IR, incidence rate; CI, confidence interval; HR, hazard ratio. § Adjusted for baseline covariates: smoking (yes/no, not known), diabetes duration, hemoglobin A1c level, body mass index, creatinine, known metformin usage years, and new or existing users. Site-specific analysis for colorectal cancer was also adjusted by gender. \* Reference. Number in bold means a significant difference at P<0.05 level.* | | | | | | | | |  |

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| **Supplementary Table 3. Incidence and relative risk of obesity-related cancer for sulphonylurea users: analysis based on a 5-year lag period** | | | | | | | |
| **SUs** | **Cancers (n)** | **PYS** | **IR (95% CI) (per 100,000 PYS)** | **Unadjusted** | | **Adjusted§** | |
|
| **Baseline sulphonylurea** | **Cumulative exposure** | **Baseline sulphonylurea** | **Cumulative exposure** |
| **HR (95%CI)** | **HR (95%CI)** | **HR (95%CI)** | **HR (95%CI)** |
| **Male** |  |  |  |  |  |  |  |
| Gliclazide\* | 61 | 20939.0 | 291.3 (289.0–293.7) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 168 | 64811.2 | 259.2 (258.0–260.5) | 0.89 (0.48–1.65) | 1.02 (0.94–1.11) | 1.02 (0.49–2.12) | 1.00 (0.90–1.10) |
| Other sulphonylureas (Glibenclamide excluded) | 155 | 60045.1 | 258.1 (256.8–259.4) | 0.85 (0.45–1.62) | 1.03 (0.94–1.12) | 0.95 (0.44–2.05) | 1.00 (0.90–1.11) |
| **Female** |  |  |  |  |  |  |  |
| Gliclazide\* | 48 | 18748.0 | 256.0 (253.7–258.4) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 183 | 63194.0 | 289.6 (288.3–290.9) | 1.23 (0.66–2.28) | 1.00 (0.92–1.10) | 1.30 (0.64–2.66) | 0.99 (0.90–1.10) |
| Other sulphonylureas (Glibenclamide excluded) | 161 | 58198.4 | 276.6 (275.3–278.0) | 1.16 (0.61–2.20) | 1.01 (0.92–1.11) | 1.23 (0.59–2.59) | 1.00 (0.90–1.10) |
| **Site-specific cancers** | | | | | | | |
| ***Advanced prostate cancer*** | | | | | | | |
| Gliclazide\* | 21 | 20939 | 100.3 (98.9–101.7) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 50 | 64811.2 | 77.2 (76.5–77.8) | 0.57 (0.19–1.75) | 1.07 (0.92–1.25) | 0.73 (0.18–3.00) | 1.04 (0.86–1.25) |
| Other sulphonylureas (Glibenclamide excluded) | 48 | 60045.1 | 79.9 (79.2–80.7) | 0.57 (0.18–1.78) | 1.08 (0.92–1.25) | 0.69 (0.17–2.92) | 1.04(0.87–1.26) |
| ***Breast cancer*** | | | | | | | |
| Gliclazide\* | 22 | 18748.0 | 117.4 (115.8–118.9) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 76 | 63194.0 | 120.3 (119.4–121.1) | 1.17 (0.45–3.07) | 1.00 (0.86–1.15) | 1.17 (0.36–3.78) | 0.99 (0.84–1.16) |
| Other sulphonylureas (Glibenclamide excluded) | 68 | 58198.5 | 116.8 (116.0–117.7) | 1.10 (0.41–2.97) | 1.00 (0.87–1.16) | 1.12 (0.34–3.71) | 0.99 (0.84–1.17) |
| ***Colorectal cancer*** | | | | | | | |
| Gliclazide\* | 36 | 39687.0 | 90.7 (65.4–125.7) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 119 | 128005.1 | 93.0 (77.7–111.3) | 0.86 (0.41–1.80) | 1.04 (0.94–1.16) | 0.86 (0.38–1.99) | 1.03 (0.92–1.15) |
| Other sulphonylureas (Glibenclamide excluded) | 104 | 118243.5 | 88.0 (72.6–106.6) | 0.77 (0.36–1.65) | 1.06 (0.95–1.17) | 0.73 (0.31–1.73) | 1.05 (0.93–1.19) |
