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| --- | --- | --- | --- | --- | --- | --- |
| Author, Year of publication | Study design | Sample, N | Follow-up | comparison | Main result | Subgroup analysis |
| Orkaby13 , 2017 | Retrospective cohort study, US veterans without dementia | T2DM, >65yr  28,640 | 5yr | Met new users (17,200) vs SU new users (11,440) | Met reduced dementia | More effective < 75 yr |
| Kim14, 2018 | Retrospective, Propensity Score Match, Korean National health Insurance Data | T2DM, >60yr  15,104 | 1362days  (2008~2015), median 3.7 yr | DPP-4i new users(7552) vs SU new users(7552) | DPP-4i reduced all-cause dementia and AD(HR=0.66 and 0.64, respectivelly)  No effect on VaD (HR=0.66, 0.38-1.14) | Effect on subtype dementia, such as all-cause dementia, AD, VaD,  no effect <75yr and group with microcomplication |
| Lu15 , 2018 | Restrospective, Propensity Score Match, Taiwan National Health Insurance Data | T2DM, ≥65yr  51,415 | 2000~2013 | Met + TZD(Piog) vs Met + SU | Met + TZD reduced dementia (HR 0.56) | More effective ≥65 yr |
| Bohlken16, 2018 | Matched case-control study, German general practice Data | DM, dementia (8276) vs non-dementia (8276) | 2013~2017 | Medications to dementia/non-dementia | Met or MET+SU reduced dementia (OR=0.71 and 0.90)  TZD reduced dementia (OR = 0.80)  Insulin increased dementia (OR = 1.34) |  |
| Tseng17, 2018 | Restrospective, Propensity Score Match, Taiwan National Health Insurance Data | T2DM  22,022 | 1998-2008  FU to 2011 | TZD(Piog)(11,011) vs never users of TZD(Piog)(11,011) | TZD reduced dementia (HR=0.716) | Dose(duration of medication)-response association  Effective more on those not exposed to Met (HR 0.494) |
| Tseng CH18 , 2019 | Restrospective, Propensity Score Match, Taiwan National Health Insurance Data | T2DM  15,676 | 1999-2005  FU to 2011 | Met ever users vs never users | Met reduced dementia (HR=0.55, 0.71, respectively) in unmatched and matched cohort | Dose(duration of medication)-response association |
| Chen19 , 2020 | Restrospective, Propensity Score Match, Taiwan National Health Insurance Data | T2DM, ≥50 yr,  11,612 | 2008~2015, mean 7yr | DPP-4i new user vs non DPP-4 user | DPP-4i reduced All-cause dementia(HR=0.81), VaD(HR=0.612), but not in AD(HR=0.89, 95% CI) | Effect on subtype dementia, such as all-cause dementia, AD, VaD,  More effective < 65 yr and group without complication |
| Wiun-Andersen20, 2019 | Nested case-control Danish National Diabetes Register Data | T2DM,  58,095 | 1995-2012, FU to 2018 | Medications to dementia(11,619)/non-dementia (46,476) | Met, DPP-4i, GLP1 analogs, and SGLT-2i reduced dementia(ORs=0.94, 0.80, 0.58, 0.58, respectivelly. |  |

