

Supplementary file

Supplementary S1 Read codes used for Type 2 diabetes

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| 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 |

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| 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 |

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| 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 |

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| 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 |

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| 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 |
| Gastroenteritis 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 disease classified to other chapters | A7y0000 | C |
| [X]Coronavirus infection, unspecified | AyuDC00 | C |
| [X]Coronavirus/cause/diseases classified to other chapters | AyuKL00 | C |
| Encephalopathy 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) |
| <u>Demographic characteristics</u> | | | | | | | | |
| 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/m ²) (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) |
| <u>Behavioural risk factors</u> | | | | | | | | |
| 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) |
| <u>Diabetes complications</u> | | | | | | | | |
| 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) |

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|-----------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Sight threatening 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) |

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|------------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 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) |

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|-----------------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| 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/m ² | 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/m ² | 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) |
| <u>Demographic characteristics</u> | | | | |
| 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/m ²) (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) |
| <u>Behavioural risk factors</u> | | | | |
| 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) |
| <u>Diabetes complications</u> | | | | |
| 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 threatening retinopathy (%) | 3507 (11.9) | 1098 (12.7) | 1058 (12.3) | 1095 (12.7) |
| <u>Comorbidities</u> | | | | |
| 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)

| | Confirmed COVID-19 | | Suspected/Confirmed COVID-19 | | COVID-19 related death | | All-cause mortality | | Back pain | |
|---|---------------------|------------------------|------------------------------|------------------------|------------------------|------------------------|---------------------|------------------------|---------------------|------------------------|
| Outcomes | 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) [‡] | 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) ^{* ‡} | 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.

[‡] Summarized results of Cox regression analyses from all multiple imputed propensity score matched cohorts using Rubin's Rule