**Supplementary files**

S1 Read codes used for Type 2 diabetes

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S4 Baseline demographic characteristics, behavioural risk factors, diabetes complications, comorbidities, metabolic characteristics, and medications for the rest four imputed propensity score matched datasets

S5 Risk of developing COVID-19, mortality, and back pain among those with a current combination prescription of metformin and other glucose-lowering agents compared to a current prescription of other glucose-lowering agents only (reference group) by sex and by body mass index (Subgroup analyses)

S6 Baseline demographic characteristics, behavioural risk factors, diabetes complications, comorbidities, metabolic characteristics, and medications (Sensitivity analysis)

S7 Risk of developing COVID-19, mortality, and back pain among those with a current combination prescription of metformin and other glucose-lowering agents compared to a current prescription of other glucose-lowering agents only (Sensitivity analysis)

**Supplementary S1 Read codes used for Type 2 diabetes**

C106100 Diabetes mellitus, adult onset, + neurological manifestation

C109611 Type II diabetes mellitus with retinopathy

C109212 Type 2 diabetes mellitus with neurological complications

C109.13 Type II diabetes mellitus

C109.12 Type 2 diabetes mellitus

C109211 Type II diabetes mellitus with neurological complications

C10FE00 Type 2 diabetes mellitus with diabetic cataract

C10FQ00 Type 2 diabetes mellitus with exudative maculopathy

C109.11 NIDDM - Non-insulin dependent diabetes mellitus

C109J00 Insulin treated Type 2 diabetes mellitus

C10FM00 Type 2 diabetes mellitus with persistent microalbuminuria

C10F111 Type II diabetes mellitus with ophthalmic complications

C109F00 Non-insulin-dependent d m with peripheral angiopath

C10F911 Type II diabetes mellitus without complication

C10F511 Type II diabetes mellitus with gangrene

C109B00 Non-insulin dependent diabetes mellitus with polyneuropathy

C10FA11 Type II diabetes mellitus with mononeuropathy

C100112 Non-insulin dependent diabetes mellitus

C109500 Non-insulin dependent diabetes mellitus with gangrene

C10FJ11 Insulin treated Type II diabetes mellitus

C109100 Non-insulin-dependent diabetes mellitus with ophthalm comps

C10FF11 Type II diabetes mellitus with peripheral angiopathy

C109J12 Insulin treated Type II diabetes mellitus

C10FR11 Type II diabetes mellitus with gastroparesis

C109J11 Insulin treated non-insulin dependent diabetes mellitus

C109F12 Type 2 diabetes mellitus with peripheral angiopathy

C10D.00 Diabetes mellitus autosomal dominant type 2

C10F100 Type 2 diabetes mellitus with ophthalmic complications

C10FN11 Type II diabetes mellitus with ketoacidosis

C109F11 Type II diabetes mellitus with peripheral angiopathy

C10F900 Type 2 diabetes mellitus without complication

C109B12 Type 2 diabetes mellitus with polyneuropathy

C10F500 Type 2 diabetes mellitus with gangrene

C109B11 Type II diabetes mellitus with polyneuropathy

C10FA00 Type 2 diabetes mellitus with mononeuropathy

C109612 Type 2 diabetes mellitus with retinopathy

C109511 Type II diabetes mellitus with gangrene

C10FH00 Type 2 diabetes mellitus with neuropathic arthropathy

C109512 Type 2 diabetes mellitus with gangrene

C104100 Diabetes mellitus, adult onset, with renal manifestation

C109111 Type II diabetes mellitus with ophthalmic complications

C10FD00 Type 2 diabetes mellitus with hypoglycaemic coma

C109112 Type 2 diabetes mellitus with ophthalmic complications

C10FP00 Type 2 diabetes mellitus with ketoacidotic coma

C10FL00 Type 2 diabetes mellitus with persistent proteinuria

C10F011 Type II diabetes mellitus with renal complications

C109E00 Non-insulin depend diabetes mellitus with diabetic cataract

C10F411 Type II diabetes mellitus with ulcer

C109A00 Non-insulin dependent diabetes mellitus with mononeuropathy

C109900 Non-insulin-dependent diabetes mellitus without complication

C107100 Diabetes mellitus, adult, + peripheral circulatory disorder

C10z100 Diabetes mellitus, adult onset, + unspecified complication

C109400 Non-insulin dependent diabetes mellitus with ulcer

C10FE11 Type II diabetes mellitus with diabetic cataract

C109000 Non-insulin-dependent diabetes mellitus with renal comps

C10FQ11 Type II diabetes mellitus with exudative maculopathy

C10FM11 Type II diabetes mellitus with persistent microalbuminuria

C10F000 Type 2 diabetes mellitus with renal complications

C109E11 Type II diabetes mellitus with diabetic cataract

C109E12 Type 2 diabetes mellitus with diabetic cataract

C10F400 Type 2 diabetes mellitus with ulcer

C109912 Type 2 diabetes mellitus without complication

C109412 Type 2 diabetes mellitus with ulcer

C109411 Type II diabetes mellitus with ulcer

C10FK00 Hyperosmolar non-ketotic state in type 2 diabetes mellitus

C109012 Type 2 diabetes mellitus with renal complications

C109011 Type II diabetes mellitus with renal complications

C10FG00 Type 2 diabetes mellitus with arthropathy

C10F311 Type II diabetes mellitus with multiple complications

C109H00 Non-insulin dependent d m with neuropathic arthropathy

C109D00 Non-insulin dependent diabetes mellitus with hypoglyca coma

C10F711 Type II diabetes mellitus - poor control

C10FC11 Type II diabetes mellitus with nephropathy

C10FH11 Type II diabetes mellitus with neuropathic arthropathy

C105100 Diabetes mellitus, adult onset, + ophthalmic manifestation

C107400 NIDDM with peripheral circulatory disorder

C109300 Non-insulin-dependent diabetes mellitus with multiple comps

C10FD11 Type II diabetes mellitus with hypoglycaemic coma

C10FP11 Type II diabetes mellitus with ketoacidotic coma

C109H12 Type 2 diabetes mellitus with neuropathic arthropathy

C10F300 Type 2 diabetes mellitus with multiple complications

C10FL11 Type II diabetes mellitus with persistent proteinuria

C109H11 Type II diabetes mellitus with neuropathic arthropathy

C109D12 Type 2 diabetes mellitus with hypoglycaemic coma

C109D11 Type II diabetes mellitus with hypoglycaemic coma

C10F700 Type 2 diabetes mellitus - poor control

C102100 Diabetes mellitus, adult onset, with hyperosmolar coma

C10FC00 Type 2 diabetes mellitus with nephropathy

C10y100 Diabetes mellitus, adult, + other specified manifestation

C109311 Type II diabetes mellitus with multiple complications

C10FJ00 Insulin treated Type 2 diabetes mellitus

C109312 Type 2 diabetes mellitus with multiple complications

C10FF00 Type 2 diabetes mellitus with peripheral angiopathy

C10F.11 Type II diabetes mellitus

C109K00 Hyperosmolar non-ketotic state in type 2 diabetes mellitus

C10FR00 Type 2 diabetes mellitus with gastroparesis

C10P111 Type 2 diabetes mellitus in remission

C10F211 Type II diabetes mellitus with neurological complications

C109G00 Non-insulin dependent diabetes mellitus with arthropathy

C10FN00 Type 2 diabetes mellitus with ketoacidosis

C109C00 Non-insulin dependent diabetes mellitus with nephropathy

C10F611 Type II diabetes mellitus with retinopathy

C10FB11 Type II diabetes mellitus with polyneuropathy

C109700 Non-insulin dependent diabetes mellitus - poor control

C109600 Non-insulin-dependent diabetes mellitus with retinopathy

C10FK11 Hyperosmolar non-ketotic state in type II diabetes mellitus

C109200 Non-insulin-dependent diabetes mellitus with neuro comps

C10FG11 Type II diabetes mellitus with arthropathy

C10F.00 Type 2 diabetes mellitus

C109.00 Non-insulin dependent diabetes mellitus

C10P100 Type II diabetes mellitus in remission

C10F200 Type 2 diabetes mellitus with neurological complications

C109G12 Type 2 diabetes mellitus with arthropathy

C109C11 Type II diabetes mellitus with nephropathy

C109C12 Type 2 diabetes mellitus with nephropathy

C10F600 Type 2 diabetes mellitus with retinopathy

D10z100 Diabetes mellitus, adult onset, no mention of complication

C10FB00 Type 2 diabetes mellitus with polyneuropathy

C109711 Type II diabetes mellitus - poor control

C109712 Type 2 diabetes mellitus - poor control

**Supplementary S2** **Read codes used for suspected or confirmed COVID-19**

|  |  |  |
| --- | --- | --- |
| **Description** | **Code** | **Confirmed(C)/**  **Suspected(S)** |
| Has immunity to SARS-CoV-2 | 43dt400 | C |
| SARS-CoV-2 IgG detected | 43dtA00 | C |
| SARS-CoV-2 IgM detected | 43dtG00 | C |
| Detection of SARS-CoV-2 by PCR | 43hF.00 | C |
| Coronavirus nucleic acid detection | 43jS.00 | C |
| 2019-nCoV (novel coronavirus) detected | 4J3R100 | C |
| Gastroenteri due to SARS-CoV-2 | A076400 | C |
| Coronavirus infection | A795.00 | C |
| Disease caused by 2019-nCoV (novel coronavirus) | A795100 | C |
| Coronavirus as cause of dis classified to other chapters | A7y0000 | C |
| [X]Coronavirus infection, unspecified | AyuDC00 | C |
| [X]Coronavirus/cause/diseases classified to other chapters | AyuKL00 | C |
| Encephalopat due to SARS-CoV-2 | F289.00 | C |
| Otitis media due to SARS-CoV-2 | F529.00 | C |
| Myocarditis due to SARS-CoV-2 | G520800 | C |
| Cardiomyopathy due SARS-CoV-2 | G558500 | C |
| URTI due to SARS-CoV-2 | H051100 | C |
| Pneumonia due to SARS-CoV-2 | H204.00 | C |
| COVID-19 confirmed by laboratory test | A795200 | C |
| COVID-19 confirmed using clinical diagnostic criteria | A795300 | C |
| Suspected coronavirus infection | 1JX..00 | S |
| Suspected disease caused by 2019-nCoV (novel coronavirus) | 1JX1.00 | S |
| Telephone consultation for suspected 2019-nCoV (novel corona | 9N31200 | S |

**Supplementary** **S3 Flow diagram in detail**

Adult individuals (≥18 years old) with a record of type 2 diabetes and registered with an eligible general practice no later than 30th January 2019 (one year before the index date) were eligible for this study (N = 131,341). Any individuals who were diagnosed with diabetes before the age of 12 years or with a record of type 1 diabetes (N = 7,411), adverse reaction to glucose-lowering agents, pancreatitis or pregnancy in the preceding year (N = 2,705), estimated glomerular filtration rate (eGFR) measurement less than 30 mL/min/1.73m2 before the index date (N = 2,919), were excluded. There were 118,306 individuals who met our selection criteria.

We then excluded individuals who were not prescribed any of the nine glucose-lowering agents (N = 24,686). Following this, we excluded patients who did not have evidence of any prescription during study period (N = 21,986).

Among individuals who were on a current metformin prescription (N = 59,724), we excluded those who were on metformin monotherapy (N = 30,166). Therefore, there were 29,558 individuals who are on a current metformin prescription (extending into the pandemic period) and co-prescribed at least one of the eight other glucose-lowering agents. These patients were included in the exposed cohort.

Among individuals who were not on a current metformin prescription and have a prescription for any of the eight other glucose-lowering agents extending into the pandemic period (N = 11,910), we excluded those who were prescribed metformin within 90 days preceding the index date (recent users, N = 1,639). Overall, there are 10,271 individuals who were not current or recent users of metformin and had a prescription for any of other eight glucose-lowering agents extending into the pandemic period. These patients were included in the comparator cohort. Of 10,271 individuals, 8,640 with a historical prescription of metformin were then included in the comparator group of the sensitivity analyses.