Table . Human retrospective observational studies describing the association between anti-diabetic medications and dementia risk since 2017. T2DM:type 2 diabetes mellitus, yr: year, SU: Sulfonylurea, Met: Metformin, TZD: thiazolidinediones, DPP-4i: dipeptidyl peptidase 4 inhibitor, Piog: pioglitazone, SGLT-2i:sodium glucose co-transporter 2 inhibitor, AD: Alzhiemer’s dementia, VaD: vascular dementia, HR; hazard ration, OR: odds ratios, Modified from the table of Moran C, et al [36]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Total | Only Insulin | Monotherapy | Dual therapy | More than dual therapy | P-value |
| Number | 1578322 | 46784 | 629358 | 726484 | 175696 |
| Age | 60.66 ± 10.22 | 61.41 ± 10.27 | 61.09 ± 10.3 | 60.14 ± 10.19 | 61.07 ± 9.92 | <.0001 |
| Gender, male | 860623 (54.53) | 26698 (57.07) | 329803 (52.4) | 406359 (55.94) | 97763 (55.64) | <.0001 |
| DM duration, ≥ 5yrs | 1337859 (84.76) | 38677 (82.67) | 467249 (74.24) | 659965 (90.84) | 171968 (97.88) | <.0001 |
| Income, low 20% | 355678 (22.54) | 10649 (22.76) | 139195 (22.12) | 163639 (22.52) | 42195 (24.02) | <.0001 |
| Hypertension | 1021526 (64.72) | 30942 (66.14) | 410066 (65.16) | 465643 (64.1) | 114875 (65.38) | <.0001 |
| Dyslipidemia | 791672 (50.16) | 21904 (46.82) | 312435 (49.64) | 368437 (50.72) | 88896 (50.6) | <.0001 |
| Smoking |  |  |  |  |  | <.0001 |
| Non | 952362 (60.34) | 28236 (60.35) | 391328 (62.18) | 427942 (58.91) | 104856 (59.68) |  |
| Ex | 293112 (18.57) | 9187 (19.64) | 116807 (18.56) | 136468 (18.78) | 30650 (17.44) |  |
| Current | 332848 (21.09) | 9361 (20.01) | 121223 (19.26) | 162074 (22.31) | 40190 (22.87) |  |
| Drinking |  |  |  |  |  | <.0001 |
| Non | 1021239 (64.7) | 33508 (71.62) | 408042 (64.83) | 462479 (63.66) | 117210 (66.71) |  |
| Mild | 428642 (27.16) | 10316 (22.05) | 170931 (27.16) | 202643 (27.89) | 44752 (25.47) |  |
| Heavy | 128441 (8.14) | 2960 (6.33) | 50385 (8.01) | 61362 (8.45) | 13734 (7.82) |  |
| Regular exercise | 348718 (22.09) | 10199 (21.8) | 139660 (22.19) | 161844 (22.28) | 37015 (21.07) | <.0001 |
| Insulin | 118517 (7.51) | 46784 (100) | 41331 (6.57) | 25291 (3.48) | 5111 (2.91) | <.0001 |
| Body Mass Index (kg/m2) | 25.1 ± 3.29 | 24.33 ± 3.34 | 25.15 ± 3.27 | 25.19 ± 3.29 | 24.8 ± 3.29 | <.0001 |
| SBP (mmHg) | 128.99 ± 15.71 | 128.5 ± 17.14 | 129.41 ± 15.75 | 128.77 ± 15.6 | 128.52 ± 15.64 | <.0001 |
| DBP (mmHg) | 78.38 ± 9.99 | 76.76 ± 10.51 | 78.8 ± 10.07 | 78.29 ± 9.91 | 77.7 ± 9.8 | <.0001 |
| Total cholesterol ( mg/dL) | 191.33 ± 41.97 | 186.94 ± 43.82 | 195.43 ± 42.28 | 189.18 ± 41.5 | 186.7 ± 41.08 | <.0001 |
