# Appendix

# Appendix to Chapter 1

## A1.1 Search strategy for pre-clinical evidence on the effects of statins in depression

***MEDLINE Ovid SP***

#1 exp Depressive disorder/
#2 Depression/
#3 (depress$ OR dysthymi$ OR mood OR affective disorder* OR affective symptom*).ti,ab,kf
#4 or/1-3
#5 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
#6 (statin$ OR atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin).tw
#7 or/5-6
#8 4 AND 7

***Embase Ovid SP***

#1 exp Depression/
#2 (depress$ OR dysthymi$ OR mood OR affective disorder* OR affective symptom*).ti,ab,kw
#3 or/1-2
#4 exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
#5 (statin$ OR atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin).tw
#6 or/4-5
#7 3 AND 6

***PsycINFO Ovid SP***

#1 depression.hw

#2 (depress$ OR dysthymi$ OR mood OR affective disorder* OR affective symptom*).ti,ab,id
#3 or/1-2
#4 exp statins/
#5 (statin$ OR atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin).tw
#6 or/4-5
#7 3 AND 6

## A1.2 Search strategy for clinical evidence on the effects of statins in depression

("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]) OR *statin OR statins) AND ("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depressive Disorder, Treatment-Resistant"[Mesh] OR "Depressive Disorder, Major"[Mesh] OR "Sleep"[Mesh] OR "Sleep Wake Disorders"[Mesh] OR "Sleep Initiation and Maintenance Disorders"[Mesh] OR "Sleep Stages"[Mesh] OR "Sleep, REM"[Mesh] OR "Sleep Disorders, Circadian Rhythm"[Mesh] OR "Anhedonia"[Mesh] OR "Anxiety"[Mesh] OR "Anxiety Disorders"[Mesh] OR "Psychomotor Disorders"[Mesh] OR depression OR depressive OR sleep OR insomnia OR sleep disorder OR anhedonia OR anxiety OR psychomotor retardation OR psychomotor impairment OR anx* OR antidepress*)

## A1.3 Studies for clinical evidence on the effects of statins in depression

***A1.3 Table 1*** *Effects of statins on the risk of developing depression in non-depressed patients*

| Study ID | Design | Population | Exposure | Comparison | Follow-up | Primary outcome | Major findings | Association |
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| *Meta-analyses* | | | | | | | | |
| Lee 2020 | Pair-wise meta-analysis | 13 observational studies, 5,035,070 participants | Statin use | No use | NR | Diagnosis of depression | OR 0.87<br>95%CI 0.74 to 1.02, p NR | = |
| Parsaik 2014 | Pair-wise meta-analysis | 7 observational studies, 9,187 participants | Statin use | No use | 5 years | Diagnosis of depression | OR 0.68<br>95%CI 0.52 to 0.89, p 0.01 | + |
| Zhang 2022 | Pair-wise meta-analysis | 19 observational studies, 178,278 participants | Statin use | No use | NR | Diagnosis of depression | OR 0.78<br>95%CI 0.57 to 1.06, p 0.12 | = |
| *Cohort studies* | | | | | | | | |
| Asplund 2011 | Cohort | 70,706 ischemic stroke patients | Statin prescription on discharge | No prescription on discharge | 3 months | Diagnosis of post-stroke depression or antidepressant prescription (self-reported) | OR 0.99<br>95%CI 0.95 to 1.03, p NR | = |
| Chuang 2014 | Historical cohort | 26,852 hyperlipidaemic patients | Statin use | No use | 4 years | Diagnosis of depression | HR 0.81<br>95%CI 0.69 to 0.96, p <0.05 | + |
| Dave 2018 | Historical cohort | 299,298 statin users | Lipophilic statin use (atorvastatin, lovastatin, simvastatin) | Hydrophilic statin use (pravastatin, rosuvastatin) | 3 years | Diagnosis of depression | Lipophilic *vs* hydrophilic statin HR 1.05<br>95%CI 1.00 to 1.10, p 0.078<br>Simvastatin *vs* hydrophilic statin HR 1.09<br>95%CI 1.02 to 1.16, p 0.003 | N/A |
| Glaus 2015 | Cohort | 1,631 adults | Statin use (self-reported) | No use (self-reported) | 5.2 years | Diagnosis of depression | HR 1.25<br>95%CI 0.73 to 2.14, p >0.05 | = |
| Huang 2017 | Cohort | 408 HNC hyperlipidaemic patients | Statin use | No use | 1 year | Diagnosis of depression | HR 0.85<br>95%CI 0.46 to 1.57, p 0.42 | = |

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|---|---|---|---|---|---|---|---|---|
| Kang 2016 | Cohort | 286 ischemic stroke adults | Statin use | No use | 1 year | Diagnosis of post-stroke depression | Wald 8.477<br>95%CI NR, p 0.004 | + |
| Kang 2015 | Cohort | 11,218 ischemic stroke patients | Statin use | No use | 1 year | Diagnosis of post-stroke depression | HR 1.59<br>95%CI 1.30 to 1.95, p <0.001 | - |
| Katzan 2017 | Historical cohort | 803 ischemic stroke patients with elevated hs-CRP | Statin use | No use | NR | PHQ-9 | MD -1.91<br>95%CI -3.34 to -0.47, p NR | + |
| Kessing 2019 | Historical cohort | 497,080 statin users | Statin use | No use | 21 years | Diagnosis of depression or antidepressant prescription | Trend test for statin prescription 0.92<br>95%CI 0.92 to 0.95, p <0.001 | + |
| Kim 2018 | Cohort | 711 ACS patients | Statin use | No use | 1 year | Diagnosis of depression | Prevalence difference -9.5% for statin users<br>95%CI NR, p 0.037 | + |
| Kim 2014 | Cohort | 288 ischemic stroke patients | Statin use | No use | 1 year | Diagnosis of post-stroke depression | OR 0.54<br>95%CI 0.49 to 0.87, p NR | + |
| Khokhar 2018 | Historical cohort | 100,515 TBI patients aged ≥65 years | Statin use | No use | 6 months | Diagnosis of depression | RR 0.85<br>95%CI 0.79 to 0.90, p NR | + |
| Köhler-Forsberg 2019 | Historical cohort | 387,954 adults | Statin prescription redemption | No prescription | 6.8 years | Diagnosis of depression | HR 1.33<br>95%CI 1.31 to 1.35, p NR | - |
| Li 2021 | Cohort | 1,371 ischemic stroke patients | Statin use pre- and post-stroke | Statin use pre-stroke | 1 year | Diagnosis of post-stroke depression | HR 1.99<br>95%CI NR, p 0.037 | - |
| Mansi 2013 | Historical cohort | 13,944 adults | Statin use | No use | 4.5 years | Diagnosis of mood disorder | OR 1.02<br>95%CI 0.94 to 1.11, p 0.6 | = |
| Medici 2017 | Cohort | 12,176 ICU patients | Statin use | No use | 3 years | Diagnosis of depression or antidepressant prescription | RR 1.04<br>95%CI 0.96 to 1.13, p NR | = |
| Molero 2020 | Historical cohort, within-subject | 1,149,384 statin users | Statin use | No use | 8 years | Diagnosis of depressive episode (unplanned hospital visit or specialised outpatient care) | HR 0.91<br>95%CI 0.88 to 0.94, p NR | + |
| Otte 2012 | Cohort | 776 CAD patients | Statin use | No use | 6 years | Diagnosis of depression (PHQ≥10) | OR 0.62<br>95%CI 0.41 to 0.95, p 0.026 | + |

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| | Cross-sectional | 965 CAD patients | Statin use | No use | N/A | Diagnosis of depression (PHQ≥10) | OR 0.66<br>95%CI 0.45 to 0.98, p 0.04 | + |
| Pasco 2010 | Historical cohort | 345 adult women | Statin or aspirin use (self-reported) | No use | 10 years | Diagnosis of first-episode depression | HR 0.20<br>95%CI 0.04 to 0.85, p 0.03 | + |
| | Case-control | 345 adult women | Statin use prior to depression onset (self-reported) | No use | 10 years | Diagnosis of first-episode depression | OR 0.13<br>95%CI 0.02 to 1.02, p >0.05 | = |
| Redlich 2014 | Cohort | 4,607,990 adults | Statin prescription | No prescription | 3 years | Diagnosis of depression | OR 0.92<br>95%CI 0.89 to 0.96, p 0.016 | + |
| Smeeth 2009 | Cohort | 729,529 adults | Statin prescription | No prescription | 4.3 years | Antidepressant prescription | HR 1.01<br>99%CI 0.96 to 1.06, p NR | = |
| Stafford 2011 | Cohort | 193 MI, PTCA, or CABG hospitalised patients | Statin prescription | No prescription | 9 months | Diagnosis of depression | OR 0.21<br>95%CI 0.05 to 0.88, p 0.032 | + |
| Wang 2017 | Cohort | 1,023 ischemic stroke patients | Statin use | No use | 3 months, 3 years | Diagnosis of depression | 3-month OR 0.69<br>95%CI 0.49 to 0.96, p 0.028<br><br>3-year OR 0.40<br>95%CI 0.20 to 0.90, p 0.021 | + |
| Wee 2016 | Cohort | 3,792 TBI patients | Statin use in hyperlipidaemia (SHL) | Untreated hyperlipidaemia (UHL), normolipidaemia [NL] | 3 years | Diagnosis of depression | SHL vs NL HR 1.02<br>95%CI 0.55 to 1.89, p 0.9611<br><br>SHL vs UHL HR 0.63<br>95%CI 0.34 to 1.17, p 0.143 | = |
| Williams 2016 | Historical cohort | 836 adult men | Statin or aspirin use | No use | 6 years | Diagnosis of mood disorder | HR 0.55<br>95%CI 0.23 to 1.32, p 0.18 | = |
| | Case-control | 937 adult men | Statin or aspirin use | No use | N/A | Diagnosis of mood disorder | OR 0.1<br>95%CI 0.1 to 0.4, p <0.001 | + |
| Wium-Andersen 2017a | Historical cohort | 91,842 ACS patients, 91,860 non-ACS | Statin use | No use | 12 years | Diagnosis of early (<1 year) or late (1-12 years) | Early depression<br>ACS HR 0.94 | + |

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| | | matched individuals | | | | depression or antidepressant prescription | 95%CI 0.86 to 0.94, p NR<br>Non-ACS HR 1.04<br>95%CI 0.96 to 1.12, p NR<br><br>Late depression<br>ACS HR 0.96<br>95%CI 0.82 to 0.90, p NR<br>Non-ACS HR 1.00<br>95%CI 0.95 to 1.06, p NR | |
| Wium-Andersen 2017b | Historical cohort | 147,487 ischemic stroke patients, 160,235 non-stroke matched individuals | Statin use | No use | 1 year, 12 years | Diagnosis of early (<1 year) or late (1-12 years) depression or antidepressant prescription | Early depression<br>Stroke HR 0.71<br>95%CI 0.70 to 0.73, p NR<br>Non-stroke HR 1.00<br>95%CI 0.94 to 1.05, p NR<br><br>Late depression<br>Stroke HR 0.90<br>95%CI 0.87 to 0.93, p NR<br>Non-stroke HR 0.90<br>95%CI 0.86 to 0.94, p NR | + |
| Yeh 2019 | Historical cohort | 9,139 asthma-COPD overlap syndrome patients | Statin use | No use | 11 years | Diagnosis of depression | HR 0.36<br>95%CI 0.25 to 0.53, p <0.001 | + |
| Young-Xu 2003 | Cohort | 371 CAD patients | Statin use | No use | 4 years | Diagnosis of depression (Kellner Symptom questionnaire ≥7) | OR 0.63<br>95%CI 0.43 to 0.93, p NR | + |
| *Case-control studies* | | | | | | | | |
| Yang 2003 | Case-control | 366 hyperlipidaemic patients | Statin use | No use | N/A | Diagnosis of depression | OR 0.4<br>95%CI 0.2 to 0.9, p <0.05 | + |
| *Cross-sectional studies* | | | | | | | | |

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| Agustini 2019 | Cross-sectional | 19,114 community-dwelling participants aged ≥70 years | Statin use (self-reported) | No use (self-reported) | N/A | Diagnosis of depression (CES-D≥ 8) | OR 1.09<br>95%CI 0.98 to 1.20, p 0.11 | = |
| Alghamdi 2018 | Cross-sectional (mendelian randomisation) | 188,000 adults | Statin use | No use | N/A | Diagnosis of depression | OR 1.12<br>95%CI 1.04 to 1.18, p <0.001 | - |
| Asuzu 2015 | Cross-sectional | 208 healthy older adults | Statin use | No use | N/A | Diagnosis of depression | OR 2.50<br>95%CI 1.10 to 5.60, p 0.004 | - |
| Boumendil 1995 | Cross-sectional | 17,244 adults | Simvastatin use (self-reported) | No use (self-reported) | N/A | Absenteeism due to depression | PR 2.18<br>95%CI 1.18 to 4.03, p NR | - |
| Feng 2008 | Cross-sectional | 2,804 adults | Statin use (self-reported) | No use (self-reported) | N/A | Diagnosis of depression (GDS≥ 5) | OR 0.71<br>95%CI 0.52 to 0.97, p NR | + |
| Leutner 2021 | Cross-sectional | 7,481,168 adults | Statin use | No use | N/A | Diagnosis of depression | OR 1.22<br>95%CI 1.20 to 1.25, p NR | - |
| Lindberg 1998 | Cross-sectional | 166 antidepressant and statin users | Statin prescription redemption | No prescription redemption | N/A | Antidepressant prescription redemption before vs after redemption of statin | RR 1.06<br>95%CI 0.79 to 1.45, p NR | = |
| Williams 2015 | Cross-sectional | 638 White Europeans, 695 South Asians and African-Caribbean | Statin prescription | No prescription | N/A | Diagnosis of depression (GDS≥ 4) | White European OR 0.54<br>95%CI 0.26 to 1.13, p NR<br>South Asian and African-Caribbean OR 1.67<br>95%CI 0.97 to 2.88, p NR | = |
| *Case series* | | | | | | | | |
| Cham 2016 | Case series | 11 male and 1 female patients | Statin treatment (simvastatin, atorvastatin, rosuvastatin, lovastatin, pravastatin) for 1 | N/A | N/A | N/A | Episodes of violent ideation, irritability, depression, and suicide were reported. All 12 cases resolved upon discontinuation and recurred with re-challenge when attempted. Four cases met Naranjo criteria for definite causality, 4 for probable causality, 4 for possible causality. | - |

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| | | | day to several months | | | | | |
| Davidson 1996 | Case series | 6 hyperlipidaemic male patients | Pravastatin, lovastatin, simvastatin | N/A | N/A | N/A | The CES-D scale was completed before and after statin treatment in 6 male hypercholesterolemic patients. Patients' cholesterol levels were reduced after the 6 weeks, 4 patients' depression scores increased, of which 2 met criteria for mild clinical depression. | - |
| Duits 1993 | Case series | 4 female patients | Simvastatin | N/A | N/A | N/A | Two patients developed psychotic, obsessive, depressive symptoms, and suicidal/homicidal thoughts, and required treatment with clomipramine and cognitive therapy.<br>One patient developed paranoid thoughts, suicidality, agitation, and depressive symptoms after 4 days of simvastatin; symptoms resolved upon discontinuation.<br>One patient suffered a depressive syndrome with psychotic features after 3 months of simvastatin; management with discontinuation, antipsychotic and antihypertensive medications was necessary. | - |
| Lechleitner 1992 | Case series | 4 hyperlipidaemic female patients | Pravastatin 10mg for 12 weeks | N/A | N/A | N/A | 3 patients developed mild-moderate depressive symptoms reversed by discontinuation. 1 patient developed severe psychiatric symptoms and suicidality, improved on discontinuation and did not re-occur with lovastatin treatment. | - |
| Rosenson 1993 | Case series | 2 hyperlipidaemic male patients | Lovastatin 20-60mg/die | N/A | N/A | N/A | 2 patients developed sleep disturbances, anxious mood, and irritability after several weeks of lovastatin treatment (20 mg/die and 60mg/die); symptoms reversed 48h after discontinuation, and reoccurred upon re-challenge, but not upon starting of pravastatin treatment. | - |
| Tatley 2007 | Case series | Adverse reaction reports to New Zealand Centre for Adverse | Statin treatment (simvastatin, atorvastatin, Fluvastatin, pravastatin) | N/A | N/A | N/A | 203 reports of psychiatric adverse events associated with statins (67 reports of mood disorders, 30 of cognitive disorders, 51 of sleep disorders, 14 of perception disorders, 107 other reactions such as asthenia, fatigue, lethargy). | - |

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| | | Reaction Monitoring | | | | | Fifty-seven reactions were severe, 34 had documented recurrence upon re-challenge | |

ACS: Acute Coronary Syndrome, CABG: Coronary Artery Bypass Graft, CAD: Coronary Artery Disease, CES-D: Centre for Epidemiological Studies-Depression scale, CI: Confidence Interval, COPD: Chronic Obstructive Pulmonary Disease, GDS: Geriatric Depression Scale, hs-CRP: high-sensitivity C-reactive protein, HNC: Head and Neck Cancer, HR: Hazard Ratio, ICU: Intensive Care Unit, MD: Mean Difference, MI: Myocardial Infarction, PHQ: Patient Health Questionnaire, PR: Prevalence Ratio, PTCA: Percutaneous Transluminal Coronary Angioplasty, OR: Odds Ratio, RR: Relative Risk, SD: Standard Deviation, TBI: Traumatic Brain Injury

***A1.3 Table 2*** *Effects of statins on depressive symptoms in non-depressed participants*

| Study ID | Design | Population | Intervention/Exposure | Comparison | Follow-up | Primary outcome | Major findings | Association |
|---|---|---|---|---|---|---|---|---|
| *Meta-analyses* | | | | | | | | |
| Köhler-Forsberg 2019 | Pair-wise meta-analysis | 7 RCTs, 1,576 depressed and non-depressed participants | Atorvastatin, simvastatin, lovastatin, pravastatin | Placebo | 6 weeks to 4 years | Any standardised depression scale | SMD -0.26<br>95% CI -0.48 to -0.04, p 0.02 | + |
| O'Neil 2012 | Pair-wise meta-analysis | 7 RCTs, 2,105 depressed and non-depressed participants | Simvastatin, lovastatin, pravastatin | Placebo | 4 weeks to 4 years | Any standardised depression scale | SMD -0.43<br>95%CI -0.61 to -0.24, p NR | = |
| Lee 2021 | Network meta-analysis | 13 RCTs, 2,479 depressed and non-depressed participants | Atorvastatin, simvastatin, lovastatin, pravastatin, rosuvastatin | Placebo (network including any other statin) | 4 weeks to 4 years | Any standardised depression scale | SMD -0.35<br>95%CI -0.59 to -0.11, p 0.004 | + |
| Yatham 2019 | Pair-wise meta-analysis | 10 RCTs, 2,517 depressed and non-depressed participants | Atorvastatin, simvastatin, lovastatin, pravastatin | Placebo | 6 weeks to 4 years | Any standardised depression scale | SMD -0.31<br>95%CI -0.52 to -0.09, p 0.005 | + |
| *Clinical trials* | | | | | | | | |
| Carlsson 2002 | RCT crossover | 41 hyperlipidaemic adults aged ≥70 years | Pravastatin 20mg → pravastatin 20mg + tocopherol 400IU | Placebo + tocopherol → | 1 year | GDS | SMD 0.07<br>95%CI -0.57 to 0.71, p 0.622 | = |

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| | | | | pravastatin + tocopherol | | | | |
| Chan 2017 | RCT | 140 secondary progressive multiple sclerosis patients | Simvastatin 80mg | Placebo | 2 years | HDRS | SMD -1.00<br>95%CI -3.20 to 1.20, p 0.37 | = |
| Gengo 1995 | RCT crossover | 36 hyperlipidaemic patients | Lovastatin 40mg, pravastatin 40mg | Placebo | 4 weeks | POMS | SMD -0.63<br>95%CI -1.21 to -0.05, p 0.032 | + |
| Harrison 1994 | RCT crossover | 25 healthy volunteers | Simvastatin 40mg, pravastatin 40mg | Placebo | 4 weeks | HADS | SMD 0.05<br>95%CI -0.51 to 0.60, p 0.866 | = |
| Hyyppä 2003 | RCT crossover | 120 hyperlipidaemic men aged 35-64 years | Simvastatin 20mg | Placebo | 24 weeks | BDI | MD 0.06<br>95%CI 0.01 to 0.12, p 0.0159 | - |
| Krysiak 2018 | Non-randomised non-controlled trial | 14 hyperlipidaemic women, 14 normolipidaemic women | Atorvastatin 20-40mg in hyperlipidaemia | No treatment in normolipidaemia | 24 weeks | BDI | Baseline 11.6 (3.7) vs 7.6 (3.9)<br>SMD NR<br>95%CI NR, p <0.05<br><br>End of study 9.4 (3.0) vs 8.0 (4.3)<br>SMD NR<br>95%CI NR, p NR | + |
| Morales 2006 | RCT | 80 older adults aged ≥65 years | Simvastatin 20mg | Placebo | 15 weeks | CES-D | SMD 0.00<br>95%CI -0.46 to 0.46, p NR | = |
| Muldoon 2000 | RCT | 209 hyperlipidaemic adults | Lovastatin 20mg | Placebo | 6 months | HDRS | SMD 0.21<br>95%CI -0.07 to 0.49, p >0.2 | = |
| Ormiston 2003 | Non-randomised non-controlled trial | 12 healthy volunteers | Atorvastatin 10-20mg, lovastatin 20-40mg | N/A | 1 year | BDI | $t_{11}$ 2.27<br>95%CI NR, , p <0.05 | + |

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| Robertson 2017 | RCT | 52 mild TBI patients | Atorvastatin 1mg/kg/die (up to 80mg/die) | Placebo | 3 months | CES-D | SMD 0.05<br>95%CI -0.49 to 0.59, p 0.857 | = |
| Santanello 1997 | RCT | 431 adults aged ≥65 years | Lovastatin 20-40mg | Placebo | 6 months | CES-D | SMD -0.08<br>95%CI -0.29 to 0.14, p 0.53 | = |
| Sparks 2005 | RCT | 63 mild-to-moderate Alzheimer disease patients | Atorvastatin 80mg | Placebo | 52 weeks | GDS | MD -2.52<br>95%CI -3.18 to -1.87, p NR | + |
| Sheridan 2014 | RCT | 60 hepatitis C patients | Fluvastatin 40-80mg68 | Placebo | 3 months | HADS | Change HADS MD -0.11<br>SE 0.76, , p 0.886 | = |
| Stewart 2000 | RCT | 1,130 adults with CAD and hyperlipidaemia | Pravastatin 40mg | Placebo | 4 years | GHQ | MD 0.49<br>95%CI -0.30 to 1.28, p 0.23 | = |
| Visseren 2001 | RCT | 87 T2DM and dyslipidaemia patients | Fluvastatin 40mg | Placebo | 3 months | Zung self-rating depression scale | SMD -0.28<br>95%CI -0.70 to 0.14, p NR | = |
| Wardle 1996 | RCT | 621 adults with CAD | Simvastatin 20-40mg | Placebo | 152 weeks | POMS | SMD -0.40<br>95%CI -0.60 to -0.21, p <0.001 | = |
| *Cohort studies* | | | | | | | | |
| Al Badarin 2013 | Cohort | 1,691 ACS patients | Statin prescription | No prescription | 1 year | PHQ-9 | MD -0.05<br>95%CI -0.67 to 0.58, p 0.88 | = |
| Feng 2010 | Cohort | 1,803 adults | Statin use | No use | 1.5 years | GDS | Regression coefficient -0.12<br>95%CI NR, F 1.44, p 0.23 | = |
| Hoogwegt 2013 | Cohort | 409 ICD-implanted patients | Statin use | No use | 1 year | HADS | MD -0.97<br>95%CI -1.99 to 0.05, p 0.60 | = |
| *Cross-sectional studies* | | | | | | | | |
| Agostini 2007 | Cross-sectional | 756 community-dwelling | Statin use | No use | N/A | CES-D | SMD -0.18<br>95%CI -0.69 to 0.33, p 0.49 | = |