**Supplementary S4 Baseline demographic characteristics, behavioural risk factors, diabetes complications, comorbidities, metabolic characteristics, and medications for the rest four imputed propensity score matched datasets**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **the 2nd imputed PPS matched dataset** | | **the 3rd imputed PPS matched dataset** | | **the 4th imputed PPS matched dataset** | | **the 5th imputed PPS matched dataset** | |
|  | **Exposed  Group (MF+)  (n = 10,183)** | **Comparator group (MF-) (n = 10,183)** | **Exposed  Group (MF+)  (n = 10,183)** | **Comparator group (MF-) (n = 10,183)** | **Exposed  Group (MF+)  (n = 10,183)** | **Comparator group (MF-) (n = 10,183)** | **Exposed  Group (MF+)  (n = 10,183)** | **Comparator group (MF-) (n = 10,183)** |
| ***Demographic characteristics*** |  |  |  |  |  |  |  |  |
| Mean age (years) (SD) | 67.31 (11.77) | 67.68(13.12) | 67.29 (11.71) | 67.68(13.12) | 67.21 (11.82) | 67.68(13.12) | 67.27 (11.73) | 67.68(13.12) |
| Male sex (%) | 5354 (52.6) | 5326 (52.3) | 5372 (52.8) | 5326 (52.3) | 5347 (52.5) | 5326 (52.3) | 5307 (52.1) | 5326 (52.3) |
| Mean BMI (kg/m2) (SD)) | 31.94 (6.65) | 31.81 (6.83) | 31.97 (6.80) | 31.81 (6.83) | 31.90 (6.71) | 31.81 (6.83) | 31.94 (6.76) | 31.81 (6.83) |
| BMI category (%) |  |  |  |  |  |  |  |  |
| Underweight/Normal Weight (<24.9) | 1153 (11.3) | 1338 (13.1) | 1195 (11.7) | 1338 (13.1) | 1186 (11.6) | 1338 (13.1) | 1176 (11.5) | 1338 (13.1) |
| Overweight(25-29.9) | 3114 (30.6) | 3038 (29.8) | 3102 (30.5) | 3038 (29.8) | 3145 (30.9) | 3038 (29.8) | 3141 (30.8) | 3038 (29.8) |
| Obesity (>=30) | 5730 (56.3) | 5639 (55.4) | 5707 (56.0) | 5639 (55.4) | 5696 (55.9) | 5639 (55.4) | 5682 (55.8) | 5639 (55.4) |
| Missing | 186 (1.8) | 168 (1.6) | 179 (1.8) | 168 (1.6) | 156 (1.5) | 168 (1.6) | 184 (1.8) | 168 (1.6) |
| ***Behavioural risk factors*** |  |  |  |  |  |  |  |  |
| Smoking status (%) |  |  |  |  |  |  |  |  |
| Non-smokers | 5137 (50.4) | 5057 (49.7) | 5047 (49.6) | 5057 (49.7) | 4988 (49.0) | 5057 (49.7) | 5082 (49.9) | 5057 (49.7) |
| Ex-smokers | 3646 (35.8) | 3701 (36.3) | 3680 (36.1) | 3701 (36.3) | 3739 (36.7) | 3701 (36.3) | 3652 (35.9) | 3701 (36.3) |
| Current smokers | 1356 (13.3) | 1373 (13.5) | 1413 (13.9) | 1373 (13.5) | 1410 (13.8) | 1373 (13.5) | 1400 (13.7) | 1373 (13.5) |
| Missing | 44 (0.4) | 52 (0.5) | 43 (0.4) | 52 (0.5) | 46 (0.5) | 52 (0.5) | 49 (0.5) | 52 (0.5) |
| Excessive alcohol use (%) | 649 (6.4) | 657 (6.5) | 654 (6.4) | 657 (6.5) | 649 (6.4) | 657 (6.5) | 664 (6.5) | 657 (6.5) |
|  |  |  |  |  |  |  |  |  |
| Mean diabetes duration (yrs) (SD) | 11.65 (6.67) | 11.58 (7.00) | 11.55 (6.64) | 11.58 (7.00) | 11.57 (6.60) | 11.58 (7.00) | 11.59 (6.64) | 11.58 (7.00) |
| ***Diabetes complications*** |  |  |  |  |  |  |  |  |
| Peripheral neuropathy (%) | 763 (7.5) | 776 (7.6) | 760 (7.5) | 776 (7.6) | 785 (7.7) | 776 (7.6) | 767 (7.5) | 776 (7.6) |
| Diabetic foot disease (%) | 512 (5.0) | 518 (5.1) | 540 (5.3) | 518 (5.1) | 512 (5.0) | 518 (5.1) | 507 (5.0) | 518 (5.1) |
| Sight threating retinopathy (%) | 1245 (12.2) | 1264 (12.4) | 1247 (12.2) | 1264 (12.4) | 1253 (12.3) | 1264 (12.4) | 1250 (12.3) | 1264 (12.4) |
|  |  |  |  |  |  |  |  |  |
| ***Comorbidities*** |  |  |  |  |  |  |  |  |
| Hypertension (%) | 6232 (61.2) | 6178 (60.7) | 6181 (60.7) | 6178 (60.7) | 6128 (60.2) | 6178 (60.7) | 6180 (60.7) | 6178 (60.7) |
| Ischaemic heart disease (%) | 2204 (21.6) | 2237 (22.0) | 2212 (21.7) | 2237 (22.0) | 2199 (21.6) | 2237 (22.0) | 2207 (21.7) | 2237 (22.0) |
| Atrial Fibrillation (%) | 1026 (10.1) | 1077 (10.6) | 1033 (10.1) | 1077 (10.6) | 1064 (10.4) | 1077 (10.6) | 1047 (10.3) | 1077 (10.6) |
| Stroke/TIA (%) | 978 (9.6) | 970 (9.5) | 935 (9.2) | 970 (9.5) | 925 (9.1) | 970 (9.5) | 938 (9.2) | 970 (9.5) |
| Heart failure (%) | 709 (7.0) | 745 (7.3) | 739 (7.3) | 745 (7.3) | 711 (7.0) | 745 (7.3) | 717 (7.0) | 745 (7.3) |
| Peripheral Vascular Disease (%) | 486 (4.8) | 500 (4.9) | 487 (4.8) | 500 (4.9) | 489 (4.8) | 500 (4.9) | 504 (4.9) | 500 (4.9) |
| Chronic kidney disease (%) | 1888 (18.5) | 2428 (23.8) | 1891 (18.6) | 2428 (23.8) | 1875 (18.4) | 2428 (23.8) | 1857 (18.2) | 2428 (23.8) |
| Cancers\* (%) | 1494 (14.7) | 1474 (14.5) | 1460 (14.3) | 1474 (14.5) | 1470 (14.4) | 1474 (14.5) | 1456 (14.3) | 1474 (14.5) |
| Chronic respiratory disease (%) | 990 (9.7) | 1016 (10.0) | 1006 (9.9) | 1016 (10.0) | 1028 (10.1) | 1016 (10.0) | 1013 (9.9) | 1016 (10.0) |
| Liver Disease (%) | 579 (5.7) | 619 (6.1) | 567 (5.6) | 619 (6.1) | 593 (5.8) | 619 (6.1) | 583 (5.7) | 619 (6.1) |
| Rheumatoid Arthritis (%) | 229 (2.2) | 212 (2.1) | 213 (2.1) | 212 (2.1) | 220 (2.2) | 212 (2.1) | 225 (2.2) | 212 (2.1) |
| NAFLD/NASH (%) | 261 (2.6) | 261 (2.6) | 251 (2.5) | 261 (2.6) | 250 (2.5) | 261 (2.6) | 258 (2.5) | 261 (2.6) |