| *For all the models, age was used as the timescale and baseline year was used as a stratification variable. Abbreviations: SU, Sulphonylurea; PYS, person-years; IR, incidence rate; CI, confidence interval; HR, hazard ratio. § Adjusted for baseline covariates: smoking (yes/no, not known), diabetes duration, hemoglobin A1c level, body mass index, creatinine, known metformin usage years, and new or existing users. Site-specific analysis for colorectal cancer was also adjusted by gender. \* Reference. Number in bold means a significant difference at P<0.05 level.* | | | | | | | |

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| **Supplementary Table 4. Incidence and relative risk of obesity–related cancer for sulphonylurea users: intention–to–treat analysis** | | | | | | | |
| **SUs** | **Cancers (n)** | **PYS** | **IR (95% CI) (per 100.000 PYS)** | **Unadjusted** | | **Adjusted§** | |
|
| **Baseline sulphonylurea** | **Cumulative exposure** | **Baseline sulphonylurea** | **Cumulative exposure** |
| **HR (95%CI)** | **HR (95%CI)** | **HR (95%CI)** | **HR (95%CI)** |
| **Male** |  |  |  |  |  |  |  |
| Gliclazide\* | 158 | 21536.2 | 733.7 (628.1–857.0) | 1.00 | 1.00 | 1.00 | 1.00 |
| Glibenclamide | 36 | 5584.5 | 644.6 (465.5–892.8) | 0.80 (0.38–1.68) | 0.97 (0.83–1.13) | 0.96 (0.42–2.20) | 0.94 (0.79–1.13) |
| Glimepiride | 189 | 26963.3 | 701.0 (608.1–808.0) | 1.07 (0.70–1.64) | 0.97 (0.89–1.05) | 1.07 (0.66–1.73) | 0.96 (0.88–1.06) |
| Tolbutamide | 265 | 35735.8 | 741.6 (657.7–836.1) | 0.82 (0.55–1.22) | 1.03 (0.96–1.10) | 0.93 (0.59–1.45) | 1.00 (0.93–1.08) |
| **Female** |  |  |  |  |  |  |  |
| Gliclazide\* | 139 | 19495.7 | 713.0 (604.1–841.4) | 1.00 | 1.00 | 1.00 | 1.00 |
| Glibenclamide | 50 | 6034.7 | 828.5 (628.7–1091.9) | 1.40 (0.79–2.48) | 0.95 (0.84–1.07) | 1.39 (0.69–2.80) | 0.92 (0.79–1.06) |
| Glimepiride | 158 | 24891.3 | 634.8 (543.4–741.5) | 0.93 (0.61–1.41) | 1.00 (0.91–1.09) | 1.01 (0.64–1.60) | 0.98 (0.89–1.07) |
| Tolbutamide | 265 | 36339.5 | 729.2 (646.8–822.2) | 0.91 (0.62–1.31) | 1.03 (0.95–1.10) | 0.89 (0.58–1.35) | 1.02 (0.94–1.10) |
| **Site-specific cancers** | | | | | | | |
| ***Advanced prostate cancer*** | | | | | | | |
| Gliclazide\* | 58 | 21536 | 269.3 (267.1–271.5) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 152 | 68284 | 222.6 (221.5–223.7) | 0.76 (0.43–1.34) | 1.01 (0.90–1.12) | 0.93 (0.50–1.77) | 0.97 (0.85–1.10) |
| Other sulphonylureas (Glibenclamide excluded) | 141 | 62699 | 224.9 (223.7–226.1) | 0.75 (0.42–1.33) | 1.01 (0.91–1.13) | 0.91 (0.48–1.73) | 0.98 (0.86–1.12) |
| ***Breast cancer*** | | | | | | | |
| Gliclazide\* | 63 | 19496 | 323.2 (320.6–325.7) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 214 | 67266 | 318.1 (316.8–319.5) | 1.02 (0.61–1.71) | 1.00 (0.89–1.11) | 0.89 (0.50–1.58) | 1.01 (0.89–1.15) |
| Other sulphonylureas (Glibenclamide excluded) | 190 | 61231 | 310.3 (308.9–311.7) | 0.93 (0.55–1.57) | 1.01 (0.90–1.13) | 0.84 (0.47–1.51) | 1.02 (0.90–1.16) |
| ***Colorectal cancer*** | | | | | | | |
| Gliclazide\* | 100 | 40580.6 | 246.4 (202.6–299.7)) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 338 | 134271.7 | 251.7 (226.3–280.0) | 1.02 (0.68–1.53) | 1.00 (0.92–1.08) | 0.89 (0.57–1.38) | 1.02 (0.93–1.12) |
| Other sulphonylureas (Glibenclamide excluded) | 314 | 122758.6 | 255.8 (229.0–285.7) | 1.05 (0.70–1.59) | 1.00 (0.92–1.08) | 0.92 (0.59–1.43) | 1.02 (0.92–1.12) |