| Fasting glucose (mg/dL) | 142.41 ± 48.3 | 150.06 ± 62.98 | 135.83 ± 43.05 | 145.2 ± 49.63 | 152.45 ± 52.71 | <.0001 |
| eGFR (mL/min/m2) | 83.56 ± 35.6 | 75.4 ± 41.99 | 83.53 ± 34.8 | 84.23 ± 35.98 | 83.04 ± 34.74 | <.0001 |

Table 2. Baseline characteristics of the group classified by only insulin and the number of anti-diabetic medication. Data are presented as mean ± S.D. or Number(%). DM: Diabetes Mellitus, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, eGFR: Estimated Glomerular Filtration Rate.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | With Insuiln | | | | | | | | |
|  | Met + SU | Met + DPP-4i | Met + TZD | Met + AGI | SU + TZD | SU + AGI | Other dual therapy | More than dual therapy | P-value |
| **Number** | 16217 | 1504 | 453 | 3274 | 391 | 1617 | 1835 | 5111 |
| **Age (year)** | 59.75 ± 9.95 | 58.95 ± 10.29 | 59.17 ± 9.83 | 60.42 ± 9.58 | 61.53 ± 9.71 | 62.83 ± 9.6 | 60.54 ± 9.92 | 60.71 ± 9.8 | <.0001 |
| **Gender, male (%)** | 8651 (53.35) | 832 (55.32) | 259 (57.17) | 1717 (52.44) | 228 (58.31) | 871 (53.87) | 1041 (56.73) | 2830 (55.37) | <.0001 |
| **DM duration, ≥ 5yrs(%)** | 14126 (87.11) | 946 (62.9) | 393 (86.75) | 3110 (94.99) | 333 (85.17) | 1496 (92.52) | 1664 (90.68) | 4556 (89.14) | <.0001 |
| **Income, low 20% (%)** | 3940 (24.3) | 367 (24.4) | 114 (25.17) | 719 (21.96) | 97 (24.81) | 355 (21.95) | 386 (21.04) | 1244 (24.34) | <.0001 |
| **Hypertension (%)** | 10763 (66.37) | 931 (61.9) | 309 (68.21) | 2291 (69.98) | 271 (69.31) | 1124 (69.51) | 1247 (67.96) | 3349 (65.53) | <.0001 |
| **Dyslipidemia (%)** | 9315 (57.44) | 773 (51.4) | 264 (58.28) | 1924 (58.77) | 211 (53.96) | 945 (58.44) | 1052 (57.33) | 2754 (53.88) | <.0001 |
| **Smoking (%)** |  |  |  |  |  |  |  |  | <.0001 |
| Non | 9750 (60.12) | 849 (56.45) | 261 (57.62) | 2022 (61.76) | 225 (57.54) | 1000 (61.84) | 1094 (59.62) | 3037 (59.42) |  |
| Ex | 2765 (17.05) | 258 (17.15) | 87 (19.21) | 580 (17.72) | 63 (16.11) | 314 (19.42) | 368 (20.05) | 828 (16.2) |  |
| Current | 3702 (22.83) | 397 (26.4) | 105 (23.18) | 672 (20.53) | 103 (26.34) | 303 (18.74) | 373 (20.33) | 1246 (24.38) |  |
| **Drinking (%)** |  |  |  |  |  |  |  |  | <.0001 |
| Non | 11271 (69.5) | 964 (64.1) | 311 (68.65) | 2386 (72.88) | 259 (66.24) | 1182 (73.1) | 1312 (71.5) | 3603 (70.5) |  |
| Mild | 3711 (22.88) | 403 (26.8) | 113 (24.94) | 695 (21.23) | 100 (25.58) | 330 (20.41) | 402 (21.91) | 1152 (22.54) |  |
| Heavy | 1235 (7.62) | 137 (9.11) | 29 (6.4) | 193 (5.89) | 32 (8.18) | 105 (6.49) | 121 (6.59) | 356 (6.97) |  |
| **Regular exercise (%)** | 3208 (19.78) | 304 (20.21) | 84 (18.54) | 688 (21.01) | 78 (19.95) | 351 (21.71) | 428 (23.32) | 1021 (19.98) | <.0001 |