| Blood & bone marrow cancer (%) | 151 (1.5) | 162 (1.6) | 152 (1.5) | 162 (1.6) | 149 (1.5) | 162 (1.6) | 164 (1.6) | 162 (1.6) |
|  |  |  |  |  |  |  |  |  |
| ***Metabolic characteristics*** |  |  |  |  |  |  |  |  |
| Diastolic BP (mmHg) |  |  |  |  |  |  |  |  |
| <90 | 9492 (93.2) | 9450 (92.8) | 9483 (93.1) | 9450 (92.8) | 9498 (93.3) | 9450 (92.8) | 9462 (92.9) | 9450 (92.8) |
| ≥90 | 677 (6.6) | 720 (7.1) | 686 (6.7) | 720 (7.1) | 673 (6.6) | 720 (7.1) | 709 (7.0) | 720 (7.1) |
| Missing | 14 (0.1) | 13 (0.1) | 14 (0.1) | 13 (0.1) | 12 (0.1) | 13 (0.1) | 12 (0.1) | 13 (0.1) |
| Systolic BP (mmHg) |  |  |  |  |  |  |  |  |
| <140 | 7066 (69.4) | 7073 (69.5) | 7022 (69.0) | 7073 (69.5) | 7073 (69.5) | 7073 (69.5) | 7070 (69.4) | 7073 (69.5) |
| ≥140 | 3103 (30.5) | 3097 (30.4) | 3147 (30.9) | 3097 (30.4) | 3098 (30.4) | 3097 (30.4) | 3101 (30.5) | 3097 (30.4) |
| Missing | 14 (0.1) | 13 (0.1) | 14 (0.1) | 13 (0.1) | 12 (0.1) | 13 (0.1) | 12 (0.1) | 13 (0.1) |
| Total cholesterol (mmol/L) |  |  |  |  |  |  |  |  |
| <5.2 | 8157 (80.1) | 8064 (79.2) | 8167 (80.2) | 8064 (79.2) | 8103 (79.6) | 8064 (79.2) | 8147 (80.0) | 8064 (79.2) |
| 5.2 to 6.2 | 1233 (12.1) | 1367 (13.4) | 1209 (11.9) | 1367 (13.4) | 1246 (12.2) | 1367 (13.4) | 1224 (12.0) | 1367 (13.4) |
| ≥6.2 | 724 (7.1) | 675 (6.6) | 743 (7.3) | 675 (6.6) | 759 (7.5) | 675 (6.6) | 736 (7.2) | 675 (6.6) |
| Missing | 69 (0.7) | 77 (0.8) | 64 (0.6) | 77 (0.8) | 75 (0.7) | 77 (0.8) | 76 (0.7) | 77 (0.8) |
| HDL-cholesterol (mmol/L) |  |  |  |  |  |  |  |  |
| <1.55 | 8742 (85.8) | 8669 (85.1) | 8763 (86.1) | 8669 (85.1) | 8797 (86.4) | 8669 (85.1) | 8716 (85.6) | 8669 (85.1) |
| ≥1.55 | 1266 (12.4) | 1296 (12.7) | 1240 (12.2) | 1296 (12.7) | 1201 (11.8) | 1296 (12.7) | 1277 (12.5) | 1296 (12.7) |
| Missing | 175 (1.7) | 218 (2.1) | 180 (1.8) | 218 (2.1) | 185 (1.8) | 218 (2.1) | 190 (1.9) | 218 (2.1) |
| eGFR (mL/min/1.73m2) |  |  |  |  |  |  |  |  |
| >=60 (Stage 1&2) | 7517 (73.8) | 7258 (71.3) | 7590 (74.5) | 7258 (71.3) | 7555 (74.2) | 7258 (71.3) | 7562 (74.3) | 7258 (71.3) |
| 30 to 60 (Stage 3) | 2624 (25.8) | 2885 (28.3) | 2554 (25.1) | 2885 (28.3) | 2591 (25.4) | 2885 (28.3) | 2580 (25.3) | 2885 (28.3) |
| Missing | 42 (0.4) | 40 (0.4) | 39 (0.4) | 40 (0.4) | 37 (0.4) | 40 (0.4) | 41 (0.4) | 40 (0.4) |
| ACR (mg/mmol) |  |  |  |  |  |  |  |  |
| < 3 mg/mmol | 4892 (48.0) | 4819 (47.3) | 4869 (47.8) | 4819 (47.3) | 4932 (48.4) | 4819 (47.3) | 4901 (48.1) | 4819 (47.3) |
| ≥30 mg/mmol | 471 (4.6) | 470 (4.6) | 452 (4.4) | 470 (4.6) | 451 (4.4) | 470 (4.6) | 465 (4.6) | 470 (4.6) |
| 3 to 30 mg/mmol | 2287 (22.5) | 2258 (22.2) | 2260 (22.2) | 2258 (22.2) | 2266 (22.3) | 2258 (22.2) | 2265 (22.2) | 2258 (22.2) |
| Missing | 2533 (24.9) | 2636 (25.9) | 2602 (25.6) | 2636 (25.9) | 2534 (24.9) | 2636 (25.9) | 2552 (25.1) | 2636 (25.9) |
| HbA1c (mmol/mol) |  |  |  |  |  |  |  |  |
| < 48 mmol/mol (6.5%) | 908 (8.9) | 1042 (10.2) | 894 (8.8) | 1042 (10.2) | 914 (9.0) | 1042 (10.2) | 916 (9.0) | 1042 (10.2) |
| ≥58 mmol/mol (7.5%) | 6459 (63.4) | 6369 (62.5) | 6463 (63.5) | 6369 (62.5) | 6406 (62.9) | 6369 (62.5) | 6468 (63.5) | 6369 (62.5) |
| 48 to 58 mmol/mol (6.5-7.5%) | 2653 (26.1) | 2624 (25.8) | 2644 (26.0) | 2624 (25.8) | 2679 (26.3) | 2624 (25.8) | 2627 (25.8) | 2624 (25.8) |
| Missing | 163 (1.6) | 148 (1.5) | 182 (1.8) | 148 (1.5) | 184 (1.8) | 148 (1.5) | 172 (1.7) | 148 (1.5) |
|  |  |  |  |  |  |  |  |  |
| ***Medications*** |  |  |  |  |  |  |  |  |
| Metformin (%) |  |  |  |  |  |  |  |  |
| Current users | 10183(100.0) | 0 (0.0) | 10183(100.0) | 0 (0.0) | 10183(100.0) | 0 (0.0) | 10183(100.0) | 0 (0.0) |
| Recent users | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Historical users | 0 (0.0) | 8587 (84.3) | 0 (0.0) | 8587 (84.3) | 0 (0.0) | 8587 (84.3) | 0 (0.0) | 8587 (84.3) |
| Non-users | 0 (0.0) | 1596 (15.7) | 0 (0.0) | 1596 (15.7) | 0 (0.0) | 1596 (15.7) | 0 (0.0) | 1596 (15.7) |
| DPP4i (%) |  |  |  |  |  |  |  |  |
| Current users | 4117 (40.4) | 4222 (41.5) | 4112 (40.4) | 4222 (41.5) | 4181 (41.1) | 4222 (41.5) | 4193 (41.2) | 4222 (41.5) |
| Recent users | 152 (1.5) | 146 (1.4) | 141 (1.4) | 146 (1.4) | 135 (1.3) | 146 (1.4) | 150 (1.5) | 146 (1.4) |
| Historical users | 1874 (18.4) | 1795 (17.6) | 1794 (17.6) | 1795 (17.6) | 1820 (17.9) | 1795 (17.6) | 1795 (17.6) | 1795 (17.6) |
| Non-users | 4040 (39.7) | 4020 (39.5) | 4136 (40.6) | 4020 (39.5) | 4047 (39.7) | 4020 (39.5) | 4045 (39.7) | 4020 (39.5) |
| SGLT2i (%) |  |  |  |  |  |  |  |  |
| Current users | 2891 (28.4) | 2780 (27.3) | 2936 (28.8) | 2780 (27.3) | 2888 (28.4) | 2780 (27.3) | 2873 (28.2) | 2780 (27.3) |
| Recent users | 103 (1.0) | 102 (1.0) | 105 (1.0) | 102 (1.0) | 97 (1.0) | 102 (1.0) | 105 (1.0) | 102 (1.0) |
| Historical users | 854 (8.4) | 836 (8.2) | 828 (8.1) | 836 (8.2) | 858 (8.4) | 836 (8.2) | 859 (8.4) | 836 (8.2) |