| *For all the models. age was used as the timescale and baseline year was used as a stratification variable. Abbreviations: SU. Sulphonylurea; PYS. person–years; IR. incidence rate; CI. confidence interval; HR. hazard ratio. § Adjusted for baseline covariates: smoking (yes/no. not known). diabetes duration. hemoglobin A1c level. body mass index. creatinine. known metformin usage years. and new or existing users. Site–specific analysis for colorectal cancer was also adjusted by gender. \* Reference. Number in bold means a significant difference at P<0.05 level.* | | | | | | | |

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| **Supplementary Table 5. Incidence and relative risk of obesity-related cancer for sulphonylurea users: complete case analysis** | | | | | | | |
| **SUs** | **Cancers (n)** | **PYS** | **IR (95% CI) (per 100,000 PYS)** | **Unadjusted** | | **Adjusted§** | |
|
| **Baseline sulphonylurea** | **Cumulative exposure** | **Baseline sulphonylurea** | **Cumulative exposure** |
| **HR (95%CI)** | **HR (95%CI)** | **HR (95%CI)** | **HR (95%CI)** |
| **Male** |  |  |  |  |  |  |  |
| Gliclazide\* | 107 | 16975.1 | 724.6 (607.6–864.1) | 1.00 | 1.00 | 1.00 | 1.00 |
| Glibenclamide | 18 | 3592.7 | 695.9 (470.8–1028.4) | 1.06 (0.43–2.57) | 0.90 (0.71–1.14) | 1.06 (0.43–2.59) | 0.90 (0.71–1.14) |
| Glimepiride | 134 | 21568.5 | 704.7 (601.5–825.7) | 1.11 (0.68–1.80) | 0.96 (0.87–1.06) | 1.08 (0.66–1.76) | 0.96 (0.87–1.06) |
| Tolbutamide | 177 | 27696.8 | 718.5 (625.6–825.2) | 0.90 (0.57–1.42) | 1.01 (0.93–1.09) | 0.89 (0.57–1.41) | 1.01 (0.93–1.10) |
| **Female** |  |  |  |  |  |  |  |
| Gliclazide\* | 107 | 15164.8 | 705.6 (584.2–852.2) | 1.00 | 1.00 | 1.00 | 1.00 |
| Glibenclamide | 28 | 3699.2 | 756.9 (523.4–1094.7) | 1.36 (0.66–2.84) | 0.94 (0.78–1.13) | 1.51 (0.72–3.16) | 0.93 (0.77–1.12) |
| Glimepiride | 126 | 19782.4 | 636.9 (535.2–758.0) | 0.96 (0.59–1.54) | 0.99 (0.89–1.10) | 0.96 (0.60–1.54) | 0.99 (0.89–1.10) |
| Tolbutamide | 195 | 27404.9 | 711.6 (618.7–818.4) | 0.84 (0.55–1.29) | 1.04 (0.95–1.13) | 0.84 (0.55–1.29) | 1.04 (0.95–1.13) |
| **Site-specific cancers** | | | | | | | |
| ***Advanced prostate cancer*** | | | | | | | |
| Gliclazide\* | 36 | 16975.1 | 212.1 (209.9–214.3) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 99 | 52858.0 | 187.3 (186.1–188.5) | 0.85 (0.41–1.78 | 0.99 (0.87–1.13) | 0.86 (0.41–1.79) | 0.99 (0.86–1.13) |
| Other sulphonylureas (Glibenclamide excluded) | 95 | 49265.3 | 192.8 (191.6–194.1) | 0.85 (0.40–1.78) | 1.00 (0.87–1.14) | 0.85 (0.40–1.78) | 0.99 (0.87–1.14) |
| ***Breast cancer*** | | | | | | | |
| Gliclazide\* | 38 | 15164.8 | 250.6 (248.1–253.1) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 134 | 50886.5 | 263.3 (261.9–264.8) | 1.18 (0.60–2.32) | 0.99 (0.87–1.13) | 1.21 (0.61–2.36) | 0.98 (0.86–1.12) |
| Other sulphonylureas (Glibenclamide excluded) | 124 | 47187.3 | 262.8 (261.3–264.3) | 1.13 (0.57–2.24) | 0.99 (0.87–1.13) | 1.15 (0.58–2.27) | 0.99 (0.87–1.13) |
| ***Colorectal cancer*** | | | | | | | |
| Gliclazide\* | 65 | 32139.9 | 202.2 (158.6–257.8) | 1.00 | 1.00 | 1.00 | 1.00 |
| Other sulphonylureas | 229 | 103744.4 | 220.7 (194.0–251.2) | 0.95 (0.58–1.57) | 1.02 (0.93–1.13) | 0.95 (0.57–1.57) | 1.02 (0.93–1.12) |