| **Body Mass Index (kg/m2)** | 25.05 ± 3.32 | 24.93 ± 3.65 | 25.85 ± 3.95 | 24.65 ± 3.28 | 25 ± 3.54 | 24.56 ± 3.38 | 24.5 ± 3.34 | 24.71 ± 3.41 | <.0001 |
| **SBP (mmHg)** | 128.65 ± 16.18 | 128.55 ± 16.78 | 129.66 ± 15.74 | 127.51 ± 16 | 128.57 ± 17.25 | 128.07 ± 16.38 | 126.89 ± 16.69 | 127.84 ± 16.22 | <.0001 |
| **DBP (mmHg)** | 77.54 ± 10.07 | 78.65 ± 10.67 | 77.52 ± 10.07 | 76.49 ± 9.94 | 77.5 ± 11.01 | 76.58 ± 10.17 | 76.07 ± 10.09 | 77.18 ± 10.05 | <.0001 |
| **Total cholesterol (mg/dL)** | 185.37 ± 44.04 | 196.38 ± 47.97 | 187.3 ± 40.8 | 179.03 ± 41.76 | 193.43 ± 41.6 | 184.02 ± 44.44 | 178.99 ± 43.04 | 188.66 ± 43.87 | <.0001 |
| **Fasting Glucose (mg/dL)** | 160.27 ± 64.6 | 169.48 ± 66.66 | 130.9 ± 40.0 | 150.05 ± 63.21 | 165.71 ± 69.96 | 156.04 ± 63.95 | 152.27 ± 65.48 | 168.37 ± 68.41 | <.0001 |
| **eGFR (mL/min/m2)** | 83.03 ± 34.88 | 87.01 ± 46.72 | 85.1 ± 39.1 | 82.89 ± 35.9 | 76.6 ± 46.36 | 73.08 ± 28.62 | 78.64 ± 54.25 | 81.98 ± 34.35 | <.0001 |

**Table 3. Baseline characteristics of those treated with dual oral anti-diabetic medication with insulin**, **Data are presented as mean ± S.D. or Number(%).**  **SU: Sulfonylurea, Met: Metformin, TZD: thiazolidinediones, DPP-4i: dipeptidyl peptidase 4 inhibitor, Megl: Meglitinide, AGI: alpha-glucosidase inhibitor.**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **With Insulin** | | | | | | | | | | |
|  | | N | | n | | PY | | Incident Rate  (Per 1,000 PY) | MODEL 1  HR (95% CI) | MODEL 2  HR (95% CI) | MODEL 3  HR (95% CI) |
| **All-cause dementia** | |  | |  | |  | |  |  |  |  |
| Met + SU | | 16217 | | 1454 | | 90359.31 | | 16.0913 | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| Met + DPP-4i | | 1504 | | 103 | | 7974.05 | | 12.9169 | 0.816 (0.668, 0.996) | 0.908 (0.742, 1.111) | 0.906 (0.741, 1.108) |
| Met + TZD | | 453 | | 38 | | 2651.43 | | 14.3319 | 0.876 (0.635, 1.209) | 1.034 (0.749, 1.427) | 1.05 (0.761, 1.449) |
| Met + AGI | | 3274 | | 334 | | 19394.95 | | 17.221 | 1.054 (0.936, 1.187) | 1.023 (0.908, 1.152) | 1.028 (0.912, 1.159) |
| SU + TZD | | 391 | | 41 | | 2251.44 | | 18.2106 | 1.107 (0.812, 1.511) | 1.014 (0.743, 1.383) | 1.011 (0.741, 1.38) |
| SU + AGI | | 1617 | | 220 | | 9070.97 | | 24.2532 | 1.484 (1.288, 1.71) | 1.163 (1.009, 1.34) | 1.143 (0.991, 1.318) |
| Other dual therapy | | 1835 | | 176 | | 10670.98 | | 16.4933 | 1.01 (0.863, 1.181) | 0.953 (0.814, 1.114) | 0.946 (0.808, 1.107) |
| > Dual therapy | | 5111 | | 563 | | 29278.5 | | 19.2291 | 1.179 (1.069, 1.299) | 1.134 (1.029, 1.25) | 1.102 (1, 1.215) |
| **Alzheimer’s dementia** | |  | |  | |  | |  |  |  |  |