| Non-users | 6335 (62.2) | 6465 (63.5) | 6314 (62.0) | 6465 (63.5) | 6340 (62.3) | 6465 (63.5) | 6346 (62.3) | 6465 (63.5) |
| Meglitinides (%) |  |  |  |  |  |  |  |  |
| Current users | 15 (0.1) | 13 (0.1) | 15 (0.1) | 13 (0.1) | 20 (0.2) | 13 (0.1) | 16 (0.2) | 13 (0.1) |
| Recent users | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Historical users | 108 (1.1) | 118 (1.2) | 128 (1.3) | 118 (1.2) | 120 (1.2) | 118 (1.2) | 122 (1.2) | 118 (1.2) |
| Non-users | 10060 (98.8) | 10052 (98.7) | 10040 (98.6) | 10052 (98.7) | 10043 (98.6) | 10052 (98.7) | 10045 (98.6) | 10052 (98.7) |
| Acarbose (%) |  |  |  |  |  |  |  |  |
| Current users | 19 (0.2) | 15 (0.1) | 15 (0.1) | 15 (0.1) | 14 (0.1) | 15 (0.1) | 16 (0.2) | 15 (0.1) |
| Recent users | 1 (0.0) | 1 (0.0) | 3 (0.0) | 1 (0.0) | 0 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) |
| Historical users | 104 (1.0) | 103 (1.0) | 107 (1.1) | 103 (1.0) | 101 (1.0) | 103 (1.0) | 100 (1.0) | 103 (1.0) |
| Non-users | 10059 (98.8) | 10064 (98.8) | 10058 (98.8) | 10064(98.8) | 10068 (98.9) | 10064(98.8) | 10066 (98.9) | 10064(98.8) |
| GLP1 (%) |  |  |  |  |  |  |  |  |
| Current users | 594 (5.8) | 586 (5.8) | 619 (6.1) | 586 (5.8) | 607 (6.0) | 586 (5.8) | 630 (6.2) | 586 (5.8) |
| Recent users | 165 (1.6) | 156 (1.5) | 154 (1.5) | 156 (1.5) | 161 (1.6) | 156 (1.5) | 163 (1.6) | 156 (1.5) |
| Historical users | 1030 (10.1) | 954 (9.4) | 1006 (9.9) | 954 (9.4) | 998 (9.8) | 954 (9.4) | 960 (9.4) | 954 (9.4) |
| Non-users | 8394 (82.4) | 8487 (83.3) | 8404 (82.5) | 8487 (83.3) | 8417 (82.7) | 8487 (83.3) | 8430 (82.8) | 8487 (83.3) |
| Insulin (%) |  |  |  |  |  |  |  |  |
| Current users | 993 (9.8) | 1006 (9.9) | 970 (9.5) | 1006 (9.9) | 975 (9.6) | 1006 (9.9) | 1000 (9.8) | 1006 (9.9) |
| Recent users | 358 (3.5) | 360 (3.5) | 347 (3.4) | 360 (3.5) | 338 (3.3) | 360 (3.5) | 351 (3.4) | 360 (3.5) |
| Historical users | 1155 (11.3) | 1169 (11.5) | 1195 (11.7) | 1169 (11.5) | 1189 (11.7) | 1169 (11.5) | 1183 (11.6) | 1169 (11.5) |
| Non-users | 7677 (75.4) | 7648 (75.1) | 7671 (75.3) | 7648 (75.1) | 7681 (75.4) | 7648 (75.1) | 7649 (75.1) | 7648 (75.1) |
| Thiazolidinedione (%) |  |  |  |  |  |  |  |  |
| Current users | 541 (5.3) | 542 (5.3) | 542 (5.3) | 542 (5.3) | 587 (5.8) | 542 (5.3) | 547 (5.4) | 542 (5.3) |
| Recent users | 26 (0.3) | 32 (0.3) | 32 (0.3) | 32 (0.3) | 30 (0.3) | 32 (0.3) | 33 (0.3) | 32 (0.3) |
| Historical users | 1460 (14.3) | 1388 (13.6) | 1404 (13.8) | 1388 (13.6) | 1392 (13.7) | 1388 (13.6) | 1418 (13.9) | 1388 (13.6) |
| Non-users | 8156 (80.1) | 8221 (80.7) | 8205 (80.6) | 8221 (80.7) | 8174 (80.3) | 8221 (80.7) | 8185 (80.4) | 8221 (80.7) |
| Sulphonylureas (%) |  |  |  |  |  |  |  |  |
| Current users | 4546 (44.6) | 4473 (43.9) | 4472 (43.9) | 4473 (43.9) | 4490 (44.1) | 4473 (43.9) | 4421 (43.4) | 4473 (43.9) |
| Recent users | 224 (2.2) | 231 (2.3) | 232 (2.3) | 231 (2.3) | 227 (2.2) | 231 (2.3) | 232 (2.3) | 231 (2.3) |
| Historical users | 2489 (24.4) | 2491 (24.5) | 2466 (24.2) | 2491 (24.5) | 2487 (24.4) | 2491 (24.5) | 2521 (24.8) | 2491 (24.5) |
| Non-users | 2924 (28.7) | 2988 (29.3) | 3013 (29.6) | 2988 (29.3) | 2979 (29.3) | 2988 (29.3) | 3009 (29.5) | 2988 (29.3) |
| Immunosuppressive drugs(%) | 566 (5.6) | 578 (5.7) | 544 (5.3) | 578 (5.7) | 565 (5.5) | 578 (5.7) | 557 (5.5) | 578 (5.7) |
| Systemic corticosteroids (%) | 1324 (13.0) | 1354 (13.3) | 1284 (12.6) | 1354 (13.3) | 1306 (12.8) | 1354 (13.3) | 1361 (13.4) | 1354 (13.3) |
| ACEi/ARB (%) | 7425 (72.9) | 7316 (71.8) | 7288 (71.6) | 7316 (71.8) | 7302 (71.7) | 7316 (71.8) | 7348 (72.2) | 7316 (71.8) |
| Other antihypertensives (%) | 7391 (72.6) | 7337 (72.1) | 7299 (71.7) | 7337 (72.1) | 7285 (71.5) | 7337 (72.1) | 7297 (71.7) | 7337 (72.1) |
| Anticoagulants (%) | 1706 (16.8) | 1731 (17.0) | 1691 (16.6) | 1731 (17.0) | 1703 (16.7) | 1731 (17.0) | 1706 (16.8) | 1731 (17.0) |
| Antiplatelets (%) | 5382 (52.9) | 5411 (53.1) | 5303 (52.1) | 5411 (53.1) | 5320 (52.2) | 5411 (53.1) | 5391 (52.9) | 5411 (53.1) |
| Lipid-lowering drugs (%) | 8673 (85.2) | 8686 (85.3) | 8698 (85.4) | 8686 (85.3) | 8700 (85.4) | 8686 (85.3) | 8715 (85.6) | 8686 (85.3) |
| BMI=Body mass index, TIA=transient ischaemic attack, NAFLD/NASH= non-alcoholic fatty liver disease or non-alcoholic steatohepatitis, ACR=albumin creatinine ratio, BP=blood pressure, eGFR=estimated glomerular filtration rate, HbA1c=haemoglobin A1c, HDL=high density lipoprotein, ACEi=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, DPP4i=dipeptidyl peptidase-4 inhibitors, GLP1=glucagon-like peptide 1 receptor agonist, SGLT2i=sodium-glucose co-transporter-2 inhibitors  Exposed group: patients with a current combination prescription of metformin and other glucose-lowering agents; Comparator group: patients with a current prescription of other glucose-lowering agents  \*Excluding melanoma, and blood and bone marrow cancers | | | | | | | | |