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| | | veterans aged ≥65 years | | | | | | |
| Mandas 2014 | Cross-sectional | 329 adults with dyslipidaemia aged ≥65 years | Statin use | No use | N/A | GDS | SMD 0.46<br>95%CI NR, p 0.0183 | - |
| Olson 2008 | Cross-sectional | 525 women undergoing coronary angiography | Cholesterol-lowering drug use (self-reported) | No use (self-reported) | N/A | BDI | SMD NR<br>95%CI NR, p 0.94 | = |

ACS: Acute Coronary Syndrome, BDI: Beck Depression Inventory, BSI : Brief Symptom Inventory, CAD: Coronary Artery Disease, CES-D: Centre for Epidemiological Studies – Depression scale, CI: Confidence Interval, GDS: Geriatric Depression Scale, GHQ: General Health Questionnaire, HADS: Hospital Anxiety and Depression Scale, HDRS: Hamilton Depression Rating Scale, ICD: Implantable Cardioverter-Defibrillator, MD: Mean Difference, MSQ: Mood States Questionnaire, PHQ: Patient Health Questionnaire, POMS: Profile Of Mood Scores, PR: Prevalence Ratio, OR: Odds Ratio, RCT: Randomised Controlled Trial, SD: Standard Deviation, SMD: Standardized Mean Difference, T2DM: Type 2 Diabetes Mellitus, TBI: Traumatic Brain Injury

***A1.3 Table 3*** *Effects of statins on the risk of developing depressive episodes or on depressive symptoms in depressed patients*

| Study ID | Design | Population | Intervention/Exposure | Comparison | Follow-up | Primary outcome | Major findings | Association |
|---|---|---|---|---|---|---|---|---|
| *Meta-analyses* | | | | | | | | |
| Bai 2020 | Pair-wise meta-analysis | 3 RCTs, 166 MDD patients | TAU + statin | TAU + placebo | 6 to 12 weeks | Any standardised depression scale | SMD -0.65<br>95%CI -0.96 to -0.33, p <0.0001 | + |
| Hang 2021 | Network meta-analysis | 3 RCTs, 164 MDD patients (network including 39 RCTs, 2871 MDD patients) | TAU + statin | TAU + placebo (network including NSAIDs, corticosteroids, pioglitazone, minocycline, NAC, omega-3 FA | 6 to 12 weeks (network including 2 to 16 weeks) | Any standardised depression scale | RR 0.68<br>95%CI 0.38 to 1.18, p NR | = |

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| Salagre 2016 | Pair-wise meta-analysis | 3 RCTs, 165 MDD patients | TAU + statin | TAU + placebo | 6 to 12 weeks | Any standardised depression scale | SMD -0.73<br>95%CI -1.04 to -0.42, p <0.001 | + |
| *Clinical trials* | | | | | | | | |
| Abbasi 2015 | RCT | 46 post-CABG patients with mild to moderate depression | Simvastatin 20mg | Atorvastatin 20mg | 6 weeks | HDRS | SMD 3.63<br>95%CI 0.44 to 6.51, p 0.03 | N/A |
| Berk 2020 | RCT | 130 MDD patients aged 15 to 25 years | TAU + rosuvastatin 10mg | TAU + placebo | 12 weeks | MADRS | SMD -4.2<br>95%CI -9.1 to 0.6, p 0.089 | = |
| Ghanizadeh 2013 | RCT | 68 MDD patients | Fluoxetine 40mg + lovastatin 30mg | Fluoxetine 40mg + placebo | 6 weeks | HDRS | SMD -0.77<br>95%CI -1.30 to -0.24, p <0.001 | + |
| Gougol 2015 | RCT | 48 MDD patients | Fluoxetine 20mg + simvastatin 20mg | Fluoxetine 20mg + placebo | 6 weeks | HDRS | SMD -0.73<br>95%CI -1.34 to -0.11, p NR | + |
| Haghighi 2014 | RCT | 60 MDD patients | Citalopram 40mg + atorvastatin 20mg | Citalopram 40mg + placebo | 12 weeks | HDRS | SMD -0.70<br>95%CI -1.22 to -0.18, p NR | + |
| Massardo 2022 | RCT | 20 MDD patients | SSRI + rosuvastatin 10mg | SSRI + placebo | 12 weeks | HDRS/BDI | Change in HDRS placebo p <0.002 vs rosuvastatin p< 0.001<br><br>Change in BDI placebo, p 0.038 vs rosuvastatin p <0.001<br>(No between-arm comparison) | = |
| Soh 2020 | RCT | 60 patients with mood disorder | Lithium + atorvastatin 20mg | Lithium + placebo | 12 weeks | Relapse (MADRS≥10) | $\chi^2_1$ 0.15<br>95%CI NR, p 0.70 | = |
| *Cohort studies* | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Kim 2015 | Cohort | 300 ACS patients with comorbid depression | Escitalopram + statin, statin-only use | Escitalopram-only, placebo-only | 1 year | Response (HDRS, BDI) | HDRS response OR 2.23<br>95%CI 1.11 to 4.51, p 0.025<br><br>BDI response OR 2.82<br>95%CI 1.35 to 5.90, p 0.006 | + |
| | | 146 ACS patients with comorbid depression | Statin use | TAU | 1 year | Response (HDRS, BDI) | HDRS response OR 1.19<br>95%CI 0.45 to 3.18 , p 0.726<br><br>BDI response OR 0.89<br>95%CI 0.36 to 2.22, p 0.798 | = |
| Köhler 2016 | Historical cohort | 872,216 SSRI users | SSRI + statin use | SSRI-only use | 3 years | Depressive episode (hospital contact) | HR 0.64<br>95%CI 0.55 to 0.75, p NR | + |

ACS: Acute Coronary Syndrome, BDI: Beck Depression Inventory, CABG: Coronary Artery Bypass Graft, CI: Confidence Interval, FA: fatty acids, HDRS: Hamilton Depression Rating Scale, HR: Hazard Ratio, MADRS: Montgomery-Åsberg Depression Rating Scale, MD: Mean Difference, MDD: Major Depressive Disorder, NAC: N-acetyl cysteine, PR: Prevalence Ratio, OR: Odds Ratio, RCT: Randomised Controlled Trial, SD: Standard Deviation, SMD: Standardized Mean Difference, SSRI: Selective Serotonin Reuptake Inhibitors, TAU: Treatment As Usual

***A1.3 Table 4*** *Effects of statins on depressive-inflammatory symptoms in depressed patients*

| Study ID | Design | Population | Intervention/Exposure | Comparison | Follow-up | Primary outcome | Major findings | Association |
|---|---|---|---|---|---|---|---|---|
| ***Anhedonia*** | | | | | | | | |
| - | | | | | | | | |
| ***Psychomotor retardation*** | | | | | | | | |
| *Clinical trials* | | | | | | | | |
| Harrison 1994 | RCT crossover | 25 healthy volunteers | Simvastatin 40mg, pravastatin 40mg | Placebo | 4 weeks | DSST | Pravastatin mean 74.3<br>95%CI 70.3 to 78.3<br><br>Simvastatin mean 74.6<br>95%CI 70.3 to 78.9 | = |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | placebo mean 74.6<br>95%CI 70.9 to 78.3<br><br>SMD NR<br>95%CI NR, p NR | |
| Muldoon 2000 | RCT | 209 hyperlipidaemic adults | Lovastatin 20mg | Placebo | 6 months | DSST | MD 0.06<br>95%CI 0.01 to 0.12, p 0.016 | + |
| Santanello 1997 | RCT | 431 adults aged ≥65 years | Lovastatin 20, lovastatin 40mg | Placebo | 6 months | DSST | Placebo 0.33 (13.6)<br><br>Lovastatin 20mg -0.80 (13.28)<br><br>Lovastatin 40mg 1.66 (8.98)<br>[Mean (SD)]<br><br>SMD NR<br>95%CI NR, p 0.66 | = |
| ***Anxiety*** | | | | | | | | |
| *Meta-analyses* | | | | | | | | |
| Zhang 2022 | Meta-analysis | 2 observational studies, 8,692 participants | Statin use | No use | NR | HADS (anxiety subscale) or diagnosis of anxiety disorder | OR 0.79<br>95%CI 0.71 to 0.88, p <0.0001 | + |
| *Clinical trials* | | | | | | | | |
| Berk 2020 | RCT | 130 MDD patients aged 15 to 25 years | TAU + rosuvastatin 10mg | TAU + placebo | 12 weeks | GAD | SMD -0.60<br>95%CI -1.70 to 3.00, p 0.684 | = |
| Harrison 1994 | RCT crossover | 25 healthy volunteers | Simvastatin 40mg, pravastatin 40mg | Placebo | 4 weeks | HADS (anxiety subscale) | Pravastatin mean 3.20<br>95%CI 2.00 to 4.40<br><br>Simvastatin mean score 2.50<br>95%CI 1.70 to 3.30 | = |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Placebo mean score 3.10<br>95%CI 2.20 to 4.00<br><br>SMD NR<br>95%CI NR, p NR | |
| Hyyppä 2003 | RCT crossover | 120 hyperlipidaemic men | Simvastatin 20mg | Placebo | 24 weeks | BDI (anxiety items) | Mean change 0.00<br>95%CI -0.05 to 0.05, p 0.947 | = |
| Stewart 2000 | RCT | 1,130 adults with CAD and hyperlipidaemia | Pravastatin 40mg | Placebo | 4 years | GHQ (anxiety items) | MD NR<br>95%CI NR, p "non-significant" | = |
| Wardle 1996 | RCT | 621 adults with CAD | Simvastatin 20-40mg | Placebo | 152 weeks | POMS (tension/anxiety items) | $c^2$ 3.57<br>95%CI NR, p "non-significant" | = |
| *Cohort studies* | | | | | | | | |
| Hoogwegt 2013 | Cohort | 409 ICD-implanted patients | Statin use | No use | 1 year | HADS (anxiety subscale) | MD -0.81<br>95%CI -1.80 - 0.18, p 0.11 | = |
| Molero 2020 | Historical cohort | 1,149,384 statin users | Statin use | No use | 8 years | Diagnosis of anxiety disorder (unplanned hospital visit or specialised outpatient care) | HR 0.99<br>95%CI 0.95 to 1.02, p NR | = |
| Young-xu 2003 | Cohort | 371 CAD patients | Statin use | No use | 4 years | Diagnosis of anxiety (Kellner Symptom questionnaire≥ 8) | OR 0.69<br>95%CI 0.47 to 0.99, p NR | + |
| ***Sleep*** | | | | | | | | |
| *Clinical trials* | | | | | | | | |
| Carlsson 2002 | RCT crossover | 41 hyperlipidaemic adults aged ≥70 years | Pravastatin 20mg → pravastatin 20mg + tocopherol 400IU | Placebo + tocopherol → pravastatin + tocopherol | 1 year | SDS | SMD NR<br>95%CI NR, p 0.761 | = |
| Harrison 1994 | RCT crossover | 25 healthy volunteers | Simvastatin 40mg, pravastatin 40mg | Placebo | 4 weeks | LSQ | Pravastatin mean 51.4<br>95%CI 48.4 to 54.6 | = |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Simvastatin mean 47.0<br>95%CI 44.9 to 49.1<br><br>Placebo: mean 50.1<br>95%CI 46.4 to 53.8<br><br>SMD NR<br>95%CI NR, p NR | |
| Santanello 1997 | RCT | 431 adults aged ≥65 years | Lovastatin 20-40mg | Placebo | 6 months | SDS | Placebo -0.07 (2.39)<br><br>Lovastatin 20mg -0.05 (2.53)<br><br>Lovastatin 40mg 0.46 (3.07)<br>[Mean change (SD)]<br><br>SMD NR<br>95%CI NR, p 0.93 | = |
| Wardle 1996 | RCT | 621 adults with CAD | Simvastatin 20-40mg | Placebo | 152 weeks | Sleep symptoms report | Prevalence difference -5.3% (statin users)<br><br>MD NR<br>95%CI NR, p NR | + |

BDI: Beck Depression Inventory, CAD: Coronary Artery Disease, CI: Confidence Interval, DSST: Digit Symbol Substitution Test, GHQ: General Health Questionnaire, HADS: Hospital Anxiety and Depression Scale, HR: Hazard Ratio, ICD: Implantable Cardioverter-Defibrillator, LSQ: Leeds Sleep Questionnaire, MD: Mean Difference, MDD: Major Depressive Disorder, POMS: Profile Of Mood Scores, PR: Prevalence Ratio, OR: Odds Ratio, RCT: Randomised Controlled Trial,, SD: Standard Deviation, SDS: Sleep Dysfunction Scale, SMD: Standardized Mean Difference, TAU: Treatment As Usual

# Appendix to Chapter 2

## A2.1 Search strategy

***MEDLINE via Ovid SP***

#1 exp Depressive disorder/
#2 Depression/
#3 (depress$ OR dysthymi$ OR mood OR affective disorder* OR affective symptom*).ti,ab,kf
#4 or/1-3
#5 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
#6 (statin$ OR atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin).tw
#7 or/5-6
#8 exp clinical trial/
#9 4 AND 7 AND 8

***Embase via Ovid SP***

#1 exp Depression/
#2 (depress$ OR dysthymi$ OR mood OR affective disorder* OR affective symptom*).ti,ab,kw
#3 or/1-2
#4 exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
#5 (statin$ OR atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin).tw
#6 or/4-5
#7 exp clinical trial/
#8 3 AND 6 AND 7

***PsycINFO via Ovid SP***

#1 exp Major Depression/
#2 (depress$ OR dysthymi$ OR mood OR affective disorder* OR affective symptom*).ti,ab,id
#3 or/1-2
#4 exp statins/
#5 (statin$ OR atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin).tw
#6 or/4-5
#7 exp clinical trial/
#8 3 AND 6 AND 7

***CENTRAL***

#1 MeSH descriptor: [Depressive Disorder] explode all trees
#2 MeSH descriptor: [Depression] this term only
#3 (depress* OR dysthymi* OR mood OR moods OR (affective next disorder*) OR (affective next symptom*):ti,ab,kw
#4 #1 OR#2 OR #3
#5 MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees
#6 (statin* OR atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin):ti,ab,kw
#7 #5 OR #6
#8 #4 AND #7

***Clinicaltrials.gov***

Search field: Search terms
Study type: All Studies
Condition: Depression

Intervention: statin OR atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin

***WHO portal***

Search field: Search terms
Condition: Depression
Intervention: statin OR atorvastatin OR cerivastatin OR fluvastatin OR lovastatin OR pitavastatin OR pravastatin OR rosuvastatin OR simvastatin

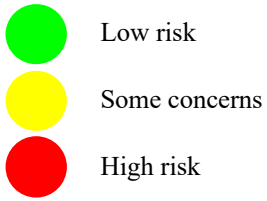
## A2.2 Baseline depression diagnosis and antidepressant use for all trials

| Study ID | Depression (n) | Antidepressant use (n) |
|---|---|---|
| **Carlsson, 2002** | - | 3/41 |
| **Chan, 2017** | - | - |
| **Gengo, 1995** | 0 | 0 |
| **Harrison, 1994** | 0 | - |
| **Hyyppä, 2003** | - | - |
| **Morales, 2006** | 0 | - |
| **Muldoon, 2000** | - | 0 |
| **Robertson, 2017** | - | - |
| **Santanello, 1997** | - | - |
| **Sheridan, 2014** | - | 11/60 |
| **Sparks, 2005** | 0 | - |
| **Stewart, 2000** | - | 42/1130 |
| **Visseren, 2001** | - | - |

"-" equals to not reported

## A2.3 RoB2 assessment of quality of trials

***Risk of bias table, summary***




| Study ID | Randomisation process | Deviations from the intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall |
|---|---|---|---|---|---|---|
| Carlsson 2002 | + | ? | + | - | + | ? |
| Chan 2017 | + | + | + | + | + | + |
| Gengo 1995 | + | + | + | + | + | + |
| Harrison 1994 | + | ? | + | + | ? | + |
| Hyyppä 2003 | + | ? | + | + | ? | + |
| Morales 2006 | + | ? | ? | + | ? | ? |
| Muldoon 2000 | + | + | + | + | ? | + |

| | | | | | | |
|---|---|---|---|---|---|---|
| Robertson 2017 |  |  |  |  |  |  |
| Santanello 1997 |  |  |  |  |  |  |
| Sheridan 2014 |  |  |  |  |  |  |
| Sparks 2005 |  |  |  |  |  |  |
| Stewart 2000 |  |  |  |  |  |  |
| Visseren 2001 |  |  |  |  |  |  |
| Wardle 1996 |  |  |  |  |  |  |

***Risk of bias table, noted***

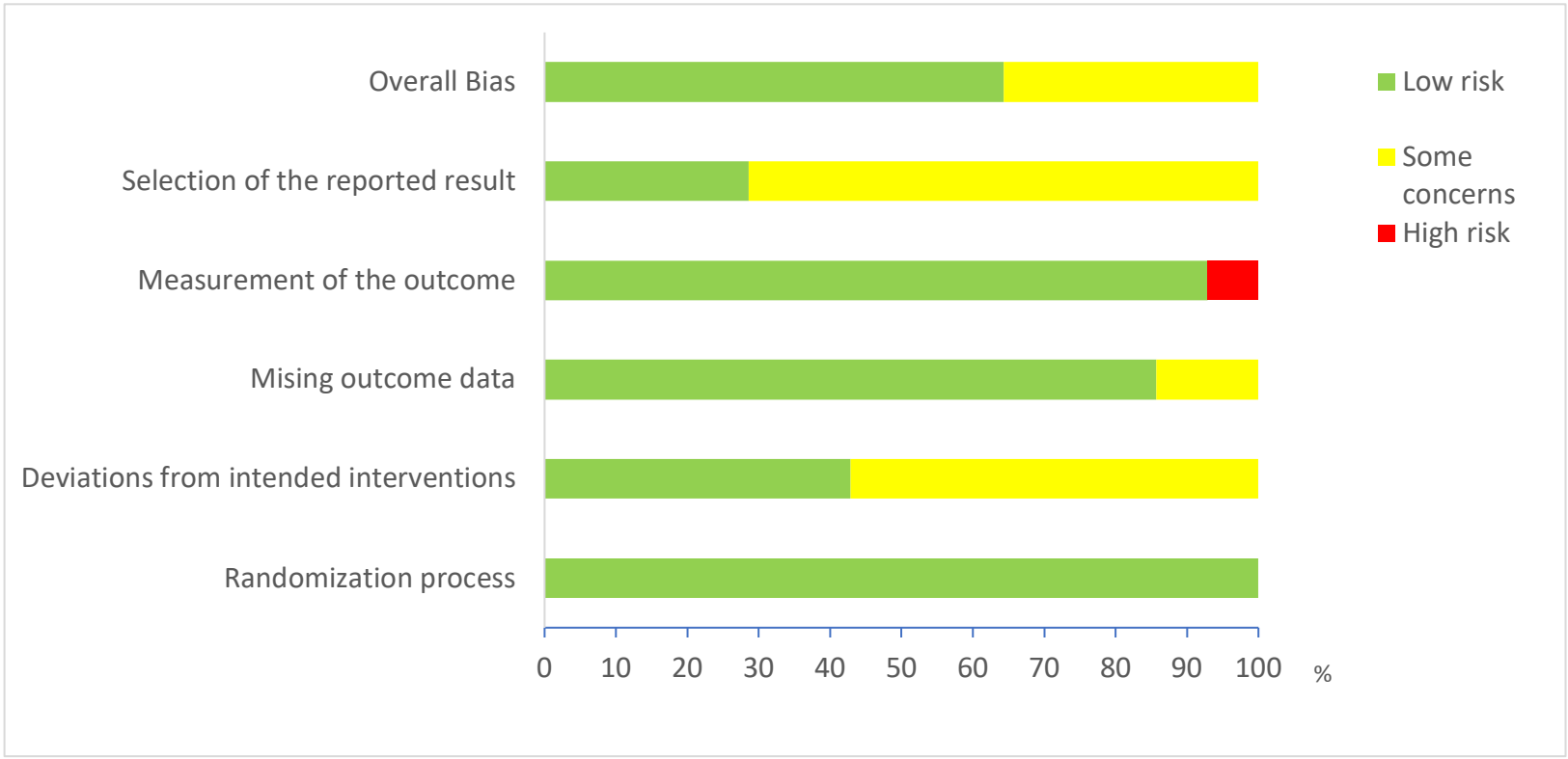
| Study ID | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall bias |
|---|---|---|---|---|---|---|
| Carlsson 2002 | **Low**<br>Double-blind, randomised, placebo-controlled, crossover study | **Some concerns**<br>Blinding affected by the lack of tocopherol-placebo | **Low**<br>Outcome data are available for 87.5% of participants, but analyses accounting for missing data were used | **High**<br>Blinding was affected by the lack of tocopherol-placebo and four participants withdrew due to adverse events | **Low**<br>Statistical analyses were pre-specified | **Some concerns**<br>It is unlikely that D4 influenced a result that is non-significant |
| Chan 2017 | **Low**<br>Randomised, double-blind, placebo-controlled trial | **Low**<br>Patients, treating physicians, and outcome assessors (including MRI scan analysts) were masked to treatment allocation, and all analysis were intention-to-treat | **Low**<br>Outcome data available for almost all participants (138/140) | **Low**<br>Patients, treating physicians, and outcome assessors (including MRI scan analysts) were masked to treatment allocation. Outcome: HDRS | **Low**<br>MS-STAT protocol registered on clinicaltrials.gov. | **Low**<br>Scored according to RoB2 algorithm |
| Gengo 1995 | **Low**<br>This is a randomised, double-blind, placebo-controlled study | **Low**<br>A total of 36 male and female patients was enrolled, and all completed the study | **Low**<br>A total of 36 male and female patients was enrolled, and all completed the study | **Low**<br>Double-blind. Outcome: Profile of Mood States | **Low**<br>The parameters of interest were prespecified and key measures were adequately powered, no corrections for multiple comparisons were applied. | **Low**<br>D5 is less likely to impact on non-significant results and protocol registration was not in use before 2007. |
| Harrison 1994 | **Low**<br>Double-blind, placebo-controlled, randomised crossover study. | **Some concerns**<br>Volunteers and investigators were blind to treatments administered. No intention to treat analysis. | **Low**<br>No subject withdrew from the study. | **Low**<br>The study was double-blind, and all participants took sequentially all three treatments. Outcome HADS | **Some concerns**<br>No protocol or predefined statistical analysis plan. | **Low**<br>Even though no ITT analysis was carried out, there were no dropouts, so it is reasonable to assume that outcome measures were available for all participants. Moreover, D5 is less likely to impact on non-significant results |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | and protocol registration was not in use before 2007 |
| Hyyppä 2003 | **Low** Randomised double-blind placebo-controlled crossover trial | **Some concerns** No intention to treat analysis | **Low** 120 participants randomised, 120 completed the study | **Low** All participants completed the study. Outcome: BSI | **Some concerns** No protocol or predefined statistical analysis plan | **Low** Even though no ITT analysis was carried out, there were no dropouts, so it is reasonable to assume that outcome measures were available for all participants. Moreover, D5 is less likely to impact on non-significant results and protocol registration was not in use before 2007 |
| Morales 2006 | **Low** The study was a randomised, double-blind, placebo-controlled clinical trial | **Some concerns** Double-blind study, but no intention-to-treat analysis | **Some concerns** Outcome data not available for all participants, and no analysis was performed to compensate for the potential bias | **Low** Double-blind study. Outcome: CES-D | **Some concerns** No protocol or predefined statistical analysis plan | **Some concerns** Scored according to RoB2 algorithm |
| Muldoon 2000 | **Low** Randomised, placebo-controlled, double-blind study | **Low** Analyses were conducted as intention-to-treat | **Low** Outcome data were not available for all participants, but intention-to-treat analysis compensate for the potential bias | **Low** The study was double-blind. Outcome: HDRS | **Some concerns** Numerous analyses were carried out, and results seem to be reported only for some of them. Nevertheless, the reported score for mood is the most comprehensive among them | **Low** D5 is less likely to impact on non-significant results and protocol registration was not in use before 2007 |
| Robertson 2017 | **Low** Randomised, double blind trial | **Some concerns** Patients and examiners were masked to the treatment group; authors did not perform an intention-to-treat analysis. | **Low** Only 4 participants (3 from placebo group, 1 from atorvastatin group) lost to follow up | **Low** The study was double-blind. Outcome: CES-D | **Some concerns** No pre-specified statistical analysis plan or study protocol | **Some concerns** Scored according to RoB2 algorithm |
| Santanello 1997 | **Low** | **Low** | **Low** | **Low** | **Some concerns** | **Low** |

| | | | | | | |
|---|---|---|---|---|---|---|
| | The study was designed as a randomised, double-blind, clinical trial | The study was double-blind, and authors employed an intention-to-treat analysis | Outcome data were not available for all participants, but intention-to-treat analysis compensate for the potential bias | Double blind trial. Outcome: CES-D | No statistical analysis plan or protocol | D5 is less likely to impact on non-significant results and protocol registration was not in use before 2007 |
| Sheridan 2014 | **Low**<br>Participants were randomised centrally via Newcastle Clinical Trials Unit using a secure web-based system | **Some concerns**<br>This pilot study was open, so that patients and physicians were aware of the treatment group to which patients had been allocated | **Low**<br>10/60 patients failed to complete the trial, of which 3 withdrew due to exacerbation of depression | **Low**<br>Assessors were aware of the intervention received by study participants, but it is unlikely that this have influenced assessment. Outcome: HADS | **Low**<br>Full details of the trial protocol are available online. | **Low**<br>D2 is less likely to impact on non-significant results |
| Sparks 2005 | **Low**<br>Randomisation was performed using the Excel spreadsheet random number generator | **Low**<br>The study was double-blind. Investigators were blinded to cholesterol profiles as well. Analyses were intention-to-treat | **Low**<br>Even though only 46 of the 71 randomised subjects completed the follow-up visit, intention-to-treat analysis compensate the potential bias | **Low**<br>Double-blind study. Outcome: GDS | **Some concerns**<br>No statistical analysis plan or protocol | **Low**<br>D5 is less likely to impact on non-significant results and protocol registration was not in use before 2007 |
| Stewart 2000 | **Low**<br>Subjects were randomised in a double-blind manner to treatment | **Low**<br>The study was double-blind, and analyses were intention-to-treat | **Low**<br>Even if the response rate at follow-up was <90%, intention-to-treat analysis compensate the potential bias | **Low**<br>The study was double-blind. Outcome: GHQ Likert scale | **Some concerns**<br>No statistical analysis plan or protocol | **Low**<br>D5 is less likely to impact on non-significant results and protocol registration was not in use before 2007 |
| Visseren 2001 | **Low**<br>Randomisation was computer-based and used random number generator | **Some concerns**<br>The study was double blind, but analyses were not conducted as intention-to-treat | **Low**<br>Outcome data were available for 86 out of 87 participants | **Low**<br>The study was double-blind. Outcome: Zung scale. | **Some concerns**<br>No statistical analysis plan or protocol | **Some concerns**<br>Scored according to RoB2 algorithm |
| Wardle 1996 | **Low**<br>Participants were randomised by telephone to the Clinical Trial Service Unit, Oxford, where one of three | **Some concerns**<br>The study was double-blind, but analyses were not intention-to-treat | **Some concerns**<br>Outcome data not available for all participants, and no analysis was performed to | **Low**<br>Double blind study. Outcome: Profile of Mood States | **Some concerns**<br>No statistical analysis plan or protocol | **Some concerns**<br>Scored according to RoB2 algorithm |

| | | | | | |
|---|---|---|---|---|---|
| | treatments was allocated by computer, using a minimisation algorithm | | compensate for the potential bias | | |