| Met + SU | | 16217 | | 1110 | | 90359.31 | | 12.2843 | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| Met + DPP-4i | | 1504 | | 83 | | 7974.05 | | 10.4088 | 0.865 (0.692, 1.081) | 0.967 (0.773, 1.211) | 0.963 (0.769, 1.206) |
| Met + TZD | | 453 | | 30 | | 2651.43 | | 11.3146 | 0.901 (0.627, 1.296) | 1.076 (0.749, 1.547) | 1.088 (0.757, 1.565) |
| Met + AGI | | 3274 | | 276 | | 19394.95 | | 14.2305 | 1.135 (0.995, 1.295) | 1.105 (0.968, 1.261) | 1.111 (0.973, 1.268) |
| SU + TZD | | 391 | | 34 | | 2251.44 | | 15.1014 | 1.195 (0.85, 1.682) | 1.097 (0.779, 1.543) | 1.1 (0.782, 1.548) |
| SU + AGI | | 1617 | | 172 | | 9070.97 | | 18.9616 | 1.513 (1.288, 1.777) | 1.18 (1.004, 1.386) | 1.164 (0.991, 1.368) |
| Other dual therapy | | 1835 | | 133 | | 10670.98 | | 12.4637 | 0.994 (0.83, 1.19) | 0.937 (0.783, 1.122) | 0.931 (0.778, 1.116) |
| > Dual therapy | | 5111 | | 426 | | 29278.5 | | 14.5499 | 1.163 (1.04, 1.3) | 1.121 (1.003, 1.254) | 1.092 (0.977, 1.222) |
| **Vascular dementia** | |  | |  | |  | |  |  |  |  |
| Met + SU | | 16217 | | 273 | | 90359.31 | | 3.02127 | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| Met + DPP-4i | | 1504 | | 10 | | 7974.05 | | 1.25407 | 0.422 (0.225, 0.793) | 0.472 (0.251, 0.89) | 0.472 (0.251, 0.889) |
| Met + TZD | | 453 | | 7 | | 2651.43 | | 2.64008 | 0.861 (0.406, 1.822) | 0.983 (0.464, 2.082) | 1.013 (0.478, 2.146) |
| Met + AGI | 3274 | | 55 | | 19394.95 | | 2.83579 | | 0.924 (0.691, 1.234) | 0.881 (0.659, 1.178) | 0.887 (0.663, 1.187) |
| SU + TZD | 391 | | 6 | | 2251.44 | | 2.66496 | | 0.865 (0.385, 1.943) | 0.795 (0.354, 1.786) | 0.777 (0.346, 1.746) |
| SU + AGI | 1617 | | 37 | | 9070.97 | | 4.07895 | | 1.331 (0.944, 1.876) | 1.073 (0.761, 1.514) | 1.055 (0.748, 1.49) |
| Other dual therapy | 1835 | | 38 | | 10670.98 | | 3.56106 | | 1.16 (0.826, 1.629) | 1.096 (0.78, 1.539) | 1.098 (0.781, 1.544) |
| > Dual therapy | 5111 | | 115 | | 29278.5 | | 3.9278 | | 1.283 (1.031, 1.595) | 1.232 (0.991, 1.533) | 1.192 (0.958, 1.484) |

Table 4. Incidence rates and hazard ratios of dementia, Alzheimer’s dementia, and vascular dementia by dual oral anti-diabetic medication with insulin exposure. N: cases followed, n: incident cases of dementia, PY: Person-Years, HR: hazard ratio, CI: confidence interval. SU: Sulfonylurea, Met: Metformin, TZD: thiazolidinediones, DPP-4i: dipeptidyl peptidase 4 inhibitor, Megl: Meglitinide, AGI: alpha-glucosidase inhibitor, MODEL 1: adjusted for gender, income, hypertension, dyslipidemia, duration of diabetes, Model 1: unadjusted, MODEL 2: adjusted for Model 2 + smoking, drinking, exercise, body mass index, fasting glucose, estimated glomerular filtration rate