**Supplementary** **S5 Risk of developing COVID-19, mortality, and back pain among those with a current combination prescription of metformin and other glucose-lowering agents compared to a current prescription of other glucose-lowering agents only (reference group) by sex and by body mass index (Subgroup analyses)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Propensity score matched analysis**  **(Adjusted HR, 95% CI)** | **Confirmed**  **COVID-19** | | **Suspected/Confirmed COVID-19** | | **COVID-19 related death** | | **All-cause mortality** | | **Back Pain** | |
| **Exposed group**  **(MF+)** | **Comparator group  (MF-)** | **Exposed group**  **(MF+)** | **Comparator group  (MF-)** | **Exposed group**  **(MF+)** | **Comparator group  (MF-)** | **Exposed group**  **(MF+)** | **Comparator group  (MF-)** | **Exposed group**  **(MF+)** | **Comparator group  (MF-)** |
| **By Sex** |  |  |  |  |  |  |  |  |  |  |
| Male | 0.95 (0.51, 1.80) | | 0.94 (0.66, 1.34) | | 0.58 (0.17, 1.98) | | 0.75 (0.57, 0.97) | | 0.88 (0.53, 1.43) | |
| Female | 0.79 (0.42, 1.49) | | 0.83 (0.61, 1.14) | | 1.41 (0.55, 3.57) | | 0.98 (0.74, 1.29) | | 1.25 (0.81, 1.93) | |
|  |  |  |  |  |  |  |  |  |  |  |
| **By BMI** |  |  |  |  |  |  |  |  |  |  |
| BMI ≥ 25 kg/m2 | 0.88 (0.53, 1.43) | | 0.88 (0.53, 1.43) | | 0.88 (0.53, 1.43) | | 0.88 (0.53, 1.43) | | 0.88 (0.53, 1.43) | |
| BMI ≥ 30 kg/m2 | 0.93 (0.47, 1.82) | | 0.85 (0.61, 1.18) | | 0.66 (0.22, 1.98) | | 0.84 (0.63, 1.13) | | 1.07 (0.74, 1.54) | |
| † Adjusted for: age, sex, smoking status, high alcohol consumption (alcoholism), body mass index categories, total cholesterol categories, high-density lipoprotein categories, albumin-creatinine ratio categories, estimated glomerular filtration rate categories, HbA1c categories, atrial fibrillation, rheumatoid arthritis, hypertension, cardiovascular disease, non-alcoholic fatty liver disease or non-alcoholic steatohepatitis, prescriptions of renin angiotensin aldosterone system inhibitors, other antihypertensive drugs, lipid-lowering drugs, antiplatelets, anticoagulants, diabetes complications, diabetes duration, respiratory disease, cancers, immunosuppressant therapies, and systemic corticosteroid use. | | | | | | | | | | |