***Risk of bias table, across trials***



## A2.4 GRADE assessment of certainty of evidence

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With Placebo | With Statins | | Risk with Placebo | Risk difference with Statins |
| **Efficacy, at endpoint (follow-up: range 4 weeks to 152 weeks; assessed with: Any standardised scale for depression)** | | | | | | | | | | | |
| 2712 (11 RCTs)[1,2,3,4,5,6,7,8,9,10,11] | not serious[a] | serious[b] | serious[c] | serious[d] | none | ⨁◯◯◯ **Very low** | 1185 | 1527 | - | - | SMD **0.18 SD lower** (0.41 lower to 0.04 higher) |
| **Efficacy, at endpoint (sensitivity analysis for heterogeneity) (follow-up: range 4 weeks to 152 weeks; assessed with: Any standardised scale for depression)** | | | | | | | | | | | |
| 2649 (10 RCTs)[2,3,4,5,6,7,8,9,10,11] | not serious[a] | not serious[e] | serious[c] | not serious[f] | none | ⨁⨁⨁◯ **Moderate** | 1154 | 1495 | - | - | SMD **0.04 SD lower** (0.12 lower to 0.04 higher) |
| **Efficacy, at endpoint (subgroup analysis for dyslipidaemia) (follow-up: range 4 weeks to 152 weeks; assessed with: Any standardised scale for depression)** | | | | | | | | | | | |

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2386 (7 RCTs)[2,3,4,5,7,8,11] | not serious[a] | not serious[e] | not serious[g] | not serious[f] | none | ⨁⨁⨁⨁ High | 1038 | 1348 | - | - | SMD **0.03 SD lower** (0.12 lower to 0.05 higher) |
| **Efficacy, at endpoint (sensitivity analysis for lipophilic statins) (follow-up: range 4 weeks to 152 weeks; assessed with: Any standardised scale for depression)** | | | | | | | | | | | |
| 1497 (9 RCTs)[1,2,3,5,6,7,9,10,11] | not serious[a] | serious[h] | serious[c] | serious[d] | none | ⨁◯◯◯ Very low | 595 | 902 | - | - | SMD **0.29 SD lower** (0.62 lower to 0.03 higher) |
| **Efficacy, early (follow-up: range 4 to 24 weeks; assessed with: Any standardised scale for depression)** | | | | | | | | | | | |
| 282 (4 RCTs)[2,6,10,11] | not serious[a] | not serious[e] | serious[c] | serious[i] | none | ⨁⨁◯◯ Low | 115 | 167 | - | - | SMD **0.09 SD lower** (0.33 lower to 0.15 higher) |
| **Efficacy, medium (follow-up: range 24 weeks to 52 weeks; assessed with: Any standardised scale for depression)** | | | | | | | | | | | |
| 1799 (5 RCTs)[1,4,5,7,8] | not serious[a] | serious[j] | not serious[g] | very serious[k] | none | ⨁◯◯◯ Very low | 843 | 956 | - | - | SMD **0.38 SD lower** (0.84 lower to 0.08 higher) |

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Efficacy, long (follow-up: range 52 weeks to 152 weeks; assessed with: Any standardised scale for depression)** | | | | | | | | | | | |
| 1761 (3 RCTs)[3,4,9] | not serious[a] | not serious[e] | not serious[g] | not serious[f] | none | ⨁⨁⨁⨁ **High** | 798 | 963 | - | - | SMD **0.06 SD lower** (0.16 lower to 0.03 higher) |
| **Acceptability, at endpoint (follow-up: range 4 weeks to 152 weeks; assessed with: Treatment discontinuation due to any cause)** | | | | | | | | | | | |
| 2446 (11 RCTs)[1,2,3,4,6,8,9,10,11,12,13] | not serious[a] | not serious[e] | serious[c] | not serious[f] | none | ⨁⨁⨁◯ **Moderate** | 225/1114 (20.2%) | 286/1332 (21.5%) | **RR 0.99** (0.85 to 1.15) | 202 per 1,000 | **2 fewer per 1,000** (from 30 fewer to 30 more) |
| **Tolerability, at endpoint (follow-up: range 4 weeks to 152 weeks; assessed with: Treatment discontinuation due to adverse events)** | | | | | | | | | | | |
| 1193 (8 RCTs)[2,3,6,8,9,10,11,12] | not serious[a] | not serious[e] | serious[c] | not serious[f] | none | ⨁⨁⨁◯ **Moderate** | 29/482 (6.0%) | 58/711 (8.2%) | **RR 1.20** (0.79 to 1.82) | 60 per 1,000 | **12 more per 1,000** (from 13 fewer to 49 more) |
| **Safety, any adverse event, at endpoint (follow-up: range 4 weeks to 152 weeks; assessed with: Number of patients with adverse events)** | | | | | | | | | | | |
| 289 (4 RCTs)[2,10,11,12] | not serious[a] | not serious[e] | not serious[g] | serious[i] | none | ⨁⨁⨁◯ **Moderate** | 20/135 (14.8%) | 24/154 (15.6%) | **RR 1.07** (0.66 to 1.73) | 148 per 1,000 | **10 more per 1,000** (from 50 fewer to 108 more) |

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Safety, self-harm, at endpoint (follow-up: range 4 weeks to 152 weeks; assessed with: Number of patients with self-harm)** | | | | | | | | | | | |
| 1439 (9 RCTs)[2,3,5,6,8,10,11,12,13] | | | | | | - | 0/543 (0.0%) | 0/896 (0.0%) | not estimable | 0 per 1,000 | |
| **Safey, suicide, at endpoint (follow-up: range 4 weeks to 152 weeks; assessed with: Number of patients with suicide)** | | | | | | | | | | | |
| 1398 (8 RCTs)[2,3,5,6,10,11,12,13] | not serious[a] | not serious[e] | serious[c] | very serious[l] | none | ⨁◯◯◯ **Very low** | 1/522 (0.2%) | 0/876 (0.0%) | **RR 0.64** (0.17 to 2.45) | 2 per 1,000 | **1 fewer per 1,000** (from 2 fewer to 3 more) |

**CI:** confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

## *Explanations*

a. Most information from trials at 'low' or 'some concerns' risk of bias. However, potential limitations are unlikely to lower confidence in the estimate of effect.
b. Large heterogeneity ($I^2$=83.12%) due to one study
c. Study population differ between studies
d. Confidence intervals include both moderate benefit and small non-benefit
e. No heterogeneity
f. Confidence intervals include only small benefit and small non-benefit (i.e., no difference is most likely outcome)
g. Overall similar trial populations
h. Large heterogeneity ($I^2$=87.17%) due to one study
i. Confidence intervals include only small benefit and small non-benefit (i.e., no difference is most likely outcome), optimal information size not met
j. Large heterogeneity ($I^2$=92.86%) due to one study
k. Confidence intervals include both large benefit and small non-benefit
l. Confidence intervals include both large benefit and large non-benefit, very low events

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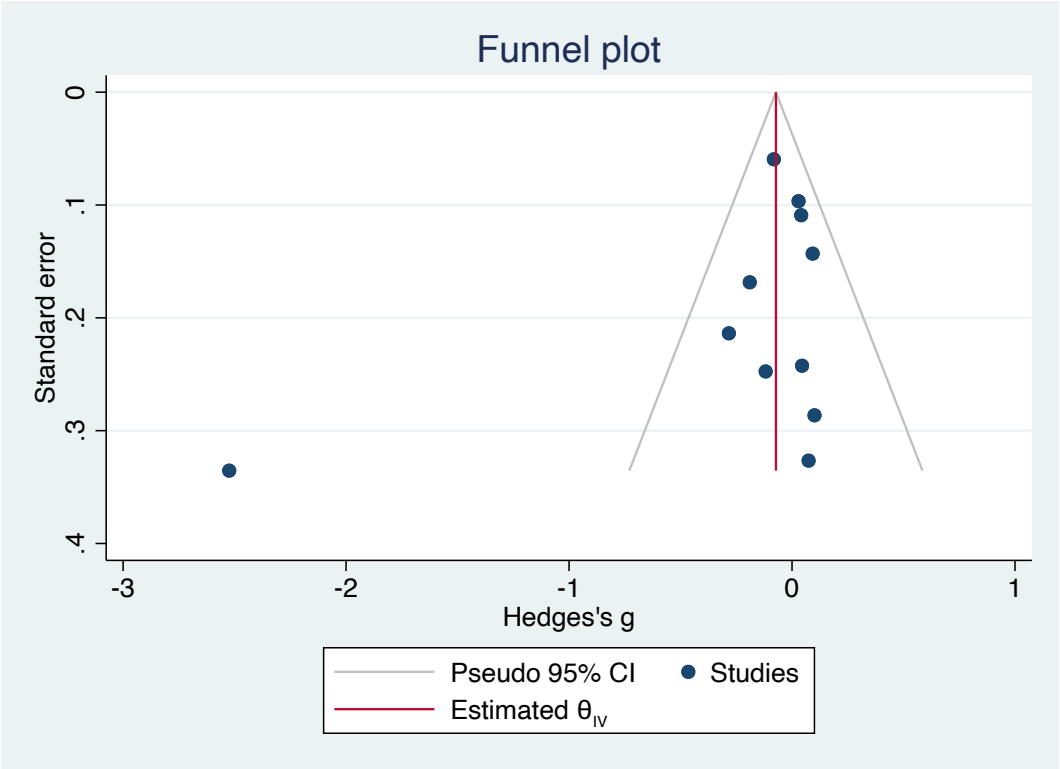
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## A2.5 Assessment of publication bias

***Funnel plot***




***Regression-based Egger test for small study effects***

Random-effects model, DerSimonian-Laird

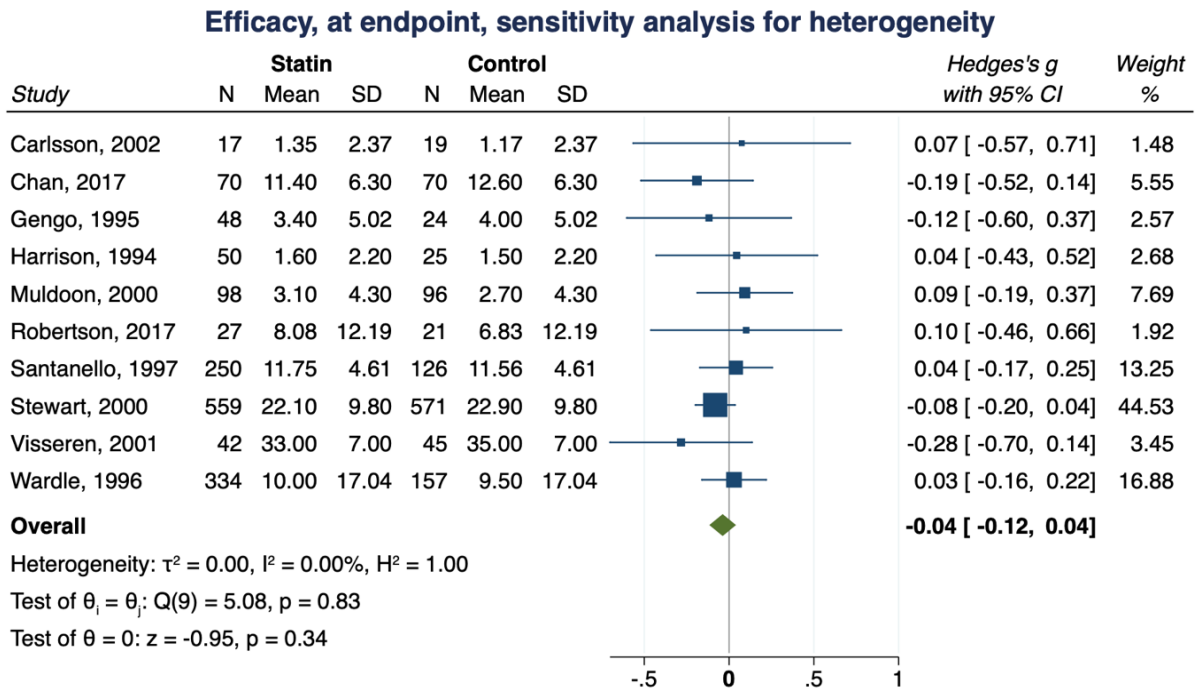
H0: beta1 0; no small-study effects

beta1 -2.98

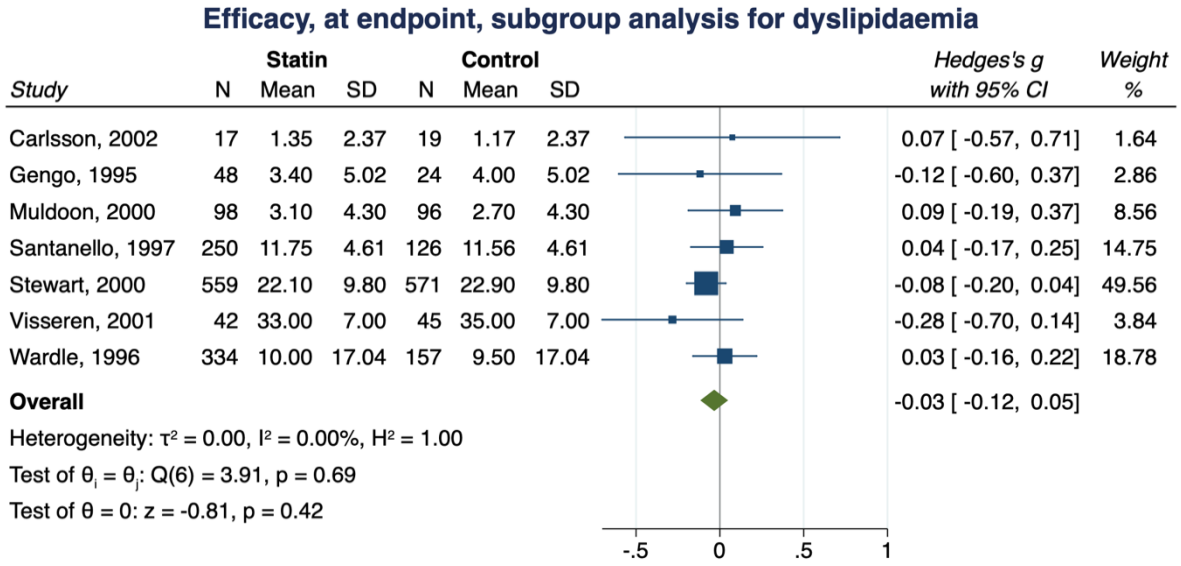
SE of beta1 1.327

z -2.25
Prob > |z| 0.0246

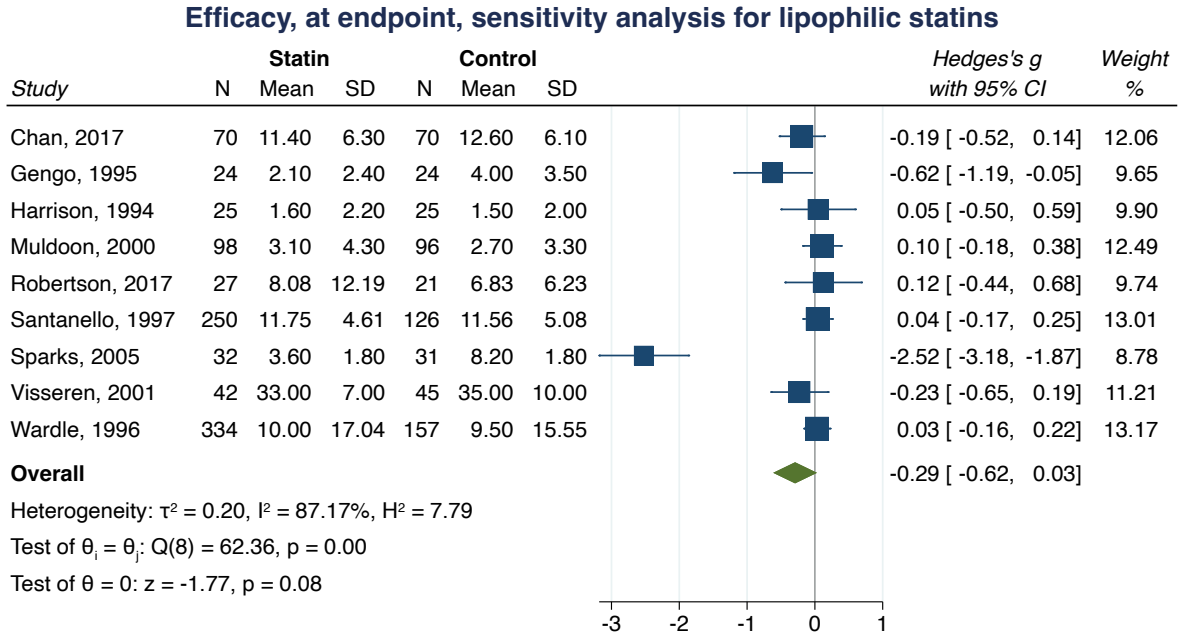
## A2.6 Sensitivity analysis (heterogeneity) for efficacy as mean value for depressive symptoms at endpoint



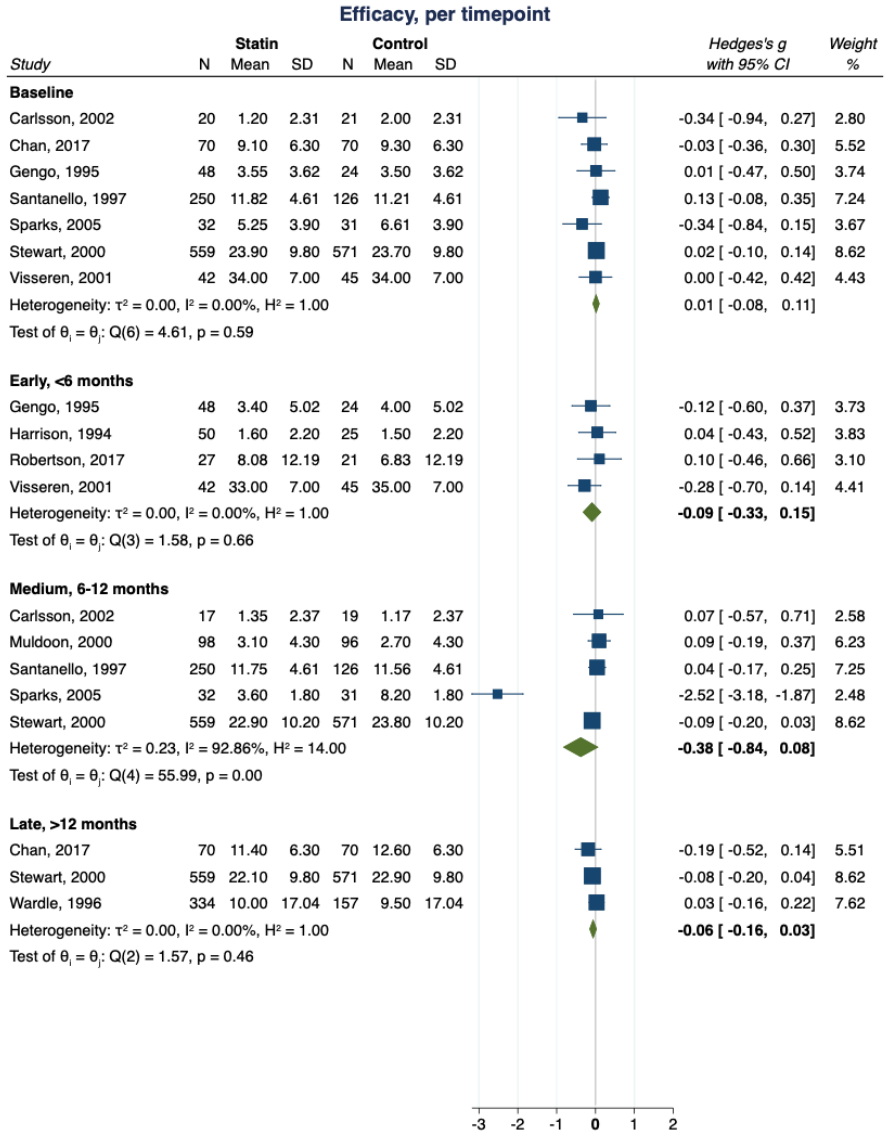
A2.7 Subgroup analysis (dyslipidaemia) for efficacy as mean value for depressive symptoms at endpoint