| Other sulphonylureas (Glibenclamide excluded) | 213 | 96452.4 | 220.8 (193.1–252.5) | 0.96 (0.58–1.60) | 1.02 (0.93–1.13) | 0.96 (0.58–1.60) | 1.02 (0.93–1.12) |
| *For all the models, age was used as the timescale and baseline year was used as a stratification variable. Abbreviations: SU, Sulphonylurea; PYS, person-years; IR, incidence rate; CI, confidence interval; HR, hazard ratio. § Adjusted for baseline covariates: smoking (yes/no, not known), diabetes duration, hemoglobin A1c level, body mass index, creatinine, known metformin usage years, and new or existing users. Site-specific analysis for colorectal cancer was also adjusted by gender. \* Reference. Number in bold means a significant difference at P<0.05 level.* | | | | | | | |

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| **Supplementary Table 6. Incidence rates and relative risk of obesity–related cancer in SU users: adjusted for history of macrovascular events and statin use** | | | | | |
| **SUs** | **Cancers (n)** | **PYS** | **IR (95% CI) (per 100.000 PYS)** | **Adjusted§** | |
| **Baseline sulphonylurea** | **Cumulative exposure** |
| **HR (95%CI)** | **HR (95%CI)** |
| **Male** |  |  |  |  |  |
| Gliclazide\* | 132 | 20939.0 | 630.4 (531.8–747.3) | 1.00 | 1.00 |
| Glibenclamide | 23 | 4766.1 | 482.6 (321.0–725.5) | 1.12 (0.45–2.77) | 0.90 (0.70-1.13) |
| Glimepiride | 160 | 25984.0 | 615.8 (527.6–718.6) | 1.09 (0.66–1.82) | 0.96 (0.87-1.06) |
| Tolbutamide | 221 | 34061.1 | 648.8 (568.9–740.0) | 0.92 (0.58–1.48) | 1.00 (0.92-1.09) |
| **Female** |  |  |  |  |  |
| Gliclazide\* | 130 | 18748.0 | 693.4 (584.2–823.0) | 1.00 | 1.00 |
| Glibenclamide | 46 | 4995.5 | 920.8 (690.6–1227.7) | 1.49 (0.71–3.13) | 0.93 (0.77-1.12) |
| Glimepiride | 149 | 23760.9 | 627.1 (534.3–735.9) | 0.98 (0.60–1.60) | 0.99 (0.89-1.09) |
| Tolbutamide | 250 | 34437.6 | 726.0 (641.6–821.4) | 0.82 (0.52–1.27) | 1.04 (0.96-1.14) |
| **Site-specific cancers** |  |  |  |  |  |
| ***Advanced prostate cancer*** |  |  |  |  |  |
| Gliclazide\* | 47 | 20939.0 | 224.5 (222.4–226.5) | 1.00 | 1.00 |
| Other sulphonylureas | 120 | 64811.2 | 185.2 (184.1–186.2) | 0.92 (0.42–1.97) | 0.98 (0.85-1.12) |
| Other sulphonylureas (Glibenclamide excluded) | 114 | 60045.1 | 189.9 (188.8–191.0) | 0.90 (0.41–1.95) | 0.99 (0.86-1.13) |
| ***Breast cancer*** |  |  |  |  |  |
| Gliclazide\* | 50 | 18748.0 | 266.7 (264.3–269.1) | 1.00 | 1.00 |
| Other sulphonylureas | 181 | 63194.0 | 286.4 (285.1–287.8) | 1.36 (0.66–2.77) | 0.97 (0.84-1.11) |
| Other sulphonylureas (Glibenclamide excluded) | 161 | 58198.5 | 276.6 (275.3–278.0) | 1.28 (0.63–2.66) | 0.97 (0.85-1.12) |
| ***Colorectal cancer*** |  |  |  |  |  |
| Gliclazide\* | 77 | 39687.0 | 194.0 (155.2–242.5) | 1.00 | 1.00 |
| Other sulphonylureas | 285 | 128005.1 | 222.6 (198.2–249.9) | 0.93 (0.55–1.58) | 1.02 (0.93-1.13) |
| Other sulphonylureas (Glibenclamide excluded) | 264 | 118243.5 | 223.2 (197.9–251.8) | 0.94 (0.55–1.60) | 1.02 (0.93-1.13) |