**Supplementary** **S6 Baseline demographic characteristics, behavioural risk factors, diabetes complications, comorbidities, metabolic characteristics, and medications (Sensitivity analysis)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Unmatched** | | **Propensity score matched†** | |
|  | **Exposed**  **Group (MF+) (n=29,558)** | **Comparator group (MF-)**  **(n=8,640)** | **Exposed**  **Group (MF+)** **(n=8,632)** | **Comparator group (MF-)** **(n= 8,632)** |
| ***Demographic characteristics*** |  |  |  |  |
| **Mean age (years) (SD)** | 64.8 (11.7) | 67.3 (12.8) | 67.0 (11.6) | 67.3 (12.8) |
| **Male sex (%)** | 18298 (61.9) | 4489 (52.0) | 4555 (52.8) | 4488 (52.0) |
| **Mean BMI (kg/m2) (SD))** | 32.1 (6.7) | 32.1 (6.8) | 32.0 (6.7) | 32.1 (6.8) |
| BMI category (%) |  |  |  |  |
| <25 | 3159 (10.7) | 1005 (11.6) | 971 (11.2) | 1003 (11.6) |
| 25 to < 30 | 9080 (30.7) | 2559 (29.6) | 2670 (30.9) | 2556 (29.6) |
| ≥30 | 16908 (57.2) | 4993 (57.8) | 4859 (56.3) | 4990 (57.8) |
| Missing | 411 (1.4) | 83 (1.0) | 132 (1.5) | 83 (1.0) |
|  |  |  |  |  |
| ***Behavioural risk factors*** |  |  |  |  |
| **Smoking status (%)** |  |  |  |  |
| Non-smokers | 14632 (49.5) | 4291 (49.7) | 4214 (48.8) | 4287 (49.7) |
| Ex-smokers | 10799 (36.5) | 3149 (36.4) | 3221 (37.3) | 3145 (36.4) |
| Current smokers | 4063 (13.7) | 1179 (13.6) | 1207 (14.0) | 1179 (13.7) |
| Missing | 64 (0.2) | 21 (0.2) | 26 (0.3) | 21 (0.2) |
| **Excessive alcohol use (%)** | 1506 (5.1) | 553 (6.4) | 547 (6.3) | 551 (6.4) |
|  |  |  |  |  |
| ***Diabetes complications*** |  |  |  |  |
| **Mean diabetes duration (yrs) (SD)** | 12.1 (6.7) | 11.9 (6.7) | 11.7 (6.6) | 11.9 (6.7) |
| **Peripheral neuropathy (%)** | 2070 (7.0) | 675 (7.8) | 688 (8.0) | 675 (7.8) |
| **Diabetic foot disease (%)** | 1335 (4.5) | 447 (5.2) | 434 (5.0) | 446 (5.2) |
| **Sight threating retinopathy (%)** | 3507 (11.9) | 1098 (12.7) | 1058 (12.3) | 1095 (12.7) |
|  |  |  |  |  |
| ***Comorbidities*** |  |  |  |  |
| **Hypertension (%)** | 17477 (59.1) | 5320 (61.6) | 5217 (60.4) | 5317 (61.6) |
| **Ischaemic heart disease (%)** | 5374 (18.2) | 1901 (22.0) | 1881 (21.8) | 1898 (22.0) |
| **Atrial Fibrillation (%)** | 2194 (7.4) | 867 (10.0) | 885 (10.3) | 865 (10.0) |
| **Stroke/TIA (%)** | 1992 (6.7) | 814 (9.4) | 801 (9.3) | 813 (9.4) |
| **Heart failure (%)** | 1322 (4.5) | 622 (7.2) | 614 (7.1) | 620 (7.2) |
| **Peripheral Vascular Disease (%)** | 1055 (3.6) | 424 (4.9) | 402 (4.7) | 421 (4.9) |
| **Chronic kidney disease (%)** | 3839 (13.0) | 1951 (22.6) | 1527 (17.7) | 1947 (22.6) |
| **Cancers\* (%)** | 3114 (10.5) | 1229 (14.2) | 1259 (14.6) | 1226 (14.2) |
| **Chronic respiratory disease (%)** | 2351 (8.0) | 846 (9.8) | 854 (9.9) | 845 (9.8) |
| **Liver Disease (%)** | 1636 (5.5) | 519 (6.0) | 480 (5.6) | 519 (6.0) |
| **Rheumatoid Arthritis (%)** | 442 (1.5) | 175 (2.0) | 174 (2.0) | 175 (2.0) |
| **NAFLD/NASH (%)** | 742 (2.5) | 236 (2.7) | 211 (2.4) | 236 (2.7) |
| **Blood & bone marrow cancer (%)** | 404 (1.4) | 142 (1.6) | 145 (1.7) | 141 (1.6) |
|  |  |  |  |  |
| ***Metabolic characteristics*** |  |  |  |  |
| **Diastolic BP (mmHg)** |  |  |  |  |
| <90 | 27474 (92.9) | 8015 (92.8) | 8061 (93.4) | 8009 (92.8) |
| ≥90 | 2052 (6.9) | 624 (7.2) | 561 (6.5) | 622 (7.2) |
| Missing | 32 (0.1) | 1 (0.0) | 10 (0.1) | 1 (0.0) |
| **Systolic BP (mmHg)** |  |  |  |  |
| <140 | 21102 (71.4) | 6009 (69.5) | 6084 (70.5) | 6006 (69.6) |
| ≥140 | 8424 (28.5) | 2630 (30.4) | 2538 (29.4) | 2625 (30.4) |
| Missing | 32 (0.1) | 1 (0.0) | 10 (0.1) | 1 (0.0) |
| **Total cholesterol (mmol/L)** |  |  |  |  |
| <5.2 | 25257 (85.4) | 6868 (79.5) | 6894 (79.9) | 6867 (79.6) |
| 5.2 to 6.2 | 2878 (9.7) | 1162 (13.4) | 1086 (12.6) | 1158 (13.4) |
| ≥6.2 | 1252 (4.2) | 580 (6.7) | 610 (7.1) | 577 (6.7) |
| Missing | 171 (0.6) | 30 (0.3) | 42 (0.5) | 30 (0.3) |
| **HDL-cholesterol (mmol/L)** |  |  |  |  |
| <1.55 | 26054 (88.1) | 7474 (86.5) | 7508 (87.0) | 7468 (86.5) |
| ≥1.55 | 3028 (10.2) | 1048 (12.1) | 983 (11.4) | 1047 (12.1) |
| Missing | 476 (1.6) | 118 (1.4) | 141 (1.6) | 117 (1.4) |
| **eGFR (mL/min/1.73m2)** |  |  |  |  |
| ≥60 (Stage 1&2) | 4991 (16.9) | 2329 (27.0) | 6527 (75.6) | 6289 (72.9) |
| 30 to 60 (Stage 3) | 24469 (82.8) | 6292 (72.8) | 2080 (24.1) | 2324 (26.9) |
| Missing | 98 (0.3) | 19 (0.2) | 25 (0.3) | 19 (0.2) |
| **ACR (mg/mmol)** |  |  |  |  |
|  |  |  |  |  |
| < 3 mg/mmol | 15119 (51.2) | 4251 (49.2) | 4219 (48.9) | 4250 (49.2) |
| 3 to 30 mg/mmol | 6144 (20.8) | 1980 (22.9) | 1930 (22.4) | 1978 (22.9) |
| ≥30 mg/mmol | 1052 (3.6) | 398 (4.6) | 376 (4.4) | 397 (4.6) |
| Missing | 7243 (24.5) | 2011 (23.3) | 2107 (24.4) | 2007 (23.3) |