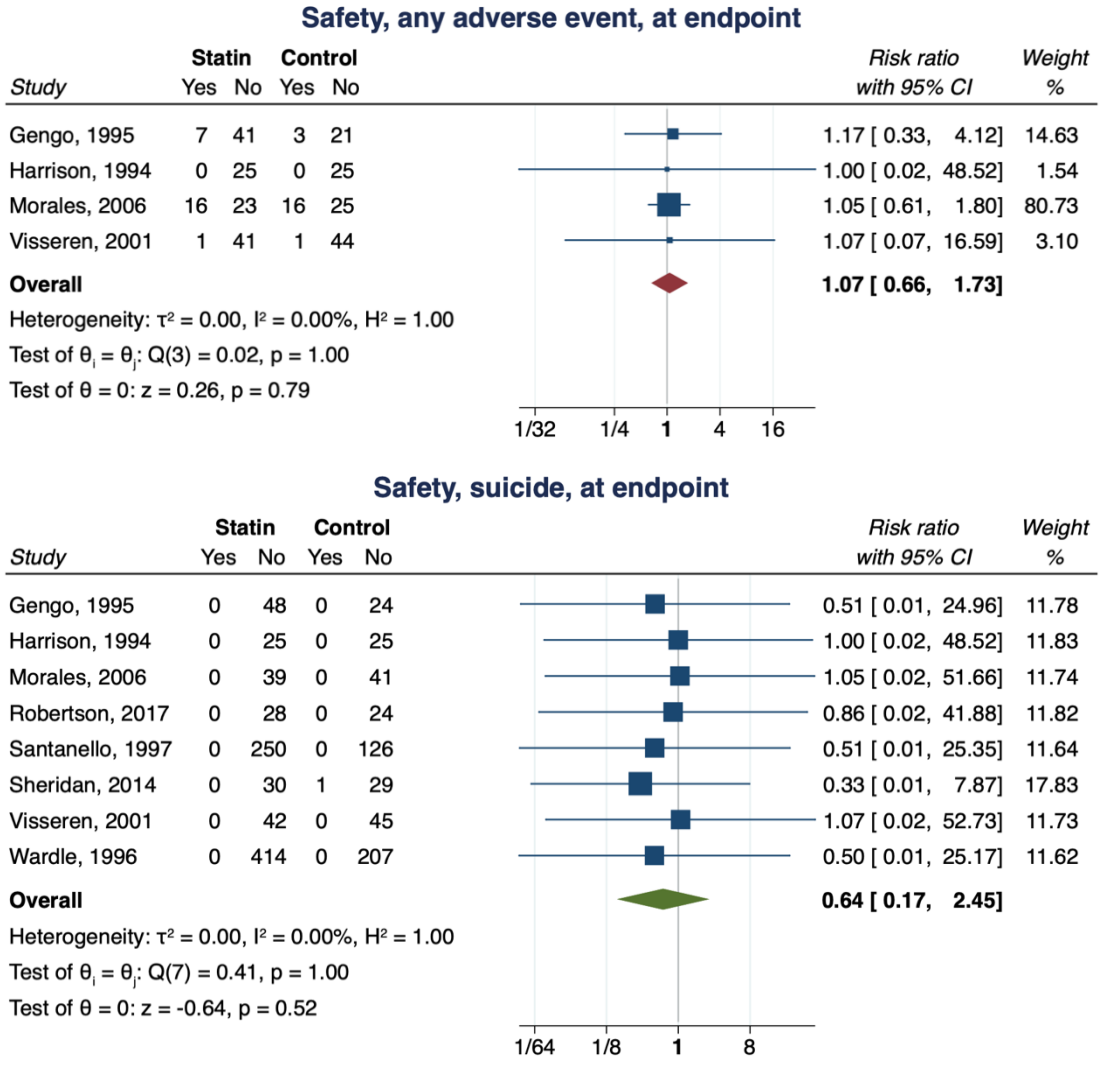
A2.8 Sensitivity analysis (lipophilic statins) for efficacy as mean value for depressive symptoms at endpoint



## A2.9 Efficacy as mean value for depressive symptoms at three timepoints



A2.10 Safety


Safety, any adverse event, at endpoint
Statin
Control
Study
Yes No Yes No
Risk ratio with 95% CI
Weight %
Gengo, 1995 7 41 3 21 1.17 [ 0.33, 4.12] 14.63
Harrison, 1994 0 25 0 25 1.00 [ 0.02, 48.52] 1.54
Morales, 2006 16 23 16 25 1.05 [ 0.61, 1.80] 80.73
Visseren, 2001 1 41 1 44 1.07 [ 0.07, 16.59] 3.10
Overall 1.07 [ 0.66, 1.73]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(3) = 0.02, p = 1.00
Test of θ = 0: z = 0.26, p = 0.79
1/32 1/4 1 4 16
Safety, suicide, at endpoint
Statin
Control
Study
Yes No Yes No
Risk ratio with 95% CI
Weight %
Gengo, 1995 0 48 0 24 0.51 [ 0.01, 24.96] 11.78
Harrison, 1994 0 25 0 25 1.00 [ 0.02, 48.52] 11.83
Morales, 2006 0 39 0 41 1.05 [ 0.02, 51.66] 11.74
Robertson, 2017 0 28 0 24 0.86 [ 0.02, 41.88] 11.82
Santanello, 1997 0 250 0 126 0.51 [ 0.01, 25.35] 11.64
Sheridan, 2014 0 30 1 29 0.33 [ 0.01, 7.87] 17.83
Visseren, 2001 0 42 0 45 1.07 [ 0.02, 52.73] 11.73
Wardle, 1996 0 414 0 207 0.50 [ 0.01, 25.17] 11.62
Overall 0.64 [ 0.17, 2.45]
Heterogeneity: τ² = 0.00, I² = 0.00%, H² = 1.00
Test of θi = θj: Q(7) = 0.41, p = 1.00
Test of θ = 0: z = -0.64, p = 0.52
1/64 1/8 1 8

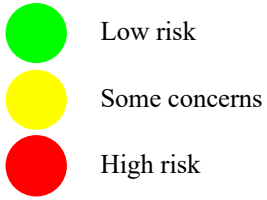
## Appendix to Chapter 3

### A3.1 Search strategy

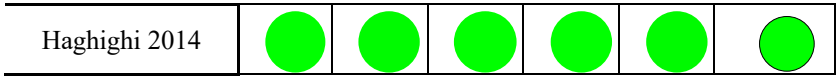
("Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh]) OR *statin OR statins) AND ("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR "Depressive Disorder, Treatment-Resistant"[Mesh] OR "Depressive Disorder, Major"[Mesh] OR depression OR depressive OR antidepress*)

### A3.2 RoB2 assessment of quality of trials

***Risk of bias table, summary***




| Study ID | Randomisation process | Deviations from the intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall |
|---|---|---|---|---|---|---|
| Berk 2020 | + | + | + | + | + | + |
| Ghanizadeh 2013 | ? | + | + | ? | ? | ? |
| Gougol 2015 | + | + | ? | + | + | ? |

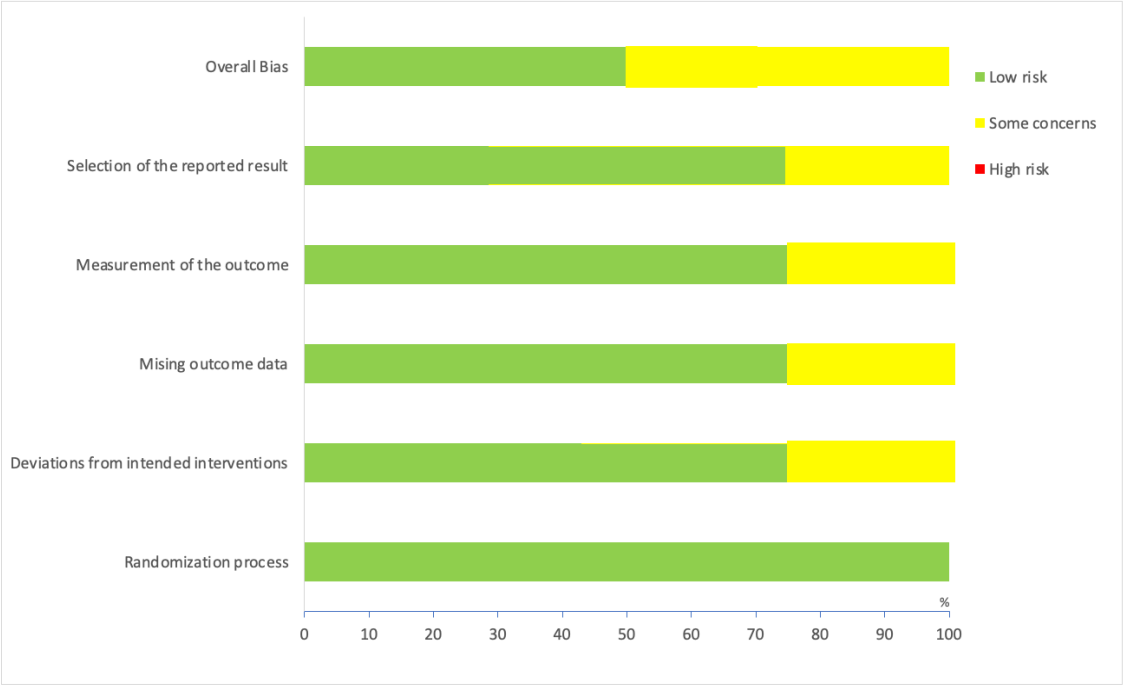

Haghighi 2014

***Risk of bias table, noted***

| Study ID | Randomisation process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall bias |
|---|---|---|---|---|---|---|
| Berk 2020 | **Low**<br>Participants were randomised according to the International Council for Harmonisation (ICH) Guidelines by an independent researcher | **Low**<br>Concealed allocation alerts were sent to the local research pharmacists with information regarding participant allocation. The pharmacist and trial coordinator then ensured that study participants received their assigned study treatment. Research coordinators and the clinical team were not aware of allocation | **Low**<br>Primary and secondary analyses were undertaken on intent-to-treat basis, including all participants as randomised, regardless of treatment received or their withdrawal from the study | **Low**<br>All tablets were over-encapsulated for blinding purposes to be identical in appearance and taste. The study biostatistician and others who were involved in preparing the trial results were blinded to intervention allocation. The trial was only unblinded after finalizing the analysis | **Low**<br>The full protocol was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12613000112763) | **Low**<br>Scored according to RoB2 algorithm |
| Ghanizadeh 2013 | **Low**<br>The allocation sequence was according to a list provided by a random number generator | **Some concerns**<br>Allocation concealment was not reported | **Low**<br>Up to 12 % drop-out rate but the missing data was balanced across groups. Reasons were given for dropouts. Intention-to-treat analysis was used | **Some concerns**<br>Patients and examiners were blind to the allocation groups and lovastatin and placebo tablets were identical; but, as the allocation concealment is not explained, it is not possible to assure that blinding was not broken | **Some concerns**<br>The trial was registered at the Iranian Clinical Trials Registry (IRCT201304203930N22). However, the trial had been registered only after recruitment had started | **Some concerns**<br>Scored according to RoB2 algorithm |
| Gougol 2015 | **Low**<br>A randomised code was generated by the permuted randomization block method (Excel software). An independent team was involved in the process | **Low**<br>Assignments were kept in sequentially numbered, sealed, opaque envelopes. They were opened sequentially only after participant details were written on the envelope | **Some concerns**<br>Up to 8.3% drop-out rate but the missing data was balanced across groups. No reason given for dropouts. The type of analysis used was not described | **Low**<br>Sealed envelopes and identical placebo and simvastatin pills were used. The study drugs were dispensed by an investigational drug pharmacist. All members | **Low**<br>This trial, with registration number IRCT201205131556N43 at the Iranian Registry of Clinical Trial | **Some concerns**<br>Scored according to RoB2 algorithm |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | of the research team, patients and their families were blind to the treatment group assignments. They were asked at the end of the study which group they thought they were assigned. Personnel were blinded to treatment allocation | | |
| Haghighi 2014 | **Low**<br>The randomisation of box numbering was made via a computer random generator | **Low**<br>The allocation procedure was done with sequentially numbered, identical boxes. The personnel who packaged and prepared the boxes was not further involved in the study | **Low**<br>The attrition rate was 0% | **Low**<br>Neither patients nor study nurses and physicians were aware of group assignments. Placebo and atorvastatin pills were identical | **Low**<br>The clinical trial registration number is: IRCT201208261743N9 | **Low**<br>Scored according to RoB2 algorithm |

***Risk of bias table, across trials***



## A3.3 GRADE assessment of certainty of evidence

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Participants (studies) Follow up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With Placebo | With Statins | | Risk with Placebo | Risk difference with Statins |
| **Efficacy, d**epressive symptoms **at 2 weeks** (follow up: 2 weeks; assessed with: **Any standardised scale for depression**) | | | | | | | | | | | |
| 105 (2 RCTs) [1,3] | not serious[a] | not serious[b] | not serious[d] | very serious[e] | none | ⨁⨁◯◯ **Low** | 53 | 52 | - | - | SMD **0.18 lower** (0.57 lower to 0.2 higher) |
| **Efficacy, d**epressive symptoms **at 4 weeks** (follow up: **4** weeks; assessed with: **Any standardised scale for depression**) | | | | | | | | | | | |
| 178 (3 RCTs) [2,3,4] | not serious[a] | not serious[b] | not serious[d] | very serious[e] | none | ⨁⨁◯◯ **Low** | 86 | 92 | - | - | SMD **0.22 lower** (0.51 lower to 0.08 higher) |
| **Efficacy, d**epressive symptoms **at 8 weeks** (follow up: **8** weeks; assessed with: **Any standardised scale for depression**) | | | | | | | | | | | |
| 238 (4 RCTs) [1,2,3,4] | not serious[a] | not serious[b] | not serious[d] | serious[f] | none | ⨁⨁⨁◯ **Moderate** | 116 | 122 | - | - | SMD **0.48 lower** (0.74 lower to 0.22 lower) |

| Certainty assessment | | | | | | | Summary of findings | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Efficacy, d**epressive symptoms **at 12 weeks** (follow up: **1**2 weeks; assessed with: **Any standardised scale for depression**) | | | | | | | | | | | |
| 134 (2 RCTs) [2,4] | not serious[a] | serious[c] | not serious[d] | serious[f] | none | ⨁⨁◯◯ **Low** | 64 | 70 | - | - | SMD **0.47 lower** (0.89 lower to 0.05 lower) |
| Acceptability**, at endpoint** (follow up: **6-12** weeks; assessed with: **Treatment discontinuation due to any cause**) | | | | | | | | | | | |
| 266 (4 RCTs) [1,2,3,4] | not serious[a] | not serious[b] | not serious[d] | very serious[e] | none | ⨁⨁◯◯ **Low** | 13/130 (10.0%) | 14/136 (10.3%) | **RR 0.99** (0.50 to 1.96) | 100 per 1,000 | **1 fewer per 1,000** (from 50 fewer to 96 more) |
| Tolerability**, at endpoint** (follow up: **6-12** weeks; assessed with: **Treatment discontinuation** due to any adverse event) | | | | | | | | | | | |
| 266 (4 RCTs) [1,2,3,4] | not serious[a] | not serious[b] | not serious[d] | very serious[e] | none | ⨁⨁◯◯ **Low** | 0/130 (0.0%) | 1/136 (0.7%) | **RR 1.40** (0.22 to 8.76) | 0 per 1,000 | **0 fewer per 1,000** (from 0 fewer to 0 fewer) |

## *Explanations*

a. Most information from trials at 'low' or 'some concerns' risk of bias. However, potential limitations are unlikely to lower confidence in the estimate of effect.
b. No heterogeneity
c. Low heterogeneity ($I^2$=33.58%)
d. Comparable studies' population, intervention, outcome
e. Wide confidence intervals, optimal information size not met
f. Optimal information size not met

## *References*


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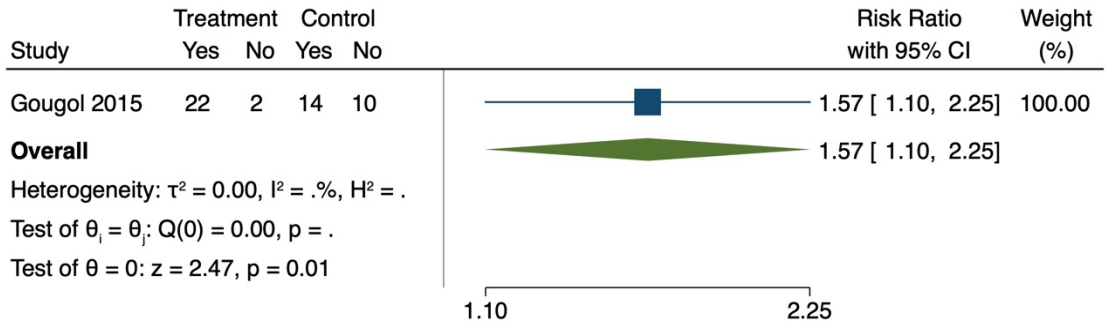
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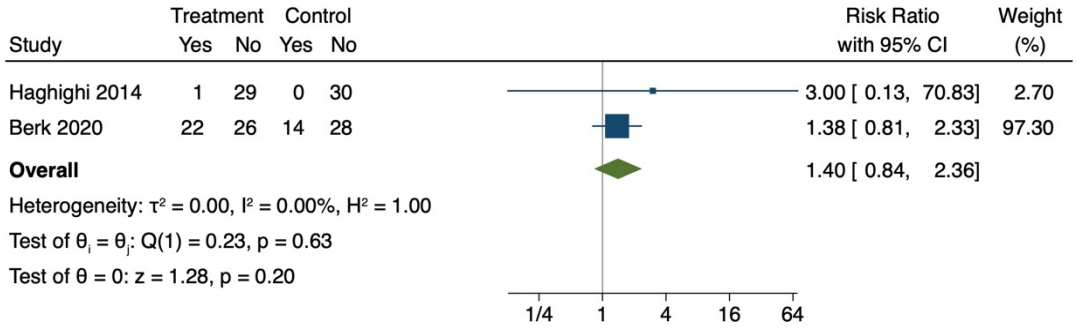
## A3.4 Additional forest plots

### *Response*

*Response, 8 weeks*

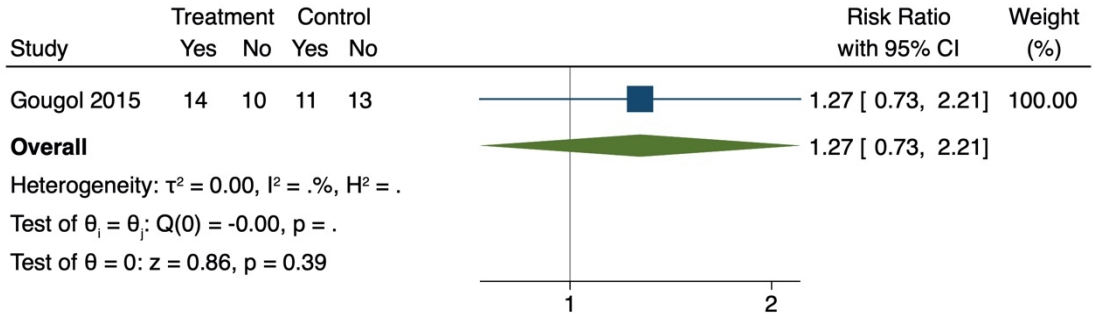



*Response, 12 weeks*

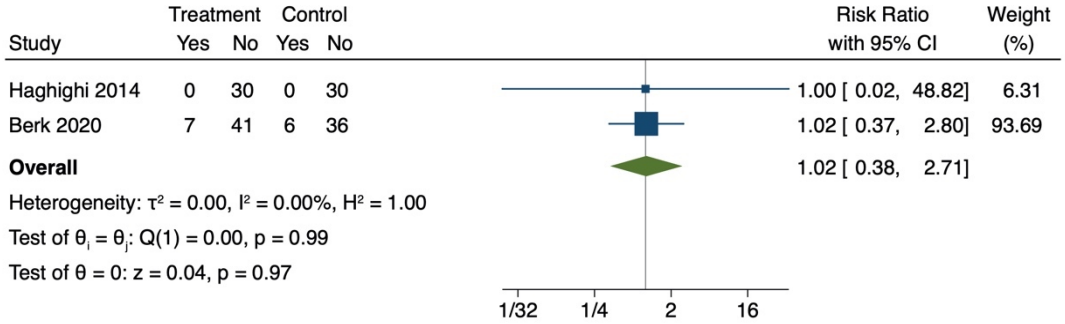



### *Remission*

*Remission, 8 weeks*




*Remission, 12 weeks*




# Appendix to Chapter 4

## A4.1 "Read codes" for depressive disorders

"Read codes" are a coded thesaurus of clinical terms used in English primary care.

***Minor depression***

Abnormal depressed feelings
Adjustment disorder with depressed mood
Adjustment reaction, predominant disturbance other emotions C/O - feeling depressed

C/O - feeling unhappy
Depressed mood
Depressive symptoms
Dysphoric mood
Emotional problem
Emotional upset
Loss of capacity for enjoyment
Loss of hope for the future
Low mood
O/E - depressed
PHQ9 score - feeling down or depressed or hopeless
Rebound mood swings
Sad mood
Stress reaction causing mixed disturbance of emotion/conduct Suspected depression
Symptoms of depression
Dysthymia

### *Major depression*

Agitated depression
Anxiety with depression
Arteriosclerotic dementia with depression Atypical depressive disorder
Brief depressive reaction
Brief depressive reaction NOS
Chronic depression
Depressed
Depression
Depression NOS
Depression confirmed
Depressive disorder NEC
Endogenous depression
Endogenous depression - recurrent Endogenous depression first episode Masked depression
Mild depression
Moderate depression

Neurotic depression reactive type Presenile dementia with depression
Prolonged depressive reaction
Psychotic reactive depression
Reactive (neurotic) depression
Recurrent depression
Recurrent major depressive episode
Recurrent major depressive episode NOS
Recurrent major depressive episodes, unspecified
Recurrent major depressive episodes, mild
Recurrent major depressive episodes, moderate
Recurrent major depressive episodes, severe, no psychosis Recurrent major depressive episodes, severe, with psychosis Recurrent major depressive episodes, partial/unspec remission Recurrent major depressive episodes, in full remission
Senile dementia with depression
Severe depression
Single major depressive episode
Single major depressive episode NOS
Single major depressive episode, in full remission Single major depressive episode, mild
Single major depressive episode, moderate
Single major depressive episode, partial or unspec remission Single major depressive episode, severe with psychosis Single major depressive episode, severe without psychosis Single major depressive episode, unspecified
[RFC] Depression
Reactive depression NOS
Antenatal depression
Atypical depression
Depression NOS
Depressive disorder NOS
Depressive episode
Depressive episode, unspecified
Depressive neurosis
Endogenous depression with psychotic symptoms Endogenous depression without psychotic symptoms
Major depression, mild
Major depression, moderately severe
Major depression, recurrent without psychotic symptoms Major depression, severe with psychotic symptoms
Major depression, severe without psychotic symptoms

Mild anxiety depression
Mild depression
Mild depressive episode
Mixed anxiety and depressive disorder
Moderate depressive episode
Monopolar depression NOS
Neurotic depression
Other depressive episodes
Other recurrent depressive disorders
Persistant anxiety depression
Prolonged single episode of reactive depression
Recurr depress disorder cur epi severe without psyc sympt Recurr severe episodes/ major depression+psychotic symptom Recurr severe episodes/psychogenic depressive psychosis Recurrent brief depressive episodes
Recurrent depress disorder cur epi severe with psyc symp Recurrent depressive disorder
Recurrent depressive disorder, current episode mild
Recurrent depressive disorder, current episode moderate Recurrent depressive disorder, unspecified
Recurrent episodes of depressive reaction
Recurrent episodes of psychogenic depression
Recurrent episodes of reactive depression
Recurrent severe episodes of psychotic depression
Recurrent severe episodes/reactive depressive psychosis Severe depressive episode with psychotic symptoms
Severe depressive episode without psychotic symptoms
Single episode agitated depressn w'out psychotic symptoms Single episode major depression w'out psychotic symptoms Single episode of depressive reaction
Single episode of major depression and psychotic symptoms Single episode of psychogenic depression
Single episode of psychogenic depressive psychosis
Single episode of psychotic depression
Single episode of reactive depression
Single episode of reactive depressive psychosis

### *Other Read codes for depression*

4 item geriatric depression scale
Acute posttrauma stress state
Acute stress reaction NOS

Assessment using Whooley depression screen Beck depression inventory
Beck depression inventory second edition score Depression - enhanced service completed Depression - enhanced services administration Depression annual review
Depression anxiety stress scales anxiety score Depression anxiety stress scales depression score Depression anxiety stress scales stress score
Depression interim review
Depression management programme
Depression medication review
Depression monitoring administration
Depression monitoring first letter
Depression monitoring second letter
Depression monitoring telephone invite
Depression monitoring third letter
Depression monitoring verbal invite
Depression resolved
Depression screen
Edinburgh postnatal depression scale
Emotional and psychosocial support and advice Geriatric Depression Screen Score
Geriatric depression scale
Geriatric depression scale – 0 point
Geriatric depression scale – 1 point
Geriatric depression scale – 10 points
Geriatric depression scale – 11 points
Geriatric depression scale – 12 points
Geriatric depression scale – 13 points
Geriatric depression scale – 14 points
Geriatric depression scale – 15 points
Geriatric depression scale – 2 points
Geriatric depression scale – 3 points
Geriatric depression scale – 4 points
Geriatric depression scale – 5 points
Geriatric depression scale – 6 points
Geriatric depression scale – 7 points
Geriatric depression scale – 8 points
Geriatric depression scale – 9 points

Geriatric depression scale – <6 points
H/O: depression
HAD scale: depression score
HAMD - Hamilton rating scale for depression
HRSD - Hamilton rating scale for depression
Hospital anxiety and depression scale
MADRS - Montgomery-Asberg depression rating scale Mixed disturbance of conduct and emotion
Mood observations
On depression register
On full dose long term treatment for depression
Other acute stress reaction NOS
Other acute stress reactions
Patient given advice about management of depression Postnatal depression
Postviral depression
Referral for depression self-help video
Referral for guided self-help for depression
Removed from depression register
Stress monitoring 1st letter
[RFC] Postnatal depression
Personal history of affective disorder
Depressive personality disorder
Manic-depress psychosis,depressd, no psychotic symptoms Manic-depress psychosis,depressed type+psychotic symptoms Mood - affective disorders
Postnatal depression NOS
Postpartum depression NOS
Recurrent depressive disorder, current episode mild
Seasonal depressive disorder

## A4.2. List of adverse events

Nausea, headache, dry mouth, insomnia, dizziness, sedation/ somnolence, diarrhoea, constipation, sexual dysfunction, fatigue, rhinitis/nasopharyngitis, hyperhidrosis, respiratory disorder (infection, cough), anxiety, decreased appetite, increased appetite, tremor, pain, vomiting, abdominal pain/discomfort, dyspepsia, agitation, visual impairment, ejaculation disorder/erectile dysfunction, weight increased,

weight decreased, arrhythmia/heart rate disorder, abnormal dreams, infection, blood pressure increased, blood pressure decreased, extrapyramidal dis- orders, suicidal ideation, suicide behaviour or self-harm, hot flush, dysuria, skin disorder, flatulence, urinary disorders, injury, yawning, eye disorders, paraesthesia, nervous system symptoms, feeling cold, menstrual disorder, chest pain, disturbance in attention, libido increased, psychiatric symptoms, fall, confusional state, salivary hypersecretion, accidental overdose, cardiovascular symptoms (e.g., angina), sleep disturbance, oedema, aggression, completed suicide, affect lability, fever, euphoric mood, hypersomnia, memory impairment, muscular skeletal problems, serotonin syndrome, withdrawal syndrome, fractures, upper gastrointestinal bleeding, bleeding at any site, epilepsy/seizures.