| *For all the models, age was used as the timescale and baseline year was used as a stratification variable. Abbreviations: SU, Sulphonylurea; PYS, person-years; IR, incidence rate; CI, confidence interval; HR, hazard ratio. § Adjusted for baseline covariates: smoking (yes/no, not known), diabetes duration, hemoglobin A1c level, body mass index, creatinine, known metformin usage years, history of macrovascular events, use of statins, and new or existing users. Site-specific analysis for colorectal cancer was also adjusted by gender. \* Reference. Number in bold means a significant difference at P<0.05 level.* | | | | | |

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| **Supplementary Table 7. Incidence rates and relative risk of obesity–related cancer in sulphonylurea users: adjusted for time-updated duration of diabetes** | | | | | |
| **SUs** | **Cancers (n)** | **PYS** | **IR (95% CI) (per 100.000 PYS)** | **Adjusted§** | |
| **Baseline sulphonylurea** | **Cumulative exposure** |
| **HR (95%CI)** | **HR (95%CI)** |
| **Male** |  |  |  |  |  |
| Gliclazide\* | 132 | 20939.0 | 630.4 (531.8–747.3) | 1.00 | 1.00 |
| Glibenclamide | 23 | 4766.1 | 482.6 (321.0–725.5) | 1.06 (0.43–2.61) | 0.90 (0.71-1.14) |
| Glimepiride | 160 | 25984.0 | 615.8 (527.6–718.6) | 1.13 (0.69–1.86) | 0.96 (0.87-1.06) |
| Tolbutamide | 221 | 34061.1 | 648.8 (568.9–740.0) | 0.94 (0.59–1.48) | 1.00 (0.92-1.09) |
| **Female** |  |  |  |  |  |
| Gliclazide\* | 130 | 18748.0 | 693.4 (584.2–823.0) | 1.00 | 1.00 |
| Glibenclamide | 46 | 4995.5 | 920.8 (690.6–1227.7) | 1.45 (0.69–3.03) | 0.93 (0.77-1.12) |
| Glimepiride | 149 | 23760.9 | 627.1 (534.3–735.9) | 0.95 (0.59–1.52) | 0.99 (0.90-1.10) |
| Tolbutamide | 250 | 34437.6 | 726.0 (641.6–821.4) | 0.83 (0.54–1.27) | 1.04 (0.96-1.13) |
| **Site-specific cancers** |  |  |  |  |  |
| ***Advanced prostate cancer*** |  |  |  |  |  |
| Gliclazide\* | 47 | 20939.0 | 224.5 (222.4–226.5) | 1.00 | 1.00 |
| Other sulphonylureas | 120 | 64811.2 | 185.2 (184.1–186.2) | 0.91 (0.43–1.92) | 0.98 (0.86-1.12) |
| Other sulphonylureas (Glibenclamide excluded) | 114 | 60045.1 | 189.9 (188.8–191.0) | 0.90 (0.42–1.90) | 0.99 (0.87-1.13) |
| ***Breast cancer*** |  |  |  |  |  |
| Gliclazide\* | 50 | 18748.0 | 266.7 (264.3–269.1) | 1.00 | 1.00 |
| Other sulphonylureas | 181 | 63194.0 | 286.4 (285.1–287.8) | 1.19 (0.61–2.32) | 0.98 (0.86-1.13) |
| Other sulphonylureas (Glibenclamide excluded) | 161 | 58198.5 | 276.6 (275.3–278.0) | 1.14 (0.58-2.25) | 0.99 (0.87-1.13) |
| ***Colorectal cancer*** |  |  |  |  |  |
| Gliclazide\* | 77 | 39687.0 | 194.0 (155.2–242.5) | 1.00 | 1.00 |
| Other sulphonylureas | 285 | 128005.1 | 222.6 (198.2–249.9) | 0.98 (0.59-1.63) | 1.02 (0.92-1.12) |
| Other sulphonylureas (Glibenclamide excluded) | 264 | 118243.5 | 223.2 (197.9–251.8) | 1.00 (0.59–1.67) | 1.02 (0.92-1.12) |
| *For all the models, age was used as the timescale and baseline year was used as a stratification variable. Abbreviations: SU, sulphonylurea; PYS, person-years; IR, incidence rate; CI, confidence interval; HR, hazard ratio. § Adjusted for baseline covariates: smoking (yes/no, not known), diabetes duration in a time-updated manner, hemoglobin A1c level, body mass index, creatinine, known metformin usage years, and new or existing users. Site-specific analysis for colorectal cancer was also adjusted by gender. \* Reference. Number in bold means a significant difference at P<0.05 level.* | | | | | |