| **HbA1c (mmol/mol)** |  |  |  |  |
| < 48 mmol/mol (6.5%) | 2654 (9.0) | 769 (8.9) | 692 (8.0) | 769 (8.9) |
| 48 to 58 mmol/mol (6.5-7.5%) | 7918 (26.8) | 2160 (25.0) | 2222 (25.7) | 2159 (25.0) |
| ≥58 mmol/mol (7.5%) | 18461 (62.5) | 5604 (64.9) | 5579 (64.6) | 5597 (64.8) |
| Missing | 525 (1.8) | 107 (1.2) | 139 (1.6) | 107 (1.2) |
|  |  |  |  |  |
| ***Medications*** |  |  |  |  |
| **Metformin (%)** |  |  |  |  |
| Current users | 29558 (100.0) | 0 (0.0) | 8632 (100.0) | 0 (0.0) |
| Recent users | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Historical users | 0 (0.0) | 8640 (100.0) | 0 (0.0) | 8632 (100.0) |
| Non-users | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **DPP4i (%)** |  |  |  |  |
| Current users | 13132 (44.4) | 3636 (42.1) | 3624 (42.0) | 3635 (42.1) |
| Recent users | 364 (1.2) | 136 (1.6) | 132 (1.5) | 135 (1.6) |
| Historical users | 4985 (16.9) | 1744 (20.2) | 1677 (19.4) | 1741 (20.2) |
| Non-users | 11077 (37.5) | 3124 (36.2) | 3199 (37.1) | 3121 (36.2) |
| **SGLT2i (%)** |  |  |  |  |
| Current users | 10661 (36.1) | 2547 (29.5) | 2615 (30.3) | 2546 (29.5) |
| Recent users | 278 (0.9) | 101 (1.2) | 100 (1.2) | 101 (1.2) |
| Historical users | 2055 (7.0) | 810 (9.4) | 803 (9.3) | 810 (9.4) |
| Non-users | 16564 (56.0) | 5182 (60.0) | 5114 (59.2) | 5175 (60.0) |
| **Meglitinides (%)** |  |  |  |  |
| Current users | 60 (0.2) | 10 (0.1) | 9 (0.1) | 10 (0.1) |
| Recent users | 6 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Historical users | 306 (1.0) | 113 (1.3) | 107 (1.2) | 113 (1.3) |
| Non-users | 29186 (98.7) | 8517 (98.6) | 8516 (98.7) | 8509 (98.6) |
| **Acarbose (%)** |  |  |  |  |
| Current users | 42 (0.1) | 9 (0.1) | 12 (0.1) | 9 (0.1) |
| Recent users | 4 (0.0) | 1 (0.0) | 0 (0.0) | 1 (0.0) |
| Historical users | 219 (0.7) | 101 (1.2) | 92 (1.1) | 101 (1.2) |
| Non-users | 29293 (99.1) | 8529 (98.7) | 8528 (98.8) | 8521 (98.7) |
| **GLP1 (%)** |  |  |  |  |
| Current users | 2081 (7.0) | 533 (6.2) | 565 (6.5) | 533 (6.2) |
| Recent users | 597 (2.0) | 145 (1.7) | 129 (1.5) | 145 (1.7) |
| Historical users | 2910 (9.8) | 914 (10.6) | 900 (10.4) | 913 (10.6) |
| Non-users | 23970 (81.1) | 7048 (81.6) | 7038 (81.5) | 7041 (81.6) |
| **Insulin (%)** |  |  |  |  |
| Current users | 1901 (6.4) | 810 (9.4) | 787 (9.1) | 807 (9.3) |
| Recent users | 859 (2.9) | 315 (3.6) | 307 (3.6) | 315 (3.6) |
| Historical users | 2613 (8.8) | 1069 (12.4) | 1038 (12.0) | 1066 (12.3) |
| Non-users | 24185 (81.8) | 6446 (74.6) | 6500 (75.3) | 6444 (74.7) |
| **Thiazolidinedione (%)** |  |  |  |  |
| Current users | 1683 (5.7) | 488 (5.6) | 474 (5.5) | 487 (5.6) |
| Recent users | 69 (0.2) | 30 (0.3) | 30 (0.3) | 30 (0.3) |
| Historical users | 4422 (15.0) | 1355 (15.7) | 1280 (14.8) | 1352 (15.7) |
| Non-users | 23384 (79.1) | 6767 (78.3) | 6848 (79.3) | 6763 (78.3) |
| **Sulphonylureas (%)** |  |  |  |  |
| Current users | 12979 (43.9) | 3707 (42.9) | 3719 (43.1) | 3706 (42.9) |
| Recent users | 565 (1.9) | 215 (2.5) | 203 (2.4) | 214 (2.5) |
| Historical users | 6363 (21.5) | 2357 (27.3) | 2291 (26.5) | 2352 (27.2) |
| Non-users | 9651 (32.7) | 2361 (27.3) | 2419 (28.0) | 2360 (27.3) |
| **Immunosuppressive drugs (%)** | 1070 (3.6) | 455 (5.3) | 447 (5.2) | 451 (5.2) |
| **Systemic corticosteroids (%)** | 3047 (10.3) | 1090 (12.6) | 1087 (12.6) | 1088 (12.6) |
| **ACEi/ARB (%)** | 21667 (73.3) | 6328 (73.2) | 6280 (72.8) | 6321 (73.2) |
| **Other antihypertensives (%)** | 19799 (67.0) | 6288 (72.8) | 6233 (72.2) | 6281 (72.8) |
| **Anticoagulants (%)** | 3628 (12.3) | 1431 (16.6) | 1419 (16.4) | 1428 (16.5) |
| **Antiplatelets (%)** | 14988 (50.7) | 4686 (54.2) | 4665 (54.0) | 4679 (54.2) |
| **Lipid-lowering drugs (%)** | 26074 (88.2) | 7530 (87.2) | 7550 (87.5) | 7525 (87.2) |
| BMI=Body mass index, TIA=transient ischaemic attack, NAFLD/NASH= non-alcoholic fatty liver disease or non-alcoholic steatohepatitis, ACR=albumin creatinine ratio, BP=blood pressure, eGFR=estimated glomerular filtration rate, HbA1c=haemoglobin A1c, HDL=high density lipoprotein, ACEi=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, DPP4i=dipeptidyl peptidase-4 inhibitors, GLP1=glucagon-like peptide 1 receptor agonist, SGLT2i=sodium-glucose co-transporter-2 inhibitors  Exposed group: patients with a current combination prescription of metformin and other glucose-lowering agents; Comparator group: patients with a current prescription of other glucose-lowering agents  \* Excluding melanoma, and blood and bone marrow cancers  † Data were presented for the first multiple imputed propensity score matched cohort. | | | | |