## A4.3 List of confounders

Age at study entry; sex; body mass index (BMI); year of diagnosis of depression; type of diagnosis of depression (major depressive disorders, minor depression, other); severity of index diagnosis of depression (mild, moderate, severe); deprivation status (Townsend deprivation score); smoking status (non-smoker, ex-smoker, light smoker 1-9 cigarettes/day, moderate smoker 10-19 cigarettes/day, heavy smoker ≥20 cigarettes/day, not recorded); alcohol intake (none, trivial <1 unit/day, light 1-2 unit/day, medium 3-6 unit/day, heavy 7-9 unit/day, very heavy >9 unit/day, not recorded); ethnic group (white, African-Caribbean, Asian, other); comorbidities (coronary heart disease, stroke, diabetes, hypertension, cancer, epilepsy/seizures, hypothyroidism, osteoarthritis, rheumatoid arthritis, suicidality, obesity, asthma/chronic obstructive airways disease, osteoporosis, liver disease, renal disease); antidepressant category [selective serotonin reuptake inhibitors (SSRIs), tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs), other antidepressant – see below]; use of other drugs (anticonvulsants, hypnotics/ anxiolytics, antihypertensive drugs, aspirin, anticoagulants, non-steroidal anti-inflammatory drugs, bisphosphonates, oral contraceptives, hormone replacement therapy).

Antidepressants were categorised according to four classes as in the British National Formulary (BNF) (https://bnf.nice.org.uk), namely:

- Selective serotonin reuptake inhibitors (SSRIs): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline;
- Tricyclics (TCAs): amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dosulepine, doxepin, imipramine, iprindole, lofepramine, maprotiline, mianserin, nortriptyline, protriptyline, trimipramine, viloxazine;
- Monoamine oxidase inhibitors (MAOIs): isocarboaxazid, moclobemide, phenelzine, tranylcypromine;
- Other antidepressants: agomelatine, duloxetine, mirtazapine, nefazodone, reboxetine, tryptophan, trazodone, venlafaxine, vortioxetine

## A4.4 Missing data

***Table A4.4*** *Missing data (percentage) imputed for the full set analysis*

| **Characteristic** | **Missing (%)** | **Complete** |
|---|---|---|
| PHQ-9 | | |
| at baseline | 853,344 (81.26) | 1,050,105 |
| at 2 months | 962,109 (91.62) | 1,050,105 |
| at 6 months | 1,024,410 (97.55) | 1,050,105 |
| at 12 months | 1,033,225 (98.39) | 1,050,105 |
| Body Mass Index | 217,391 (20.70) | 1,050,105 |
| Smoking | 75,281 (7.17) | 1,050,105 |
| Alcohol | 511,221 (48.68) | 1,050,105 |
| Ethnic group | 262,202 (24.97) | 1,050,105 |
| Townsend deprivation score | 3,505 (0.33) | 1,050,105 |

## A4.6 Number of events for all outcomes

***Table A4.6*** *Number of events (percentage), unless stated otherwise, for all outcomes at 2 months, 6 months, and 12 months*

| *Outcome* | **Statin users** | | | **Statin non-users** | | |
|---|---|---|---|---|---|---|
| | *Nº events* | *%* | *Nº patients* | *Nº events* | *%* | *Nº patients* |
| **Response** | | | | | | |
| 2mo | 1,465 | (36.29) | 4,037 | 17,359 | (34.44) | 50,398 |
| 6mo | 309 | (33.44) | 924 | 4,035 | (32.80) | 12,301 |
| 12mo | 182 | (31.33) | 581 | 2,158 | (29.07) | 7,423 |
| **Remission** | | | | | | |
| 2mo | 1,144 | (17.37) | 6,586 | 10,693 | (13.13) | 81,410 |
| 6mo | 450 | (23.17) | 1,942 | 3,708 | (15.61) | 23,753 |
| 12mo | 314 | (23.57) | 1,332 | 2,050 | (13.18) | 15,548 |

| **Change in depression score** | *Mean* | *SD* | | *Mean* | *SD* | |
|---|---|---|---|---|---|---|
| 2mo | -1.78 | (6.57) | 4,037 | -2.45 | (6.47) | 50,398 |
| 6mo | -1.74 | (7.75) | 924 | -1.50 | (8.25) | 12,301 |
| 12mo | -1.67 | (7.77) | 581 | -0.71 | (8.31) | 7,423 |
| **Any adverse event** | | | | | | |
| 2mo | 36,870 | (40.92) | 90,094 | 368,157 | (38.35) | 960,011 |
| 6mo | 55,139 | (61.20) | 90,094 | 526,875 | (54.88) | 960,011 |
| 12mo | 68,051 | (75.53) | 90,094 | 639,060 | (66.57) | 960,011 |
| **Any psychiatric symptom** | | | | | | |
| 2mo | 12,786 | (14.19) | 90,094 | 158,410 | (16.50) | 960,011 |
| 6mo | 16,774 | (18.62) | 90,094 | 203,877 | (21.24) | 960,011 |
| 12mo | 20,534 | (22.79) | 90,094 | 241,576 | (25.16) | 960,011 |
| **Anxiety** | | | | | | |
| 2mo | 6,264 | (6.95) | 90,094 | 111,440 | (11.61) | 960,011 |
| 6mo | 7,657 | (8.50) | 90,094 | 138,129 | (14.49) | 960,011 |
| 12mo | 8,730 | (9.69) | 90,094 | 158,544 | (16.51) | 960,011 |
| **Sleep disturbance** | | | | | | |
| 2mo | 619 | (0.69) | 90,094 | 5,906 | (0.62) | 960,011 |
| 6mo | 1,250 | (1.39) | 90,094 | 11,289 | (1.18) | 960,011 |
| 12mo | 2,043 | (2.27) | 90,094 | 17,248 | (1.80) | 960,011 |
| **Memory impairment** | | | | | | |
| 2mo | 771 | (0.86) | 90,094 | 1,738 | (0.18) | 960,011 |
| 6mo | 1,537 | (1.71) | 90,094 | 3,673 | (0.38) | 960,011 |
| 12mo | 2,543 | (2.82) | 90,094 | 5,981 | (0.62) | 960,011 |
| **Self-harm** | | | | | | |
| 2mo | 73 | (0.08) | 90,094 | 2,636 | (0.27) | 960,011 |
| 6mo | 123 | (0.14) | 90,094 | 4,758 | (0.50) | 960,011 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 12mo | 169 | (0.19) | 90,094 | 6,538 | (0.68) | 960,011 |
| **Suicidality** | | | | | | |
| 2mo | 448 | (0.50) | 90,094 | 7,453 | (0.78) | 960,011 |
| 6mo | 702 | (0.78) | 90,094 | 11,814 | (1.23) | 960,011 |
| 12mo | 930 | (1.03) | 90,094 | 15,497 | (1.61) | 960,011 |
| **Completed suicide** | | | | | | |
| 2mo | 7 | (0.01) | 90,094 | 230 | (0.02) | 960,011 |
| 6mo | 10 | (0.01) | 90,094 | 389 | (0.04) | 960,011 |
| 12mo | 17 | (0.02) | 90,094 | 544 | (0.06) | 960,011 |
| **All-cause mortality** | | | | | | |
| 2mo | 1,354 | (1.50) | 90,094 | 4,811 | (0.50) | 960,011 |
| 6mo | 1,354 | (1.50) | 90,094 | 4,811 | (0.50) | 960,011 |
| 12mo | 5,473 | (6.07) | 90,094 | 15,911 | (1.66) | 960,011 |

## A4.6 Regression analyses for all outcomes

***Table A4.6a*** *Regression analyses for efficacy (response) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Efficacy, response *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.09 | 0.94 | 1.28 | 0.133 | 1.05 | 0.76 | 1.46 | 0.684 | 1.17 | 0.74 | 1.87 | 0.376 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 1.43 | 1.24 | 1.66 | <0.001 | 1.47 | 1.20 | 1.81 | <0.001 | 1.35 | 1.02 | 1.79 | 0.005 |
| TCAs | 0.86 | 0.63 | 1.18 | 0.221 | 1.10 | 0.61 | 1.98 | 0.673 | 1.11 | 0.55 | 2.23 | 0.714 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | 1.10 | 0.89 | 1.35 | 0.234 | 1.14 | 0.74 | 1.73 | 0.437 | 1.07 | 0.62 | 1.86 | 0.751 |
| PHQ-9 baseline | 1.02 | 1.01 | 1.03 | <0.001 | 1.05 | 1.03 | 1.06 | <0.001 | 1.05 | 1.03 | 1.07 | <0.001 |
| BMI | 0.99 | 0.99 | 1.00 | 0.001 | 0.98 | 0.97 | 1.00 | 0.002 | 0.99 | 0.97 | 1.00 | 0.061 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.90 | 0.82 | 0.98 | 0.002 | 0.82 | 0.70 | 0.97 | 0.002 | 0.81 | 0.64 | 1.03 | 0.022 |
| Other | 0.86 | 0.64 | 1.16 | 0.192 | 0.64 | 0.37 | 1.11 | 0.036 | 0.90 | 0.52 | 1.55 | 0.604 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.90 | 0.82 | 0.99 | 0.007 | 0.92 | 0.73 | 1.15 | 0.317 | 0.77 | 0.58 | 1.03 | 0.020 |
| 3 | 0.79 | 0.71 | 0.88 | <0.001 | 0.89 | 0.71 | 1.12 | 0.186 | 0.72 | 0.55 | 0.95 | 0.003 |
| 4 | 0.75 | 0.67 | 0.85 | <0.001 | 0.69 | 0.54 | 0.88 | <0.001 | 0.64 | 0.47 | 0.87 | <0.001 |
| 5, most deprived | 0.70 | 0.60 | 0.80 | <0.001 | 0.71 | 0.55 | 0.92 | 0.001 | 0.80 | 0.56 | 1.16 | 0.123 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.88 | 0.57 | 1.38 | 0.471 | 1.40 | 0.77 | 2.54 | 0.153 | 0.82 | 0.39 | 1.73 | 0.491 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| London | 0.91 | 0.69 | 1.20 | 0.366 | 1.26 | 0.77 | 2.06 | 0.223 | 1.04 | 0.58 | 1.85 | 0.861 |
| North East | 0.91 | 0.66 | 1.25 | 0.447 | 1.01 | 0.57 | 1.80 | 0.956 | 1.00 | 0.39 | 2.57 | 0.993 |
| North West | 0.84 | 0.63 | 1.11 | 0.110 | 1.12 | 0.69 | 1.83 | 0.552 | 1.03 | 0.57 | 1.85 | 0.911 |
| South Central | 1.05 | 0.79 | 1.40 | 0.646 | 1.26 | 0.75 | 2.09 | 0.250 | 0.98 | 0.54 | 1.80 | 0.943 |
| South East | 0.95 | 0.72 | 1.26 | 0.637 | 1.13 | 0.65 | 1.97 | 0.580 | 0.89 | 0.48 | 1.64 | 0.623 |
| South West | 0.95 | 0.72 | 1.26 | 0.651 | 0.94 | 0.55 | 1.60 | 0.750 | 0.89 | 0.47 | 1.72 | 0.660 |
| West Midlands | 0.90 | 0.66 | 1.22 | 0.356 | 1.15 | 0.69 | 1.89 | 0.485 | 1.23 | 0.67 | 2.26 | 0.376 |
| Yorkshire & Humber | 0.81 | 0.59 | 1.11 | 0.089 | 1.15 | 0.66 | 1.99 | 0.526 | 1.30 | 0.58 | 2.91 | 0.394 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.02 | 0.94 | 1.10 | 0.532 | 1.04 | 0.86 | 1.26 | 0.590 | 1.01 | 0.79 | 1.29 | 0.894 |
| Light-smoker | 0.74 | 0.68 | 0.81 | <0.001 | 0.69 | 0.58 | 0.83 | <0.001 | 0.78 | 0.61 | 0.98 | 0.005 |
| Moderate-smoker | 0.59 | 0.43 | 0.81 | <0.001 | 0.71 | 0.41 | 1.24 | 0.113 | 0.24 | 0.08 | 0.71 | 0.001 |
| Heavy-smoker | 0.68 | 0.43 | 1.10 | 0.039 | 0.79 | 0.34 | 1.85 | 0.475 | 0.51 | 0.15 | 1.69 | 0.146 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.11 | 1.04 | 1.20 | <0.001 | 1.10 | 0.94 | 1.29 | 0.127 | 1.14 | 0.94 | 1.39 | 0.080 |
| Medium | 1.09 | 0.96 | 1.24 | 0.092 | 1.05 | 0.81 | 1.36 | 0.623 | 0.79 | 0.55 | 1.13 | 0.091 |
| Heavy | 0.98 | 0.73 | 1.33 | 0.893 | 0.69 | 0.38 | 1.25 | 0.108 | 0.58 | 0.22 | 1.50 | 0.140 |
| Very heavy | 0.82 | 0.59 | 1.13 | 0.109 | 0.72 | 0.40 | 1.28 | 0.138 | 0.87 | 0.40 | 1.88 | 0.643 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.71 | 0.54 | 0.94 | 0.002 | 0.82 | 0.51 | 1.30 | 0.270 | 0.60 | 0.30 | 1.17 | 0.047 |
| Asian | 0.80 | 0.65 | 0.99 | 0.007 | 0.91 | 0.60 | 1.38 | 0.568 | 0.82 | 0.43 | 1.57 | 0.440 |
| Other | 0.76 | 0.62 | 0.92 | <0.001 | 0.73 | 0.47 | 1.13 | 0.061 | 0.71 | 0.35 | 1.46 | 0.223 |
| | | | | | | | | | | | | |
| Age | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.00 | 1.01 | 0.002 | 1.01 | 1.00 | 1.02 | 0.003 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.87 | 0.80 | 0.94 | <0.001 | 0.90 | 0.77 | 1.06 | 0.095 | 1.01 | 0.82 | 1.24 | 0.889 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.98 | 0.29 | 3.26 | 0.962 | 1.54 | 0.07 | 35.27 | 0.720 | 0.60 | 0.02 | 17.26 | 0.695 |
| 2011 to 2015 | 0.90 | 0.27 | 3.02 | 0.829 | 1.58 | 0.07 | 36.10 | 0.706 | 0.62 | 0.02 | 17.77 | 0.712 |
| 2016 to 2020 | 0.85 | 0.25 | 2.86 | 0.729 | 1.92 | 0.08 | 44.61 | 0.594 | 0.62 | 0.02 | 18.24 | 0.716 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.67 | 0.52 | 0.85 | <0.001 | 0.69 | 0.40 | 1.20 | 0.082 | 0.86 | 0.44 | 1.66 | 0.554 |
| Stroke | 0.92 | 0.70 | 1.20 | 0.410 | 0.91 | 0.54 | 1.54 | 0.655 | 0.83 | 0.38 | 1.80 | 0.536 |
| Diabetes | 0.94 | 0.80 | 1.11 | 0.335 | 0.73 | 0.49 | 1.08 | 0.036 | 1.16 | 0.72 | 1.85 | 0.428 |
| Epilepsy | 1.12 | 0.80 | 1.56 | 0.396 | 0.78 | 0.40 | 1.52 | 0.338 | 0.97 | 0.44 | 2.12 | 0.924 |
| Hypothyroidism | 0.95 | 0.78 | 1.15 | 0.462 | 1.12 | 0.73 | 1.71 | 0.499 | 1.09 | 0.64 | 1.87 | 0.676 |
| Arthritis | 0.99 | 0.86 | 1.14 | 0.886 | 0.92 | 0.67 | 1.25 | 0.483 | 1.06 | 0.72 | 1.56 | 0.697 |
| Anxiety | 0.99 | 0.89 | 1.09 | 0.751 | 1.06 | 0.86 | 1.30 | 0.469 | 0.95 | 0.70 | 1.28 | 0.653 |
| Migraine | 0.94 | 0.82 | 1.07 | 0.233 | 1.04 | 0.79 | 1.36 | 0.708 | 0.98 | 0.66 | 1.43 | 0.873 |
| Cancer | 1.06 | 0.93 | 1.19 | 0.255 | 1.03 | 0.78 | 1.36 | 0.785 | 1.14 | 0.81 | 1.62 | 0.320 |
| Asthma | 0.97 | 0.89 | 1.06 | 0.389 | 0.95 | 0.79 | 1.15 | 0.521 | 1.04 | 0.79 | 1.38 | 0.708 |
| Renal failure | 0.50 | 0.24 | 1.05 | 0.016 | 0.37 | 0.05 | 3.00 | 0.224 | 1.43 | 0.27 | 7.58 | 0.585 |
| Liver failure | 0.87 | 0.59 | 1.29 | 0.369 | 1.33 | 0.64 | 2.77 | 0.315 | 0.71 | 0.23 | 2.23 | 0.446 |
| Osteoporosis | 0.97 | 0.65 | 1.43 | 0.820 | 0.74 | 0.27 | 2.03 | 0.439 | 0.90 | 0.26 | 3.07 | 0.826 |
| Suicidality | 0.85 | 0.68 | 1.05 | 0.050 | 1.05 | 0.71 | 1.56 | 0.750 | 0.61 | 0.36 | 1.04 | 0.016 |
| Antihypertensive | 0.98 | 0.85 | 1.12 | 0.682 | 1.03 | 0.75 | 1.42 | 0.804 | 0.90 | 0.59 | 1.36 | 0.508 |
| Aspirin | 1.07 | 0.87 | 1.32 | 0.390 | 1.01 | 0.64 | 1.60 | 0.948 | 0.81 | 0.45 | 1.45 | 0.349 |
| Anticoagulants | 0.88 | 0.59 | 1.32 | 0.425 | 1.02 | 0.36 | 2.91 | 0.964 | 0.83 | 0.24 | 2.87 | 0.702 |
| NSAIDs | 0.79 | 0.64 | 0.97 | 0.003 | 0.96 | 0.64 | 1.44 | 0.806 | 0.79 | 0.42 | 1.49 | 0.341 |
| Anticonvulsants | 0.71 | 0.50 | 1.00 | 0.010 | 0.79 | 0.35 | 1.77 | 0.445 | 0.59 | 0.23 | 1.56 | 0.164 |
| Hypnotics | 0.96 | 0.84 | 1.09 | 0.401 | 0.75 | 0.57 | 0.99 | 0.009 | 0.97 | 0.68 | 1.39 | 0.815 |
| Bisphosphonates | 1.36 | 0.66 | 2.80 | 0.268 | 2.62 | 0.52 | 13.32 | 0.126 | 2.75 | 0.33 | 22.62 | 0.217 |
| Contraceptives | 1.10 | 0.96 | 1.26 | 0.069 | 1.06 | 0.80 | 1.40 | 0.588 | 1.21 | 0.82 | 1.79 | 0.211 |
| *Constant* | 0.48 | 0.14 | 1.69 | 0.134 | 0.18 | 0.01 | 4.37 | 0.164 | 0.36 | 0.01 | 10.85 | 0.441 |

| **Efficacy, response *(FSA, N= 1,050,105)*** | | |
|---|---|---|
| *2 months* | *6 months* | *12 months* |

| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Statin** | 1.04 | 0.94 | 1.15 | 0.218 | 1.04 | 0.90 | 1.19 | 0.436 | 1.12 | 0.89 | 1.40 | 0.144 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 1.47 | 1.40 | 1.54 | <0.001 | 1.46 | 1.35 | 1.58 | <0.001 | 1.42 | 1.32 | 1.53 | <0.001 |
| TCAs | 0.82 | 0.65 | 1.02 | 0.018 | 1.21 | 0.97 | 1.49 | 0.020 | 1.12 | 0.89 | 1.41 | 0.142 |
| MAOIs | 0.75 | 0.18 | 3.18 | 0.582 | 0.75 | 0.10 | 5.67 | 0.685 | 0.96 | 0.12 | 7.78 | 0.952 |
| Other antidepressants | 1.11 | 1.01 | 1.23 | 0.007 | 1.20 | 1.01 | 1.41 | 0.006 | 1.14 | 0.96 | 1.37 | 0.038 |
| PHQ-9 baseline | 1.03 | 1.02 | 1.04 | <0.001 | 1.05 | 1.05 | 1.06 | <0.001 | 1.06 | 1.04 | 1.07 | <0.001 |
| BMI | 1.00 | 0.99 | 1.00 | 0.002 | 0.99 | 0.98 | 1.00 | 0.002 | 0.99 | 0.98 | 1.00 | 0.003 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.79 | 0.76 | 0.82 | <0.001 | 0.87 | 0.80 | 0.94 | <0.001 | 0.86 | 0.80 | 0.94 | <0.001 |
| Other | 0.75 | 0.64 | 0.88 | <0.001 | 0.77 | 0.64 | 0.93 | 0.001 | 0.79 | 0.65 | 0.97 | 0.004 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.92 | 0.86 | 0.98 | 0.001 | 0.91 | 0.80 | 1.03 | 0.037 | 0.86 | 0.78 | 0.95 | 0.001 |
| 3 | 0.82 | 0.77 | 0.88 | <0.001 | 0.77 | 0.68 | 0.88 | <0.001 | 0.78 | 0.71 | 0.86 | <0.001 |
| 4 | 0.77 | 0.70 | 0.83 | <0.001 | 0.72 | 0.66 | 0.79 | <0.001 | 0.73 | 0.62 | 0.86 | <0.001 |
| 5, most deprived | 0.71 | 0.65 | 0.77 | <0.001 | 0.69 | 0.59 | 0.80 | <0.001 | 0.72 | 0.61 | 0.85 | <0.001 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.00 | 0.85 | 1.17 | 0.956 | 0.91 | 0.75 | 1.10 | 0.159 | 0.98 | 0.69 | 1.40 | 0.848 |
| London | 1.03 | 0.89 | 1.19 | 0.592 | 1.03 | 0.86 | 1.23 | 0.583 | 1.15 | 0.92 | 1.44 | 0.073 |
| North East | 0.91 | 0.81 | 1.03 | 0.038 | 0.96 | 0.79 | 1.16 | 0.502 | 1.08 | 0.80 | 1.45 | 0.441 |
| North West | 0.95 | 0.80 | 1.13 | 0.400 | 0.87 | 0.73 | 1.03 | 0.023 | 0.97 | 0.83 | 1.14 | 0.607 |
| South Central | 1.10 | 0.96 | 1.25 | 0.048 | 0.99 | 0.81 | 1.20 | 0.819 | 1.01 | 0.81 | 1.25 | 0.904 |
| South East | 1.03 | 0.90 | 1.18 | 0.551 | 0.93 | 0.80 | 1.08 | 0.142 | 0.87 | 0.71 | 1.05 | 0.042 |
| South West | 1.01 | 0.89 | 1.14 | 0.848 | 0.84 | 0.70 | 1.03 | 0.020 | 0.85 | 0.66 | 1.08 | 0.059 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| West Midlands | 1.02 | 0.91 | 1.14 | 0.626 | 0.91 | 0.78 | 1.07 | 0.096 | 1.09 | 0.99 | 1.21 | 0.024 |
| Yorkshire & Humber | 0.96 | 0.81 | 1.14 | 0.448 | 0.88 | 0.72 | 1.09 | 0.096 | 1.02 | 0.82 | 1.27 | 0.745 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.02 | 0.97 | 1.08 | 0.193 | 0.98 | 0.88 | 1.09 | 0.503 | 0.94 | 0.84 | 1.04 | 0.066 |
| Light-smoker | 0.78 | 0.73 | 0.82 | <0.001 | 0.71 | 0.67 | 0.75 | <0.001 | 0.71 | 0.62 | 0.81 | <0.001 |
| Moderate-smoker | 0.74 | 0.66 | 0.83 | <0.001 | 0.68 | 0.54 | 0.86 | <0.001 | 0.60 | 0.45 | 0.80 | <0.001 |
| Heavy-smoker | 0.77 | 0.61 | 0.97 | 0.005 | 0.49 | 0.26 | 0.91 | 0.005 | 0.50 | 0.27 | 0.94 | 0.006 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.05 | 0.99 | 1.11 | 0.026 | 1.05 | 0.96 | 1.15 | 0.094 | 1.15 | 1.04 | 1.27 | 0.002 |
| Medium | 1.03 | 0.96 | 1.11 | 0.230 | 0.97 | 0.85 | 1.11 | 0.530 | 1.02 | 0.78 | 1.33 | 0.796 |
| Heavy | 0.99 | 0.76 | 1.29 | 0.889 | 0.88 | 0.58 | 1.34 | 0.360 | 0.99 | 0.64 | 1.53 | 0.956 |
| Very heavy | 0.96 | 0.85 | 1.09 | 0.344 | 0.88 | 0.61 | 1.27 | 0.292 | 1.03 | 0.75 | 1.42 | 0.741 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.75 | 0.70 | 0.80 | <0.001 | 0.81 | 0.63 | 1.04 | 0.022 | 0.79 | 0.53 | 1.18 | 0.093 |
| Asian | 0.75 | 0.69 | 0.80 | <0.001 | 0.85 | 0.73 | 0.98 | 0.004 | 0.84 | 0.70 | 1.02 | 0.016 |
| Other | 0.74 | 0.66 | 0.83 | <0.001 | 0.79 | 0.68 | 0.92 | 0.001 | 0.74 | 0.55 | 1.01 | 0.012 |
| | | | | | | | | | | | | |
| Age | 1.01 | 1.01 | 1.01 | <0.001 | 1.01 | 1.01 | 1.01 | <0.001 | 1.01 | 1.01 | 1.01 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.94 | 0.91 | 0.97 | <0.001 | 0.98 | 0.92 | 1.06 | 0.506 | 0.94 | 0.83 | 1.07 | 0.168 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.79 | 0.34 | 1.83 | 0.389 | 2.74 | 1.34 | 5.60 | 0.001 | 3.09 | 2.06 | 4.63 | <0.001 |
| 2011 to 2015 | 0.85 | 0.36 | 1.99 | 0.545 | 2.92 | 1.46 | 5.80 | 0.001 | 3.16 | 1.99 | 5.00 | <0.001 |
| 2016 to 2020 | 0.62 | 0.27 | 1.44 | 0.100 | 3.15 | 1.61 | 6.18 | <0.001 | 3.26 | 2.01 | 5.28 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.82 | 0.72 | 0.94 | 0.001 | 0.98 | 0.73 | 1.31 | 0.817 | 0.97 | 0.67 | 1.42 | 0.801 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stroke | 0.95 | 0.83 | 1.09 | 0.267 | 0.86 | 0.63 | 1.18 | 0.151 | 0.88 | 0.64 | 1.22 | 0.245 |
| Diabetes | 0.93 | 0.85 | 1.02 | 0.039 | 0.98 | 0.82 | 1.18 | 0.751 | 1.26 | 0.96 | 1.67 | 0.022 |
| Epilepsy | 1.12 | 0.90 | 1.39 | 0.150 | 0.88 | 0.55 | 1.41 | 0.389 | 1.00 | 0.68 | 1.47 | 0.987 |
| Hypothyroidism | 1.02 | 0.92 | 1.13 | 0.576 | 1.00 | 0.87 | 1.16 | 0.957 | 0.90 | 0.73 | 1.11 | 0.143 |
| Arthritis | 1.00 | 0.91 | 1.11 | 0.931 | 0.97 | 0.86 | 1.11 | 0.542 | 0.90 | 0.75 | 1.09 | 0.110 |
| Anxiety | 0.98 | 0.92 | 1.05 | 0.465 | 1.06 | 0.92 | 1.21 | 0.212 | 1.00 | 0.90 | 1.12 | 0.968 |
| Migraine | 0.96 | 0.87 | 1.05 | 0.155 | 0.93 | 0.74 | 1.18 | 0.372 | 1.01 | 0.79 | 1.30 | 0.852 |
| Cancer | 1.09 | 1.01 | 1.16 | 0.004 | 1.03 | 0.91 | 1.17 | 0.486 | 1.06 | 0.83 | 1.34 | 0.471 |
| Asthma | 1.02 | 0.98 | 1.06 | 0.170 | 0.98 | 0.88 | 1.09 | 0.503 | 0.90 | 0.74 | 1.09 | 0.109 |
| Renal failure | 0.93 | 0.63 | 1.38 | 0.578 | 0.89 | 0.43 | 1.85 | 0.623 | 1.67 | 0.84 | 3.31 | 0.040 |
| Liver failure | 0.88 | 0.75 | 1.04 | 0.043 | 0.98 | 0.76 | 1.27 | 0.843 | 0.78 | 0.52 | 1.16 | 0.073 |
| Osteoporosis | 0.95 | 0.76 | 1.18 | 0.472 | 1.00 | 0.68 | 1.46 | 0.990 | 0.99 | 0.60 | 1.65 | 0.961 |
| Suicidality | 0.89 | 0.82 | 0.97 | 0.002 | 0.82 | 0.67 | 1.00 | 0.010 | 0.91 | 0.69 | 1.19 | 0.281 |
| Antihypertensive | 1.03 | 0.92 | 1.15 | 0.501 | 1.01 | 0.88 | 1.16 | 0.816 | 1.10 | 0.95 | 1.27 | 0.076 |
| Aspirin | 1.00 | 0.87 | 1.16 | 0.944 | 0.96 | 0.74 | 1.23 | 0.591 | 0.90 | 0.63 | 1.29 | 0.366 |
| Anticoagulants | 0.99 | 0.81 | 1.21 | 0.904 | 0.92 | 0.64 | 1.32 | 0.463 | 0.90 | 0.41 | 1.96 | 0.672 |
| NSAIDs | 0.79 | 0.72 | 0.86 | <0.001 | 0.84 | 0.71 | 0.99 | 0.008 | 1.01 | 0.72 | 1.42 | 0.951 |
| Anticonvulsants | 0.80 | 0.61 | 1.06 | 0.030 | 0.86 | 0.60 | 1.24 | 0.221 | 0.75 | 0.45 | 1.24 | 0.094 |
| Hypnotics | 0.92 | 0.87 | 0.97 | <0.001 | 0.86 | 0.76 | 0.97 | 0.002 | 1.01 | 0.88 | 1.17 | 0.760 |
| Bisphosphonates | 1.20 | 0.80 | 1.80 | 0.185 | 0.90 | 0.47 | 1.72 | 0.614 | 0.73 | 0.32 | 1.64 | 0.242 |
| Contraceptives | 1.18 | 1.09 | 1.29 | <0.001 | 1.24 | 1.12 | 1.37 | <0.001 | 1.00 | 0.82 | 1.23 | 0.959 |
| *Constant* | 0.26 | 0.13 | 0.55 | <0.001 | 0.07 | 0.03 | 0.15 | <0.001 | 0.05 | 0.04 | 0.08 | <0.001 |

***Table A4.6b*** *Regression analyses for efficacy (remission) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Efficacy, remission *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.19 | 0.99 | 1.43 | 0.013 | 0.90 | 0.59 | 1.36 | 0.505 | 1.20 | 0.72 | 2.01 | 0.352 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 1.36 | 1.15 | 1.61 | <0.001 | 1.47 | 1.16 | 1.88 | <0.001 | 1.36 | 0.99 | 1.88 | 0.013 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TCAs | 0.78 | 0.50 | 1.20 | 0.133 | 1.20 | 0.59 | 2.43 | 0.508 | 1.13 | 0.49 | 2.62 | 0.698 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | 1.10 | 0.83 | 1.46 | 0.389 | 1.06 | 0.60 | 1.87 | 0.789 | 1.34 | 0.70 | 2.55 | 0.240 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 0.89 | 0.88 | 0.90 | <0.001 | 0.93 | 0.91 | 0.96 | <0.001 | 0.93 | 0.90 | 0.95 | <0.001 |
| BMI | 0.99 | 0.98 | 1.00 | 0.006 | 0.99 | 0.97 | 1.01 | 0.079 | 0.99 | 0.97 | 1.01 | 0.074 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.87 | 0.78 | 0.98 | 0.002 | 0.85 | 0.69 | 1.05 | 0.044 | 0.88 | 0.66 | 1.16 | 0.232 |
| Other | 1.10 | 0.77 | 1.56 | 0.489 | 1.06 | 0.55 | 2.02 | 0.830 | 1.11 | 0.63 | 1.95 | 0.624 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.91 | 0.80 | 1.03 | 0.054 | 0.86 | 0.67 | 1.11 | 0.132 | 0.94 | 0.66 | 1.34 | 0.653 |
| 3 | 0.79 | 0.69 | 0.91 | <0.001 | 0.86 | 0.66 | 1.12 | 0.136 | 0.82 | 0.57 | 1.19 | 0.171 |
| 4 | 0.77 | 0.66 | 0.89 | <0.001 | 0.71 | 0.54 | 0.93 | 0.001 | 0.76 | 0.51 | 1.13 | 0.075 |
| 5, most deprived | 0.73 | 0.62 | 0.87 | <0.001 | 0.73 | 0.54 | 1.00 | 0.010 | 0.81 | 0.51 | 1.29 | 0.246 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.90 | 0.51 | 1.61 | 0.644 | 1.33 | 0.70 | 2.53 | 0.256 | 0.70 | 0.26 | 1.85 | 0.340 |
| London | 0.94 | 0.63 | 1.42 | 0.713 | 1.08 | 0.68 | 1.69 | 0.679 | 0.94 | 0.49 | 1.78 | 0.789 |
| North East | 1.08 | 0.68 | 1.71 | 0.681 | 1.17 | 0.64 | 2.13 | 0.501 | 1.24 | 0.51 | 3.04 | 0.538 |
| North West | 0.86 | 0.57 | 1.30 | 0.345 | 0.98 | 0.61 | 1.56 | 0.902 | 0.93 | 0.48 | 1.80 | 0.770 |
| South Central | 1.15 | 0.74 | 1.78 | 0.407 | 1.10 | 0.64 | 1.90 | 0.650 | 0.87 | 0.44 | 1.71 | 0.599 |
| South East | 0.96 | 0.63 | 1.47 | 0.813 | 0.99 | 0.59 | 1.66 | 0.959 | 0.69 | 0.36 | 1.32 | 0.138 |
| South West | 0.96 | 0.62 | 1.50 | 0.826 | 0.80 | 0.45 | 1.42 | 0.315 | 0.55 | 0.26 | 1.17 | 0.040 |
| West Midlands | 0.93 | 0.59 | 1.45 | 0.656 | 1.07 | 0.64 | 1.79 | 0.719 | 1.01 | 0.49 | 2.08 | 0.959 |
| Yorkshire & Humber | 0.78 | 0.50 | 1.23 | 0.156 | 0.96 | 0.52 | 1.75 | 0.851 | 1.01 | 0.42 | 2.45 | 0.968 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.05 | 0.95 | 1.17 | 0.195 | 1.00 | 0.79 | 1.26 | 0.981 | 1.04 | 0.78 | 1.39 | 0.706 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Light-smoker | 0.82 | 0.74 | 0.92 | <0.001 | 0.73 | 0.58 | 0.92 | 0.001 | 0.79 | 0.58 | 1.06 | 0.040 |
| Moderate-smoker | 0.75 | 0.49 | 1.14 | 0.078 | 0.65 | 0.31 | 1.34 | 0.123 | 0.18 | 0.03 | 1.14 | 0.017 |
| Heavy-smoker | 0.80 | 0.42 | 1.51 | 0.363 | 0.73 | 0.22 | 2.44 | 0.500 | 0.41 | 0.06 | 2.90 | 0.241 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.02 | 0.93 | 1.12 | 0.552 | 1.03 | 0.85 | 1.24 | 0.690 | 1.17 | 0.93 | 1.48 | 0.085 |
| Medium | 1.03 | 0.88 | 1.21 | 0.635 | 0.96 | 0.70 | 1.31 | 0.749 | 1.00 | 0.65 | 1.53 | 0.991 |
| Heavy | 0.87 | 0.57 | 1.33 | 0.405 | 0.81 | 0.36 | 1.81 | 0.507 | 0.45 | 0.11 | 1.87 | 0.150 |
| Very heavy | 0.87 | 0.56 | 1.36 | 0.432 | 0.79 | 0.36 | 1.71 | 0.434 | 0.59 | 0.17 | 2.04 | 0.277 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.73 | 0.49 | 1.08 | 0.040 | 0.62 | 0.31 | 1.25 | 0.079 | 0.86 | 0.34 | 2.17 | 0.673 |
| Asian | 0.69 | 0.50 | 0.95 | 0.003 | 0.85 | 0.52 | 1.38 | 0.388 | 0.91 | 0.43 | 1.93 | 0.754 |
| Other | 0.90 | 0.67 | 1.20 | 0.326 | 0.86 | 0.50 | 1.49 | 0.481 | 0.75 | 0.33 | 1.70 | 0.366 |
| | | | | | | | | | | | | |
| Age | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.00 | 1.02 | 0.007 | 1.01 | 1.00 | 1.02 | 0.096 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.87 | 0.79 | 0.96 | <0.001 | 0.95 | 0.79 | 1.15 | 0.505 | 0.95 | 0.74 | 1.21 | 0.567 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.75 | 0.18 | 3.12 | 0.608 | 1.79 | 0.48 | 6.63 | 0.252 | 1.09 | 0.03 | 42.36 | 0.950 |
| 2011 to 2015 | 0.69 | 0.17 | 2.84 | 0.495 | 1.82 | 0.49 | 6.74 | 0.240 | 1.08 | 0.03 | 42.02 | 0.956 |
| 2016 to 2020 | 0.61 | 0.15 | 2.54 | 0.370 | 2.28 | 0.59 | 8.71 | 0.115 | 1.16 | 0.03 | 46.37 | 0.917 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.60 | 0.44 | 0.81 | <0.001 | 0.79 | 0.43 | 1.47 | 0.333 | 1.21 | 0.61 | 2.38 | 0.470 |
| Stroke | 0.88 | 0.62 | 1.24 | 0.326 | 0.98 | 0.51 | 1.90 | 0.951 | 0.53 | 0.24 | 1.17 | 0.040 |
| Diabetes | 0.88 | 0.71 | 1.09 | 0.127 | 0.77 | 0.51 | 1.18 | 0.117 | 1.57 | 0.92 | 2.67 | 0.029 |
| Epilepsy | 0.97 | 0.63 | 1.51 | 0.869 | 0.69 | 0.31 | 1.54 | 0.234 | 1.53 | 0.71 | 3.30 | 0.157 |
| Hypothyroidism | 1.00 | 0.79 | 1.27 | 0.992 | 1.10 | 0.68 | 1.77 | 0.616 | 1.29 | 0.69 | 2.42 | 0.296 |
| Arthritis | 1.05 | 0.88 | 1.24 | 0.507 | 1.19 | 0.82 | 1.73 | 0.234 | 0.86 | 0.53 | 1.40 | 0.426 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Anxiety | 0.96 | 0.84 | 1.09 | 0.403 | 1.08 | 0.86 | 1.36 | 0.390 | 0.92 | 0.65 | 1.30 | 0.517 |
| Migraine | 0.82 | 0.68 | 0.98 | 0.005 | 0.91 | 0.66 | 1.26 | 0.452 | 0.98 | 0.62 | 1.55 | 0.912 |
| Cancer | 1.01 | 0.86 | 1.18 | 0.914 | 0.95 | 0.68 | 1.34 | 0.707 | 1.14 | 0.73 | 1.79 | 0.440 |
| Asthma | 0.98 | 0.87 | 1.10 | 0.628 | 0.92 | 0.73 | 1.16 | 0.355 | 1.10 | 0.78 | 1.55 | 0.469 |
| Renal failure | 0.64 | 0.25 | 1.67 | 0.229 | 1.00 | | | | 0.50 | 0.05 | 5.00 | 0.441 |
| Liver failure | 0.80 | 0.48 | 1.33 | 0.253 | 1.44 | 0.61 | 3.41 | 0.279 | 0.69 | 0.16 | 2.92 | 0.505 |
| Osteoporosis | 1.12 | 0.72 | 1.76 | 0.503 | 0.93 | 0.29 | 3.00 | 0.875 | 0.80 | 0.24 | 2.72 | 0.646 |
| Suicidality | 0.85 | 0.64 | 1.13 | 0.150 | 0.98 | 0.61 | 1.58 | 0.923 | 0.67 | 0.33 | 1.34 | 0.133 |
| Antihypertensive | 0.94 | 0.79 | 1.11 | 0.310 | 1.13 | 0.78 | 1.63 | 0.389 | 0.63 | 0.37 | 1.08 | 0.028 |
| Aspirin | 1.04 | 0.79 | 1.36 | 0.714 | 1.04 | 0.64 | 1.68 | 0.845 | 1.14 | 0.60 | 2.16 | 0.609 |
| Anticoagulants | 0.83 | 0.50 | 1.36 | 0.323 | 1.13 | 0.39 | 3.32 | 0.762 | 1.58 | 0.53 | 4.67 | 0.279 |
| NSAIDs | 0.81 | 0.60 | 1.08 | 0.058 | 1.02 | 0.62 | 1.68 | 0.915 | 1.03 | 0.53 | 2.02 | 0.909 |
| Anticonvulsants | 0.71 | 0.43 | 1.15 | 0.065 | 1.02 | 0.38 | 2.73 | 0.954 | 0.52 | 0.18 | 1.54 | 0.120 |
| Hypnotics | 0.99 | 0.83 | 1.17 | 0.858 | 0.79 | 0.56 | 1.12 | 0.085 | 1.10 | 0.73 | 1.67 | 0.535 |
| Bisphosphonates | 0.82 | 0.34 | 2.00 | 0.566 | 2.31 | 0.47 | 11.38 | 0.177 | 4.87 | 0.95 | 24.98 | 0.013 |
| Contraceptives | 1.08 | 0.91 | 1.29 | 0.250 | 1.08 | 0.77 | 1.52 | 0.566 | 0.96 | 0.58 | 1.61 | 0.844 |
| *Constant* | 1.84 | 0.42 | 8.08 | 0.288 | 0.42 | 0.10 | 1.77 | 0.120 | 0.78 | 0.02 | 31.69 | 0.860 |