**Supplementary** **S7 Risk of developing COVID-19, mortality, and back pain among those with a current combination prescription of metformin and other glucose-lowering agents compared to a current prescription of other glucose-lowering agents only (Sensitivity analysis)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcomes** | **Confirmed**  **COVID-19** | | **Suspected/Confirmed COVID-19** | | **COVID-19 related death** | | **All-cause mortality** | | **Back pain** | |
| **Exposed group (MF+)** | **Comparator group**  **(MF-)** | **Exposed group (MF+)** | **Comparator group**  **(MF-)** | **Exposed group (MF+)** | **Comparator group**  **(MF-)** | **Exposed group**  **(MF+)** | **Comparator group**  **(MF-)** | **Exposed group**  **(MF+)** | **Comparator group**  **(MF-)** |
| **Unmatched analysis** |  |  |  |  |  |  |  |  |  |  |
| Total number of patients | 29,558 | 8,640 | 29,558 | 8,640 | 29,558 | 8,640 | 29,558 | 8,640 | 29,558 | 8,640 |
| Number of outcomes | 110 | 44 | 415 | 155 | 31 | 16 | 403 | 197 | 315 | 100 |
| Person-years (py) | 20,454 | 5,934 | 20,351 | 5,897 | 20,486 | 5,949 | 20,486 | 5,949 | 20,364 | 5,907 |
| Incidence rate (per 1000 py) | 5.4 | 7.4 | 20.4 | 26.3 | 1.5 | 2.7 | 19.7 | 33.1 | 15.5 | 16.9 |
| Crude hazard ratio (95%CI) | 0.73 (0.51, 1.03) | | 0.78 (0.65, 0.93) | | 0.56 (0.31, 1.03) | | 0.59 (0.50, 0.71) | | 0.91 (0.73, 1.15) | |
| Adjusted HR (95%CI)\* | 0.76 (0.54, 1.09) | | 0.84 (0.70, 1.01) | | 0.77 (0.41, 1.44) | | 0.83 (0.70, 0.99) | | 0.94 (0.75, 1.18) | |
|  |  | |  | |  | |  | |  | |
| **Matched analysis** |  |  |  |  |  |  |  |  |  |  |
| Total number of patients† | 8,632 | 8,632 | 8,632 | 8,632 | 8,632 | 8,632 | 8,632 | 8,632 | 8,632 | 8,632 |
| Number of outcomes† | 37 | 44 | 137 | 155 | 14 | 16 | 176 | 196 | 104 | 100 |
| Person-years (py) † | 5,950 | 5,929 | 5,918 | 5,892 | 5,959 | 5,944 | 5,959 | 5,944 | 5,918 | 5,902 |
| Incidence rate (per 1000 py) † | 6.2 | 7.4 | 23.2 | 26.3 | 2.4 | 2.7 | 29.5 | 33.0 | 17.6 | 16.9 |
| Crude hazard ratio (95%CI) ǂ | 0.80 (0.45, 1.43) | | 0.87 (0.66, 1.14) | | 0.77 (0.34, 1.71) | | 0.88 (0.71, 1.10) | | 0.97 (0.65, 1.44) | |
| Adjusted HR (95%CI)\* ǂ | 0.79 (0.44, 1.40) | | 0.86 (0.65, 1.13) | | 0.78 (0.34, 1.82) | | 0.92 (0.73, 1.17) | | 0.97 (0.65, 1.44) | |
| Exposed group: patients with a current combination prescription of metformin and other glucose-lowering agents; Comparator group: patients with a current prescription of other glucose-lowering agents  \* Adjusted for: age, sex, smoking status, high alcohol consumption (alcoholism), body mass index categories, total cholesterol categories, high-density lipoprotein categories, albumin-creatinine ratio categories, estimated glomerular filtration rate categories, HbA1c categories, atrial fibrillation, rheumatoid arthritis, hypertension, cardiovascular disease, non-alcoholic fatty liver disease or non-alcoholic steatohepatitis, prescriptions of renin angiotensin aldosterone system inhibitors, other antihypertensive drugs, lipid-lowering drugs, antiplatelets, anticoagulants, diabetes complications, diabetes duration, respiratory disease, cancers, immunosuppressant therapies, and systemic corticosteroid use.  † Data were presented for the first multiple imputed propensity score matched cohort.  ǂ Summarized results of Cox regression analyses from all multiple imputed propensity score matched cohorts using Rubin’s Rule | | | | | | | | | | |