| | **Efficacy, remission *(FSA, N= 1,050,105)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.03 | 0.94 | 1.13 | 0.335 | 1.03 | 0.89 | 1.20 | 0.521 | 1.11 | 0.90 | 1.38 | 0.139 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 1.44 | 1.38 | 1.51 | <0.001 | 1.45 | 1.32 | 1.58 | <0.001 | 1.42 | 1.30 | 1.56 | <0.001 |
| TCAs | 0.84 | 0.69 | 1.03 | 0.023 | 1.24 | 0.97 | 1.58 | 0.019 | 1.14 | 0.87 | 1.50 | 0.153 |
| MAOIs | 0.67 | 0.14 | 3.16 | 0.473 | 0.74 | 0.13 | 4.11 | 0.640 | 1.12 | 0.09 | 13.51 | 0.896 |
| Other antidepressants | 1.10 | 0.99 | 1.23 | 0.019 | 1.20 | 1.01 | 1.44 | 0.009 | 1.15 | 0.96 | 1.39 | 0.037 |
| PHQ-9 baseline | 0.88 | 0.87 | 0.89 | <0.001 | 0.92 | 0.91 | 0.93 | <0.001 | 0.92 | 0.90 | 0.93 | <0.001 |
| BMI | 1.00 | 0.99 | 1.00 | 0.007 | 0.99 | 0.98 | 1.00 | 0.002 | 0.99 | 0.98 | 1.00 | 0.004 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.78 | 0.75 | 0.82 | <0.001 | 0.87 | 0.79 | 0.95 | 0.001 | 0.85 | 0.78 | 0.94 | <0.001 |
| Other | 0.77 | 0.67 | 0.89 | <0.001 | 0.80 | 0.65 | 0.99 | 0.007 | 0.82 | 0.68 | 1.00 | 0.010 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.92 | 0.86 | 0.98 | 0.002 | 0.91 | 0.80 | 1.04 | 0.049 | 0.86 | 0.78 | 0.96 | 0.001 |
| 3 | 0.83 | 0.77 | 0.90 | <0.001 | 0.78 | 0.69 | 0.88 | <0.001 | 0.78 | 0.71 | 0.85 | <0.001 |
| 4 | 0.78 | 0.71 | 0.86 | <0.001 | 0.73 | 0.67 | 0.79 | <0.001 | 0.73 | 0.62 | 0.86 | <0.001 |
| 5, most deprived | 0.73 | 0.66 | 0.80 | <0.001 | 0.70 | 0.61 | 0.80 | <0.001 | 0.72 | 0.61 | 0.86 | <0.001 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.00 | 0.86 | 1.17 | 0.956 | 0.91 | 0.76 | 1.09 | 0.133 | 0.98 | 0.68 | 1.43 | 0.887 |
| London | 1.02 | 0.88 | 1.19 | 0.673 | 1.03 | 0.86 | 1.23 | 0.596 | 1.16 | 0.93 | 1.45 | 0.058 |
| North East | 0.93 | 0.82 | 1.06 | 0.121 | 0.96 | 0.79 | 1.17 | 0.512 | 1.10 | 0.82 | 1.48 | 0.339 |
| North West | 0.96 | 0.81 | 1.14 | 0.480 | 0.87 | 0.74 | 1.03 | 0.028 | 0.98 | 0.82 | 1.18 | 0.796 |
| South Central | 1.10 | 0.96 | 1.26 | 0.057 | 0.98 | 0.80 | 1.21 | 0.797 | 1.01 | 0.81 | 1.27 | 0.870 |
| South East | 1.03 | 0.89 | 1.19 | 0.541 | 0.93 | 0.79 | 1.10 | 0.201 | 0.87 | 0.72 | 1.06 | 0.055 |
| South West | 1.00 | 0.88 | 1.14 | 0.911 | 0.84 | 0.68 | 1.03 | 0.024 | 0.84 | 0.66 | 1.08 | 0.055 |
| West Midlands | 1.03 | 0.91 | 1.15 | 0.538 | 0.92 | 0.77 | 1.09 | 0.144 | 1.10 | 0.98 | 1.24 | 0.026 |
| Yorkshire & Humber | 0.96 | 0.82 | 1.13 | 0.474 | 0.88 | 0.69 | 1.11 | 0.118 | 1.03 | 0.83 | 1.28 | 0.656 |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.02 | 0.97 | 1.07 | 0.193 | 0.98 | 0.88 | 1.08 | 0.520 | 0.93 | 0.84 | 1.04 | 0.077 |
| Light-smoker | 0.79 | 0.75 | 0.84 | <0.001 | 0.71 | 0.67 | 0.76 | <0.001 | 0.71 | 0.61 | 0.83 | <0.001 |
| Moderate-smoker | 0.76 | 0.67 | 0.86 | <0.001 | 0.70 | 0.53 | 0.92 | 0.002 | 0.59 | 0.43 | 0.82 | <0.001 |
| Heavy-smoker | 0.79 | 0.63 | 0.98 | 0.006 | 0.48 | 0.25 | 0.95 | 0.007 | 0.50 | 0.27 | 0.94 | 0.006 |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.04 | 0.98 | 1.11 | 0.059 | 1.05 | 0.96 | 1.15 | 0.099 | 1.15 | 1.04 | 1.27 | 0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medium | 1.03 | 0.95 | 1.10 | 0.307 | 0.97 | 0.86 | 1.10 | 0.487 | 1.02 | 0.77 | 1.34 | 0.840 |
| Heavy | 0.98 | 0.74 | 1.29 | 0.818 | 0.89 | 0.57 | 1.41 | 0.455 | 1.00 | 0.65 | 1.53 | 0.989 |
| Very heavy | 0.96 | 0.85 | 1.08 | 0.357 | 0.88 | 0.61 | 1.26 | 0.284 | 1.04 | 0.73 | 1.48 | 0.749 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.76 | 0.69 | 0.83 | <0.001 | 0.81 | 0.61 | 1.07 | 0.038 | 0.80 | 0.53 | 1.20 | 0.109 |
| Asian | 0.76 | 0.71 | 0.83 | <0.001 | 0.85 | 0.75 | 0.96 | 0.002 | 0.84 | 0.70 | 1.01 | 0.012 |
| Other | 0.75 | 0.65 | 0.87 | <0.001 | 0.79 | 0.68 | 0.94 | 0.001 | 0.74 | 0.52 | 1.05 | 0.023 |
| | | | | | | | | | | | | |
| Age | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.01 | 1.01 | <0.001 | 1.01 | 1.01 | 1.01 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.94 | 0.91 | 0.96 | <0.001 | 0.99 | 0.92 | 1.06 | 0.575 | 0.95 | 0.83 | 1.08 | 0.197 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.76 | 0.34 | 1.73 | 0.313 | 2.52 | 1.27 | 4.98 | 0.002 | 2.82 | 1.97 | 4.03 | <0.001 |
| 2011 to 2015 | 0.82 | 0.35 | 1.90 | 0.462 | 2.67 | 1.38 | 5.15 | 0.001 | 2.87 | 1.91 | 4.32 | <0.001 |
| 2016 to 2020 | 0.58 | 0.26 | 1.33 | 0.064 | 2.88 | 1.50 | 5.53 | 0.001 | 2.94 | 1.90 | 4.55 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.83 | 0.71 | 0.96 | 0.002 | 0.99 | 0.74 | 1.31 | 0.894 | 0.99 | 0.68 | 1.44 | 0.903 |
| Stroke | 0.95 | 0.85 | 1.06 | 0.168 | 0.86 | 0.65 | 1.15 | 0.131 | 0.88 | 0.62 | 1.26 | 0.297 |
| Diabetes | 0.93 | 0.83 | 1.03 | 0.054 | 0.99 | 0.82 | 1.21 | 0.914 | 1.28 | 0.97 | 1.70 | 0.019 |
| Epilepsy | 1.12 | 0.87 | 1.42 | 0.193 | 0.87 | 0.54 | 1.39 | 0.359 | 0.98 | 0.66 | 1.47 | 0.906 |
| Hypothyroidism | 1.01 | 0.92 | 1.11 | 0.732 | 1.00 | 0.86 | 1.17 | 0.922 | 0.90 | 0.72 | 1.12 | 0.145 |
| Arthritis | 1.00 | 0.92 | 1.09 | 0.936 | 0.98 | 0.87 | 1.10 | 0.555 | 0.89 | 0.74 | 1.07 | 0.081 |
| Anxiety | 0.98 | 0.91 | 1.05 | 0.343 | 1.06 | 0.92 | 1.22 | 0.207 | 1.01 | 0.92 | 1.11 | 0.768 |
| Migraine | 0.96 | 0.88 | 1.05 | 0.173 | 0.93 | 0.74 | 1.18 | 0.360 | 1.02 | 0.79 | 1.31 | 0.831 |
| Cancer | 1.07 | 1.00 | 1.15 | 0.009 | 1.02 | 0.90 | 1.15 | 0.637 | 1.05 | 0.83 | 1.34 | 0.493 |
| Asthma | 1.02 | 0.97 | 1.06 | 0.243 | 0.97 | 0.88 | 1.08 | 0.436 | 0.90 | 0.74 | 1.10 | 0.124 |
| Renal failure | 0.92 | 0.59 | 1.45 | 0.584 | 0.88 | 0.41 | 1.87 | 0.589 | 1.67 | 0.81 | 3.42 | 0.046 |
| Liver failure | 0.88 | 0.77 | 1.02 | 0.027 | 1.00 | 0.73 | 1.37 | 0.987 | 0.77 | 0.51 | 1.18 | 0.081 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Osteoporosis | 0.95 | 0.77 | 1.17 | 0.427 | 1.00 | 0.66 | 1.50 | 0.974 | 1.00 | 0.60 | 1.66 | 0.987 |
| Suicidality | 0.91 | 0.81 | 1.01 | 0.023 | 0.82 | 0.66 | 1.02 | 0.016 | 0.92 | 0.70 | 1.19 | 0.316 |
| Antihypertensive | 1.03 | 0.92 | 1.15 | 0.490 | 1.00 | 0.86 | 1.17 | 0.930 | 1.09 | 0.94 | 1.27 | 0.098 |
| Aspirin | 1.01 | 0.86 | 1.17 | 0.907 | 0.97 | 0.74 | 1.26 | 0.683 | 0.91 | 0.63 | 1.30 | 0.406 |
| Anticoagulants | 0.98 | 0.77 | 1.23 | 0.749 | 0.92 | 0.62 | 1.35 | 0.486 | 0.89 | 0.41 | 1.93 | 0.639 |
| NSAIDs | 0.80 | 0.73 | 0.87 | <0.001 | 0.85 | 0.72 | 1.00 | 0.011 | 1.02 | 0.73 | 1.42 | 0.878 |
| Anticonvulsants | 0.80 | 0.58 | 1.10 | 0.052 | 0.86 | 0.60 | 1.25 | 0.231 | 0.75 | 0.45 | 1.24 | 0.099 |
| Hypnotics | 0.92 | 0.88 | 0.97 | <0.001 | 0.86 | 0.76 | 0.98 | 0.003 | 1.02 | 0.88 | 1.19 | 0.681 |
| Bisphosphonates | 1.16 | 0.75 | 1.81 | 0.314 | 0.89 | 0.46 | 1.70 | 0.567 | 0.71 | 0.30 | 1.66 | 0.224 |
| Contraceptives | 1.17 | 1.08 | 1.25 | <0.001 | 1.23 | 1.11 | 1.36 | <0.001 | 0.99 | 0.80 | 1.24 | 0.925 |
| *Constant* | 1.12 | 0.52 | 2.38 | 0.651 | 0.24 | 0.11 | 0.52 | <0.001 | 0.18 | 0.13 | 0.25 | <0.001 |

***Table A4.6c*** *Regression analyses for efficacy (change in depression score) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Efficacy, change in depression score *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | -0.15 | -0.55 | 0.26 | 0.349 | 0.01 | -0.92 | 0.94 | 0.976 | -0.78 | -2.13 | 0.56 | 0.133 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | -1.22 | -1.59 | -0.85 | <0.001 | -1.61 | -2.18 | -1.03 | <0.001 | -0.94 | -1.67 | -0.21 | 0.001 |
| TCAs | 0.50 | -0.32 | 1.31 | 0.117 | -0.81 | -2.35 | 0.73 | 0.173 | 0.37 | -1.49 | 2.23 | 0.608 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | -0.70 | -1.27 | -0.13 | 0.002 | -0.89 | -2.12 | 0.33 | 0.060 | -0.27 | -1.83 | 1.29 | 0.655 |
| PHQ-9 baseline | -0.52 | -0.54 | -0.50 | <0.001 | -0.64 | -0.69 | -0.59 | <0.001 | -0.66 | -0.72 | -0.59 | <0.001 |
| BMI | 0.03 | 0.01 | 0.04 | <0.001 | 0.05 | 0.01 | 0.08 | 0.001 | 0.06 | 0.00 | 0.11 | 0.005 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.41 | 0.16 | 0.66 | <0.001 | 0.64 | 0.15 | 1.13 | 0.001 | 0.64 | -0.04 | 1.33 | 0.016 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Other | 0.51 | -0.28 | 1.30 | 0.095 | 0.59 | -0.92 | 2.10 | 0.311 | 0.30 | -1.20 | 1.80 | 0.607 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.34 | 0.07 | 0.61 | 0.001 | 0.57 | -0.08 | 1.23 | 0.024 | 0.99 | 0.14 | 1.84 | 0.003 |
| 3 | 0.77 | 0.48 | 1.06 | <0.001 | 0.60 | -0.07 | 1.26 | 0.021 | 1.29 | 0.47 | 2.11 | <0.001 |
| 4 | 1.01 | 0.68 | 1.34 | <0.001 | 1.22 | 0.56 | 1.88 | <0.001 | 1.61 | 0.70 | 2.52 | <0.001 |
| 5, most deprived | 1.21 | 0.83 | 1.58 | <0.001 | 1.12 | 0.36 | 1.87 | <0.001 | 1.25 | 0.18 | 2.33 | 0.003 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.13 | -1.16 | 1.43 | 0.789 | -0.41 | -2.36 | 1.55 | 0.591 | 0.14 | -2.18 | 2.45 | 0.878 |
| London | -0.06 | -0.96 | 0.85 | 0.873 | -0.76 | -2.18 | 0.66 | 0.167 | -0.18 | -1.95 | 1.58 | 0.791 |
| North East | 0.22 | -0.87 | 1.30 | 0.607 | 0.39 | -1.41 | 2.18 | 0.579 | 0.09 | -3.10 | 3.27 | 0.943 |
| North West | 0.37 | -0.57 | 1.31 | 0.304 | -0.31 | -1.76 | 1.15 | 0.585 | 0.17 | -1.62 | 1.97 | 0.802 |
| South Central | -0.46 | -1.37 | 0.45 | 0.192 | -0.78 | -2.31 | 0.75 | 0.187 | 0.31 | -1.50 | 2.13 | 0.658 |
| South East | -0.03 | -0.96 | 0.89 | 0.925 | -0.38 | -2.04 | 1.27 | 0.549 | 0.44 | -1.33 | 2.20 | 0.523 |
| South West | -0.18 | -1.09 | 0.73 | 0.613 | 0.34 | -1.22 | 1.90 | 0.578 | 1.02 | -1.02 | 3.05 | 0.198 |
| West Midlands | 0.12 | -0.83 | 1.07 | 0.740 | -0.47 | -1.94 | 1.01 | 0.414 | -0.48 | -2.28 | 1.32 | 0.491 |
| Yorkshire & Humber | 0.30 | -0.70 | 1.31 | 0.436 | -0.67 | -2.32 | 0.98 | 0.293 | -0.79 | -3.31 | 1.74 | 0.422 |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | -0.02 | -0.24 | 0.20 | 0.789 | -0.30 | -0.87 | 0.26 | 0.164 | 0.08 | -0.63 | 0.78 | 0.779 |
| Light-smoker | 1.00 | 0.76 | 1.25 | <0.001 | 1.29 | 0.76 | 1.81 | <0.001 | 1.12 | 0.44 | 1.81 | <0.001 |
| Moderate-smoker | 1.47 | 0.68 | 2.27 | <0.001 | 1.30 | -0.48 | 3.08 | 0.060 | 2.85 | 0.88 | 4.83 | <0.001 |
| Heavy-smoker | 0.91 | -0.21 | 2.03 | 0.035 | 1.94 | -0.72 | 4.61 | 0.060 | 3.92 | 0.62 | 7.22 | 0.002 |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | -0.29 | -0.49 | -0.10 | <0.001 | -0.23 | -0.67 | 0.22 | 0.189 | -0.43 | -1.03 | 0.18 | 0.069 |
| Medium | -0.36 | -0.71 | -0.02 | 0.006 | -0.14 | -0.90 | 0.63 | 0.649 | 0.45 | -0.52 | 1.42 | 0.234 |
| Heavy | 0.22 | -0.60 | 1.04 | 0.487 | 1.12 | -0.68 | 2.92 | 0.108 | 1.90 | -0.51 | 4.32 | 0.042 |
| Very heavy | 0.79 | -0.04 | 1.63 | 0.015 | 1.27 | -0.47 | 3.00 | 0.061 | 1.63 | -0.77 | 4.02 | 0.080 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.23 | 0.50 | 1.96 | <0.001 | 1.00 | -0.26 | 2.26 | 0.041 | 1.63 | -0.24 | 3.50 | 0.025 |
| Asian | 0.92 | 0.34 | 1.50 | <0.001 | 0.64 | -0.45 | 1.73 | 0.130 | 0.94 | -0.89 | 2.77 | 0.186 |
| Other | 0.98 | 0.46 | 1.50 | <0.001 | 1.25 | 0.02 | 2.47 | 0.009 | 1.19 | -0.78 | 3.17 | 0.119 |
| Age | -0.02 | -0.03 | -0.01 | <0.001 | -0.04 | -0.06 | -0.02 | <0.001 | -0.03 | -0.05 | 0.00 | 0.002 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.49 | 0.29 | 0.70 | <0.001 | 0.26 | -0.20 | 0.71 | 0.151 | 0.13 | -0.43 | 0.70 | 0.544 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.53 | -2.78 | 3.84 | 0.678 | 3.05 | 0.57 | 5.53 | 0.002 | -1.31 | -11.00 | 8.39 | 0.728 |
| 2011 to 2015 | 0.66 | -2.65 | 3.97 | 0.606 | 2.97 | 0.51 | 5.44 | 0.002 | -1.37 | -11.04 | 8.31 | 0.715 |
| 2016 to 2020 | 1.08 | -2.25 | 4.41 | 0.403 | 2.57 | 0.00 | 5.14 | 0.010 | -1.34 | -11.06 | 8.38 | 0.723 |
| Coronary heart disease | 0.81 | 0.17 | 1.44 | 0.001 | 0.80 | -0.61 | 2.21 | 0.143 | -0.12 | -1.83 | 1.60 | 0.860 |
| Stroke | 0.10 | -0.60 | 0.79 | 0.718 | 0.23 | -1.18 | 1.64 | 0.672 | 0.65 | -1.34 | 2.64 | 0.398 |
| Diabetes | 0.19 | -0.24 | 0.62 | 0.247 | 0.66 | -0.34 | 1.66 | 0.089 | -0.30 | -1.75 | 1.15 | 0.594 |
| Epilepsy | 0.14 | -0.78 | 1.06 | 0.696 | 1.99 | -0.09 | 4.06 | 0.014 | -0.45 | -2.66 | 1.76 | 0.599 |
| Hypothyroidism | 0.10 | -0.39 | 0.59 | 0.602 | -0.26 | -1.43 | 0.90 | 0.562 | -0.85 | -2.35 | 0.64 | 0.142 |
| Arthritis | 0.02 | -0.36 | 0.40 | 0.894 | 0.32 | -0.60 | 1.24 | 0.370 | -0.14 | -1.26 | 0.99 | 0.755 |
| Anxiety | 0.20 | -0.07 | 0.46 | 0.057 | -0.07 | -0.68 | 0.54 | 0.762 | 0.19 | -0.73 | 1.10 | 0.597 |
| Migraine | 0.36 | 0.00 | 0.72 | 0.010 | 0.21 | -0.62 | 1.03 | 0.519 | -0.11 | -1.22 | 1.01 | 0.806 |
| Cancer | -0.28 | -0.61 | 0.05 | 0.030 | -0.11 | -0.93 | 0.72 | 0.742 | -0.43 | -1.47 | 0.60 | 0.282 |
| Asthma | 0.04 | -0.19 | 0.28 | 0.631 | 0.15 | -0.38 | 0.68 | 0.462 | 0.06 | -0.74 | 0.85 | 0.857 |
| Renal failure | 0.97 | -0.52 | 2.46 | 0.093 | 5.46 | 1.13 | 9.78 | 0.001 | -0.32 | -5.59 | 4.96 | 0.877 |
| Liver failure | 0.33 | -0.70 | 1.35 | 0.409 | -0.51 | -2.80 | 1.79 | 0.569 | 0.67 | -2.32 | 3.65 | 0.563 |
| Osteoporosis | -0.49 | -1.47 | 0.49 | 0.197 | 0.54 | -2.10 | 3.18 | 0.595 | 0.22 | -2.64 | 3.09 | 0.840 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suicidality | 0.55 | 0.00 | 1.10 | 0.010 | 0.44 | -0.88 | 1.77 | 0.390 | 1.25 | -0.33 | 2.82 | 0.042 |
| Antihypertensive | -0.05 | -0.39 | 0.30 | 0.730 | -0.26 | -1.19 | 0.67 | 0.467 | 0.33 | -0.86 | 1.52 | 0.475 |
| Aspirin | 0.13 | -0.44 | 0.70 | 0.549 | 0.35 | -0.85 | 1.55 | 0.455 | 1.07 | -0.54 | 2.68 | 0.086 |
| Anticoagulants | 0.40 | -0.61 | 1.41 | 0.309 | 1.07 | -1.75 | 3.90 | 0.326 | -0.86 | -3.77 | 2.05 | 0.446 |
| NSAIDs | 0.97 | 0.44 | 1.50 | <0.001 | 0.26 | -0.94 | 1.46 | 0.573 | 0.26 | -1.58 | 2.09 | 0.719 |
| Anticonvulsants | 0.86 | -0.02 | 1.74 | 0.012 | 0.80 | -1.65 | 3.26 | 0.398 | 2.01 | -0.54 | 4.56 | 0.042 |
| Hypnotics | 0.22 | -0.13 | 0.57 | 0.109 | 0.60 | -0.18 | 1.37 | 0.048 | -0.34 | -1.40 | 0.71 | 0.403 |
| Bisphosphonates | 0.55 | -1.32 | 2.43 | 0.446 | -2.48 | -5.13 | 0.17 | 0.016 | -3.21 | -6.53 | 0.11 | 0.013 |
| Contraceptives | -0.53 | -0.88 | -0.17 | <0.001 | -0.29 | -1.12 | 0.54 | 0.366 | -0.31 | -1.44 | 0.83 | 0.485 |
| *Constant* | 2.23 | -1.23 | 5.69 | 0.097 | 2.88 | -0.17 | 5.93 | 0.015 | 6.28 | -3.45 | 16.00 | 0.096 |

| | **Efficacy, change in depression score *(FSA, N= 1,050,105)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | -0.10 | -0.35 | 0.16 | 0.272 | -0.12 | -0.73 | 0.49 | 0.509 | -0.41 | -1.31 | 0.48 | 0.140 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | -1.24 | -1.36 | -1.12 | <0.001 | -1.33 | -1.61 | -1.05 | <0.001 | -1.17 | -1.44 | -0.89 | <0.001 |
| TCAs | 0.80 | 0.09 | 1.51 | 0.006 | -0.70 | -1.68 | 0.28 | 0.040 | -0.39 | -1.49 | 0.70 | 0.232 |
| MAOIs | 0.97 | -1.83 | 3.76 | 0.338 | 0.18 | -4.61 | 4.97 | 0.909 | -0.05 | -5.92 | 5.81 | 0.978 |
| Other antidepressants | -0.35 | -0.67 | -0.02 | 0.007 | -0.66 | -1.20 | -0.12 | 0.003 | -0.41 | -1.11 | 0.29 | 0.083 |
| PHQ-9 baseline | -0.54 | -0.57 | -0.52 | <0.001 | -0.67 | -0.71 | -0.63 | <0.001 | -0.68 | -0.75 | -0.61 | <0.001 |
| BMI | 0.02 | 0.00 | 0.03 | 0.002 | 0.04 | 0.01 | 0.06 | 0.002 | 0.05 | 0.00 | 0.09 | 0.007 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.79 | 0.66 | 0.91 | <0.001 | 0.52 | 0.20 | 0.85 | 0.001 | 0.55 | 0.22 | 0.87 | 0.001 |
| Other | 0.86 | 0.30 | 1.42 | 0.001 | 0.81 | 0.03 | 1.59 | 0.009 | 0.69 | -0.08 | 1.45 | 0.016 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.30 | 0.10 | 0.49 | 0.001 | 0.37 | -0.15 | 0.89 | 0.041 | 0.54 | 0.11 | 0.98 | 0.003 |
| 3 | 0.65 | 0.40 | 0.90 | <0.001 | 0.96 | 0.46 | 1.46 | <0.001 | 0.91 | 0.55 | 1.26 | <0.001 |
| 4 | 0.88 | 0.59 | 1.17 | <0.001 | 1.19 | 0.86 | 1.53 | <0.001 | 1.15 | 0.44 | 1.85 | 0.001 |
| 5, most deprived | 1.14 | 0.86 | 1.42 | <0.001 | 1.34 | 0.76 | 1.93 | <0.001 | 1.18 | 0.51 | 1.85 | 0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.01 | -0.47 | 0.49 | 0.940 | 0.37 | -0.41 | 1.15 | 0.159 | 0.11 | -1.53 | 1.75 | 0.805 |
| London | -0.09 | -0.52 | 0.34 | 0.516 | -0.10 | -0.84 | 0.65 | 0.677 | -0.49 | -1.46 | 0.48 | 0.112 |
| North East | 0.28 | -0.06 | 0.62 | 0.026 | 0.19 | -0.58 | 0.96 | 0.437 | -0.27 | -1.53 | 0.99 | 0.467 |
| North West | 0.15 | -0.33 | 0.63 | 0.340 | 0.54 | -0.17 | 1.25 | 0.035 | 0.11 | -0.52 | 0.75 | 0.558 |
| South Central | -0.32 | -0.70 | 0.06 | 0.023 | 0.07 | -0.73 | 0.88 | 0.768 | -0.01 | -0.93 | 0.91 | 0.971 |
| South East | -0.10 | -0.48 | 0.29 | 0.448 | 0.30 | -0.25 | 0.85 | 0.113 | 0.53 | -0.22 | 1.28 | 0.043 |
| South West | -0.03 | -0.39 | 0.33 | 0.812 | 0.65 | -0.12 | 1.41 | 0.022 | 0.63 | -0.30 | 1.57 | 0.049 |
| West Midlands | -0.07 | -0.40 | 0.25 | 0.498 | 0.34 | -0.25 | 0.94 | 0.095 | -0.31 | -0.67 | 0.05 | 0.021 |
| Yorkshire & Humber | 0.12 | -0.41 | 0.65 | 0.496 | 0.47 | -0.32 | 1.26 | 0.081 | -0.06 | -0.85 | 0.73 | 0.807 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | -0.07 | -0.25 | 0.10 | 0.205 | 0.09 | -0.37 | 0.54 | 0.522 | 0.25 | -0.12 | 0.62 | 0.049 |
| Light-smoker | 0.82 | 0.60 | 1.04 | <0.001 | 1.23 | 1.00 | 1.47 | <0.001 | 1.21 | 0.69 | 1.73 | <0.001 |
| Moderate-smoker | 0.96 | 0.59 | 1.33 | <0.001 | 1.34 | 0.51 | 2.16 | 0.001 | 1.80 | 0.71 | 2.89 | 0.001 |
| Heavy-smoker | 0.84 | 0.10 | 1.58 | 0.005 | 2.53 | -0.04 | 5.10 | 0.011 | 2.39 | 0.02 | 4.76 | 0.010 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | -0.16 | -0.35 | 0.03 | 0.021 | -0.18 | -0.52 | 0.16 | 0.102 | -0.50 | -0.93 | -0.07 | 0.005 |
| Medium | -0.11 | -0.37 | 0.15 | 0.212 | 0.10 | -0.38 | 0.58 | 0.493 | -0.08 | -1.51 | 1.35 | 0.809 |
| Heavy | 0.06 | -0.75 | 0.87 | 0.815 | 0.45 | -1.18 | 2.09 | 0.353 | 0.02 | -1.73 | 1.78 | 0.964 |
| Very heavy | 0.13 | -0.30 | 0.57 | 0.353 | 0.45 | -0.92 | 1.83 | 0.279 | -0.13 | -1.25 | 0.99 | 0.700 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| African/Caribbean | 0.93 | 0.65 | 1.21 | <0.001 | 0.74 | -0.30 | 1.78 | 0.037 | 0.79 | -1.24 | 2.82 | 0.138 |
| Asian | 0.90 | 0.65 | 1.16 | <0.001 | 0.59 | 0.04 | 1.15 | 0.007 | 0.60 | -0.20 | 1.41 | 0.033 |
| Other | 0.93 | 0.60 | 1.27 | <0.001 | 0.85 | 0.26 | 1.43 | 0.001 | 1.02 | -0.27 | 2.32 | 0.026 |
| Age | -0.02 | -0.03 | -0.02 | <0.001 | -0.03 | -0.04 | -0.03 | <0.001 | -0.04 | -0.05 | -0.02 | <0.001 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.21 | 0.13 | 0.29 | <0.001 | 0.04 | -0.27 | 0.36 | 0.631 | 0.20 | -0.41 | 0.82 | 0.235 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.94 | -101.31 | 103.18 | 0.472 | -3.25 | -48.45 | 41.94 | 0.141 | -3.64 | -5.82 | -1.45 | 0.002 |
| 2011 to 2015 | 0.70 | -146.88 | 148.27 | 0.576 | -3.49 | -35.06 | 28.09 | 0.112 | -3.70 | -6.70 | -0.71 | 0.006 |
| 2016 to 2020 | 1.69 | -245.32 | 248.71 | 0.348 | -3.79 | -36.31 | 28.74 | 0.102 | -3.83 | -7.66 | 0.00 | 0.010 |
| Coronary heart disease | 0.61 | 0.16 | 1.07 | 0.002 | 0.04 | -1.16 | 1.23 | 0.914 | 0.07 | -1.69 | 1.82 | 0.882 |
| Stroke | 0.17 | -0.22 | 0.57 | 0.191 | 0.58 | -0.81 | 1.96 | 0.167 | 0.46 | -1.01 | 1.92 | 0.278 |
| Diabetes | 0.22 | -0.08 | 0.52 | 0.043 | 0.06 | -0.76 | 0.87 | 0.809 | -0.88 | -2.12 | 0.37 | 0.036 |
| Epilepsy | -0.33 | -0.97 | 0.32 | 0.135 | 0.50 | -1.46 | 2.47 | 0.374 | 0.00 | -1.44 | 1.44 | 0.998 |
| Hypothyroidism | -0.05 | -0.36 | 0.27 | 0.651 | -0.01 | -0.62 | 0.59 | 0.941 | 0.39 | -0.61 | 1.39 | 0.204 |
| Arthritis | -0.01 | -0.33 | 0.31 | 0.952 | 0.10 | -0.43 | 0.63 | 0.540 | 0.38 | -0.36 | 1.13 | 0.112 |
| Anxiety | 0.07 | -0.17 | 0.31 | 0.368 | -0.20 | -0.76 | 0.35 | 0.229 | -0.01 | -0.43 | 0.42 | 0.958 |
| Migraine | 0.15 | -0.19 | 0.50 | 0.178 | 0.28 | -0.69 | 1.25 | 0.318 | -0.05 | -1.03 | 0.92 | 0.847 |
| Cancer | -0.27 | -0.52 | -0.02 | 0.007 | -0.11 | -0.61 | 0.39 | 0.459 | -0.23 | -1.35 | 0.89 | 0.443 |
| Asthma | -0.07 | -0.18 | 0.04 | 0.089 | 0.08 | -0.35 | 0.52 | 0.514 | 0.38 | -0.56 | 1.33 | 0.146 |
| Renal failure | 0.15 | -1.17 | 1.47 | 0.718 | 0.43 | -2.48 | 3.34 | 0.608 | -1.85 | -4.77 | 1.07 | 0.057 |
| Liver failure | 0.42 | -0.21 | 1.05 | 0.061 | 0.09 | -0.94 | 1.13 | 0.769 | 0.96 | -0.64 | 2.55 | 0.074 |
| Osteoporosis | 0.18 | -0.61 | 0.96 | 0.479 | -0.01 | -1.68 | 1.66 | 0.987 | -0.02 | -2.37 | 2.34 | 0.978 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suicidality | 0.39 | 0.06 | 0.71 | 0.004 | 0.72 | -0.06 | 1.49 | 0.015 | 0.31 | -0.72 | 1.34 | 0.321 |
| Antihypertensive | -0.07 | -0.42 | 0.28 | 0.511 | -0.03 | -0.58 | 0.51 | 0.834 | -0.33 | -0.95 | 0.28 | 0.099 |
| Aspirin | -0.03 | -0.48 | 0.43 | 0.860 | 0.13 | -0.94 | 1.21 | 0.659 | 0.38 | -1.29 | 2.06 | 0.385 |
| Anticoagulants | 0.04 | -0.58 | 0.67 | 0.825 | 0.33 | -1.29 | 1.95 | 0.484 | 0.38 | -4.50 | 5.26 | 0.689 |
| NSAIDs | 0.79 | 0.50 | 1.08 | <0.001 | 0.63 | -0.03 | 1.30 | 0.012 | -0.02 | -1.47 | 1.43 | 0.960 |
| Anticonvulsants | 0.72 | -0.04 | 1.48 | 0.013 | 0.56 | -0.97 | 2.08 | 0.232 | 1.09 | -1.14 | 3.32 | 0.110 |
| Hypnotics | 0.28 | 0.11 | 0.46 | <0.001 | 0.54 | 0.03 | 1.05 | 0.008 | -0.07 | -0.65 | 0.52 | 0.708 |
| Bisphosphonates | -0.56 | -1.91 | 0.80 | 0.212 | 0.42 | -2.20 | 3.05 | 0.586 | 1.20 | -2.35 | 4.74 | 0.254 |
| Contraceptives | -0.55 | -0.85 | -0.26 | <0.001 | -0.78 | -1.21 | -0.35 | <0.001 | 0.01 | -0.84 | 0.86 | 0.959 |
| *Constant* | 3.91 | 0.18 | 7.63 | 0.009 | 9.60 | 5.18 | 14.02 | 0.001 | 10.57 | 9.44 | 11.70 | <0.001 |

***Table A4.6d*** *Regression analyses for adverse events (any adverse event) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Adverse events, any adverse event *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 0.92 | 0.84 | 1.02 | 0.032 | 0.97 | 0.89 | 1.06 | 0.333 | 0.99 | 0.91 | 1.09 | 0.873 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 2.38 | 2.21 | 2.55 | <0.001 | 1.86 | 1.75 | 1.98 | <0.001 | 1.66 | 1.56 | 1.77 | <0.001 |
| TCAs | 2.38 | 2.01 | 2.81 | <0.001 | 1.92 | 1.65 | 2.23 | <0.001 | 1.75 | 1.47 | 2.08 | <0.001 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | 2.54 | 2.23 | 2.89 | <0.001 | 2.02 | 1.78 | 2.29 | <0.001 | 1.80 | 1.59 | 2.04 | <0.001 |
| PHQ-9 baseline | 1.01 | 1.00 | 1.01 | 0.017 | 1.00 | 1.00 | 1.01 | 0.473 | 1.00 | 1.00 | 1.01 | 0.879 |
| BMI | 1.00 | 1.00 | 1.00 | 0.436 | 1.00 | 1.00 | 1.01 | 0.123 | 1.00 | 1.00 | 1.01 | 0.002 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.74 | 1.62 | 1.87 | <0.001 | 1.63 | 1.53 | 1.74 | <0.001 | 1.59 | 1.49 | 1.70 | <0.001 |
| Other | 0.75 | 0.62 | 0.89 | <0.001 | 0.82 | 0.70 | 0.95 | 0.001 | 0.81 | 0.69 | 0.95 | 0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.98 | 0.92 | 1.04 | 0.399 | 1.02 | 0.96 | 1.08 | 0.516 | 1.02 | 0.95 | 1.09 | 0.493 |
| 3 | 1.03 | 0.95 | 1.10 | 0.385 | 1.03 | 0.96 | 1.11 | 0.260 | 1.01 | 0.94 | 1.10 | 0.642 |
| 4 | 1.02 | 0.93 | 1.12 | 0.535 | 1.08 | 0.99 | 1.18 | 0.021 | 1.06 | 0.97 | 1.17 | 0.082 |
| 5, most deprived | 1.09 | 0.99 | 1.21 | 0.026 | 1.13 | 1.02 | 1.24 | 0.002 | 1.11 | 1.00 | 1.23 | 0.013 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.70 | 0.46 | 1.08 | 0.033 | 0.71 | 0.46 | 1.09 | 0.039 | 0.71 | 0.45 | 1.12 | 0.051 |
| London | 0.76 | 0.55 | 1.05 | 0.029 | 0.80 | 0.59 | 1.08 | 0.053 | 0.79 | 0.59 | 1.07 | 0.044 |
| North East | 0.84 | 0.57 | 1.21 | 0.215 | 0.85 | 0.58 | 1.23 | 0.255 | 0.91 | 0.62 | 1.34 | 0.527 |
| North West | 0.85 | 0.61 | 1.19 | 0.221 | 0.88 | 0.64 | 1.21 | 0.302 | 0.91 | 0.66 | 1.25 | 0.460 |
| South Central | 0.68 | 0.48 | 0.97 | 0.006 | 0.72 | 0.51 | 1.01 | 0.012 | 0.73 | 0.52 | 1.03 | 0.018 |
| South East | 0.83 | 0.58 | 1.18 | 0.176 | 0.89 | 0.63 | 1.25 | 0.367 | 0.88 | 0.64 | 1.22 | 0.319 |
| South West | 0.82 | 0.58 | 1.16 | 0.143 | 0.84 | 0.60 | 1.19 | 0.208 | 0.88 | 0.62 | 1.25 | 0.334 |
| West Midlands | 0.74 | 0.51 | 1.07 | 0.037 | 0.79 | 0.56 | 1.11 | 0.074 | 0.82 | 0.59 | 1.15 | 0.136 |
| Yorkshire & Humber | 0.96 | 0.64 | 1.44 | 0.802 | 0.96 | 0.65 | 1.43 | 0.796 | 0.96 | 0.65 | 1.43 | 0.805 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.06 | 1.01 | 1.12 | 0.002 | 1.05 | 1.00 | 1.10 | 0.010 | 1.05 | 1.00 | 1.11 | 0.018 |
| Light-smoker | 0.96 | 0.91 | 1.01 | 0.052 | 0.99 | 0.94 | 1.04 | 0.572 | 1.00 | 0.95 | 1.05 | 0.837 |
| Moderate-smoker | 0.99 | 0.83 | 1.19 | 0.941 | 1.00 | 0.85 | 1.18 | 0.978 | 1.03 | 0.86 | 1.23 | 0.659 |
| Heavy-smoker | 1.03 | 0.81 | 1.30 | 0.788 | 0.98 | 0.77 | 1.25 | 0.816 | 0.91 | 0.71 | 1.18 | 0.371 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.00 | 0.96 | 1.05 | 0.812 | 1.00 | 0.96 | 1.04 | 0.991 | 0.98 | 0.94 | 1.03 | 0.369 |
| Medium | 0.99 | 0.92 | 1.06 | 0.695 | 1.01 | 0.94 | 1.09 | 0.728 | 1.00 | 0.93 | 1.08 | 0.987 |
| Heavy | 1.05 | 0.90 | 1.24 | 0.406 | 0.97 | 0.83 | 1.14 | 0.661 | 0.92 | 0.77 | 1.09 | 0.189 |
| Very heavy | 0.98 | 0.84 | 1.14 | 0.697 | 1.01 | 0.87 | 1.18 | 0.824 | 0.96 | 0.82 | 1.12 | 0.481 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.92 | 0.80 | 1.06 | 0.129 | 1.08 | 0.94 | 1.25 | 0.163 | 1.19 | 1.02 | 1.40 | 0.005 |
| Asian | 0.93 | 0.82 | 1.05 | 0.107 | 1.02 | 0.90 | 1.15 | 0.704 | 1.04 | 0.91 | 1.19 | 0.432 |
| Other | 1.02 | 0.91 | 1.14 | 0.658 | 1.08 | 0.97 | 1.20 | 0.075 | 1.07 | 0.95 | 1.20 | 0.152 |
| Age | 1.00 | 1.00 | 1.01 | <0.001 | 1.00 | 1.00 | 1.01 | <0.001 | 1.01 | 1.00 | 1.01 | <0.001 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.93 | 0.89 | 0.97 | <0.001 | 0.83 | 0.80 | 0.87 | <0.001 | 0.77 | 0.74 | 0.81 | <0.001 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.37 | 0.77 | 2.45 | 0.159 | 1.51 | 0.97 | 2.37 | 0.018 | 1.68 | 1.30 | 2.18 | <0.001 |
| 2011 to 2015 | 1.63 | 0.91 | 2.92 | 0.029 | 1.65 | 1.06 | 2.58 | 0.004 | 1.79 | 1.38 | 2.31 | <0.001 |
| 2016 to 2020 | 2.06 | 1.15 | 3.69 | 0.001 | 1.87 | 1.20 | 2.93 | <0.001 | 1.79 | 1.38 | 2.32 | <0.001 |
| Coronary heart disease | 1.11 | 0.98 | 1.25 | 0.038 | 1.23 | 1.08 | 1.39 | <0.001 | 1.34 | 1.15 | 1.55 | <0.001 |
| Stroke | 1.17 | 1.02 | 1.35 | 0.003 | 1.13 | 0.98 | 1.31 | 0.022 | 1.17 | 0.99 | 1.37 | 0.014 |
| Diabetes | 1.07 | 0.98 | 1.17 | 0.052 | 1.20 | 1.10 | 1.31 | <0.001 | 1.37 | 1.24 | 1.51 | <0.001 |
| Epilepsy | 1.13 | 0.94 | 1.35 | 0.091 | 1.22 | 1.02 | 1.46 | 0.005 | 1.21 | 0.99 | 1.49 | 0.016 |
| Hypothyroidism | 1.01 | 0.90 | 1.12 | 0.871 | 1.02 | 0.91 | 1.13 | 0.686 | 1.03 | 0.91 | 1.16 | 0.561 |
| Arthritis | 1.10 | 1.01 | 1.19 | 0.003 | 1.18 | 1.08 | 1.28 | <0.001 | 1.23 | 1.12 | 1.34 | <0.001 |
| Anxiety | 1.72 | 1.61 | 1.83 | <0.001 | 1.75 | 1.64 | 1.87 | <0.001 | 1.74 | 1.63 | 1.86 | <0.001 |
| Migraine | 1.16 | 1.08 | 1.25 | <0.001 | 1.27 | 1.18 | 1.37 | <0.001 | 1.36 | 1.25 | 1.48 | <0.001 |
| Cancer | 1.09 | 1.02 | 1.18 | 0.002 | 1.17 | 1.08 | 1.25 | <0.001 | 1.21 | 1.12 | 1.32 | <0.001 |
| Asthma | 1.19 | 1.13 | 1.25 | <0.001 | 1.38 | 1.31 | 1.46 | <0.001 | 1.51 | 1.43 | 1.60 | <0.001 |
| Renal failure | 1.44 | 1.03 | 2.01 | 0.005 | 1.62 | 1.13 | 2.33 | 0.001 | 1.92 | 1.21 | 3.03 | <0.001 |
| Liver failure | 1.12 | 0.91 | 1.37 | 0.159 | 1.33 | 1.10 | 1.61 | <0.001 | 1.35 | 1.09 | 1.69 | <0.001 |
| Osteoporosis | 1.07 | 0.85 | 1.35 | 0.463 | 1.17 | 0.93 | 1.47 | 0.086 | 1.26 | 0.97 | 1.64 | 0.023 |
| Suicidality | 1.22 | 1.09 | 1.37 | <0.001 | 1.20 | 1.07 | 1.36 | <0.001 | 1.22 | 1.07 | 1.38 | <0.001 |
| Antihypertensive | 1.02 | 0.94 | 1.10 | 0.608 | 1.06 | 0.98 | 1.14 | 0.068 | 1.07 | 0.98 | 1.16 | 0.057 |
| Aspirin | 1.08 | 0.96 | 1.21 | 0.102 | 1.11 | 0.99 | 1.25 | 0.018 | 1.16 | 1.02 | 1.32 | 0.002 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Anticoagulants | 1.30 | 1.07 | 1.59 | 0.001 | 1.43 | 1.16 | 1.75 | <0.001 | 1.76 | 1.37 | 2.26 | <0.001 |
| NSAIDs | 1.04 | 0.93 | 1.16 | 0.342 | 1.12 | 1.00 | 1.25 | 0.009 | 1.24 | 1.10 | 1.39 | <0.001 |
| Anticonvulsants | 1.20 | 0.99 | 1.45 | 0.014 | 1.39 | 1.14 | 1.69 | <0.001 | 1.55 | 1.22 | 1.96 | <0.001 |
| Hypnotics | 1.20 | 1.11 | 1.30 | <0.001 | 1.14 | 1.06 | 1.23 | <0.001 | 1.13 | 1.04 | 1.23 | <0.001 |
| Bisphosphonates | 1.09 | 0.73 | 1.63 | 0.563 | 1.11 | 0.74 | 1.66 | 0.509 | 1.00 | 0.62 | 1.62 | 0.996 |
| Contraceptives | 1.01 | 0.93 | 1.09 | 0.868 | 1.08 | 1.00 | 1.17 | 0.009 | 1.07 | 0.98 | 1.16 | 0.050 |
| *Constant* | 0.15 | 0.08 | 0.30 | <0.001 | 0.33 | 0.19 | 0.58 | <0.001 | 0.51 | 0.33 | 0.77 | <0.001 |

| | **Adverse events, any adverse event *(FSA, N= 1,050,105)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 0.93 | 0.91 | 0.96 | <0.001 | 0.97 | 0.94 | 1.00 | 0.008 | 0.99 | 0.96 | 1.03 | 0.637 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 2.60 | 2.52 | 2.68 | <0.001 | 1.99 | 1.94 | 2.05 | <0.001 | 1.78 | 1.73 | 1.83 | <0.001 |
| TCAs | 2.96 | 2.82 | 3.11 | <0.001 | 2.23 | 2.13 | 2.34 | <0.001 | 2.01 | 1.91 | 2.12 | <0.001 |
| MAOIs | 2.21 | 1.26 | 3.87 | <0.001 | 1.72 | 0.99 | 2.99 | 0.011 | 1.44 | 0.81 | 2.56 | 0.105 |
| Other antidepressants | 2.70 | 2.59 | 2.81 | <0.001 | 2.10 | 2.02 | 2.18 | <0.001 | 1.85 | 1.78 | 1.93 | <0.001 |
| PHQ-9 baseline | 1.00 | 1.00 | 1.00 | 0.022 | 1.00 | 1.00 | 1.00 | 0.043 | 1.00 | 1.00 | 1.00 | 0.053 |
| BMI | 1.00 | 1.00 | 1.00 | 0.087 | 1.00 | 1.00 | 1.00 | <0.001 | 1.01 | 1.00 | 1.01 | <0.001 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.53 | 1.48 | 1.59 | <0.001 | 1.48 | 1.43 | 1.53 | <0.001 | 1.48 | 1.43 | 1.53 | <0.001 |
| Other | 0.67 | 0.63 | 0.72 | <0.001 | 0.73 | 0.68 | 0.78 | <0.001 | 0.75 | 0.69 | 0.81 | <0.001 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.01 | 0.98 | 1.04 | 0.495 | 1.02 | 0.99 | 1.06 | 0.059 | 1.03 | 0.99 | 1.06 | 0.055 |
| 3 | 1.02 | 0.98 | 1.06 | 0.255 | 1.05 | 1.01 | 1.09 | 0.002 | 1.04 | 1.00 | 1.09 | 0.013 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 1.01 | 0.96 | 1.06 | 0.684 | 1.05 | 1.00 | 1.10 | 0.020 | 1.03 | 0.97 | 1.09 | 0.186 |
| 5, most deprived | 1.09 | 1.03 | 1.15 | <0.001 | 1.13 | 1.06 | 1.20 | <0.001 | 1.09 | 1.02 | 1.16 | 0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.79 | 0.60 | 1.03 | 0.021 | 0.80 | 0.62 | 1.04 | 0.030 | 0.83 | 0.64 | 1.07 | 0.060 |
| London | 0.76 | 0.66 | 0.88 | <0.001 | 0.80 | 0.70 | 0.93 | <0.001 | 0.83 | 0.72 | 0.96 | 0.001 |
| North East | 0.91 | 0.73 | 1.15 | 0.313 | 0.94 | 0.74 | 1.18 | 0.463 | 0.98 | 0.76 | 1.26 | 0.839 |
| North West | 0.88 | 0.75 | 1.03 | 0.038 | 0.93 | 0.79 | 1.08 | 0.190 | 0.97 | 0.83 | 1.13 | 0.559 |
| South Central | 0.71 | 0.59 | 0.86 | <0.001 | 0.75 | 0.63 | 0.89 | <0.001 | 0.77 | 0.65 | 0.93 | <0.001 |
| South East | 0.75 | 0.61 | 0.91 | <0.001 | 0.79 | 0.65 | 0.95 | 0.001 | 0.81 | 0.67 | 0.98 | 0.005 |
| South West | 0.92 | 0.78 | 1.10 | 0.244 | 0.95 | 0.80 | 1.13 | 0.435 | 0.98 | 0.82 | 1.17 | 0.720 |
| West Midlands | 0.74 | 0.62 | 0.88 | <0.001 | 0.79 | 0.67 | 0.93 | <0.001 | 0.84 | 0.71 | 0.99 | 0.008 |
| Yorkshire & Humber | 0.90 | 0.74 | 1.10 | 0.190 | 0.92 | 0.75 | 1.12 | 0.284 | 0.95 | 0.77 | 1.17 | 0.506 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.03 | 1.01 | 1.05 | <0.001 | 1.05 | 1.03 | 1.07 | <0.001 | 1.06 | 1.04 | 1.09 | <0.001 |
| Light-smoker | 0.97 | 0.95 | 0.99 | <0.001 | 1.00 | 0.98 | 1.01 | 0.553 | 1.00 | 0.98 | 1.02 | 0.673 |
| Moderate-smoker | 0.96 | 0.90 | 1.01 | 0.041 | 0.98 | 0.93 | 1.04 | 0.454 | 1.00 | 0.95 | 1.06 | 0.888 |
| Heavy-smoker | 0.98 | 0.90 | 1.07 | 0.641 | 1.00 | 0.93 | 1.09 | 0.902 | 0.99 | 0.91 | 1.08 | 0.750 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.97 | 0.95 | 0.99 | 0.002 | 0.96 | 0.95 | 0.98 | <0.001 | 0.96 | 0.94 | 0.98 | <0.001 |
| Medium | 0.98 | 0.96 | 1.01 | 0.118 | 0.97 | 0.95 | 1.00 | 0.014 | 0.96 | 0.94 | 0.99 | 0.002 |
| Heavy | 0.99 | 0.94 | 1.04 | 0.594 | 0.98 | 0.93 | 1.04 | 0.385 | 0.98 | 0.93 | 1.04 | 0.388 |
| Very heavy | 0.98 | 0.92 | 1.05 | 0.383 | 0.98 | 0.93 | 1.04 | 0.347 | 0.97 | 0.92 | 1.03 | 0.223 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.96 | 0.93 | 1.00 | 0.004 | 1.00 | 0.96 | 1.04 | 0.852 | 1.01 | 0.97 | 1.05 | 0.631 |
| Asian | 1.04 | 0.98 | 1.09 | 0.084 | 1.15 | 1.08 | 1.22 | <0.001 | 1.20 | 1.12 | 1.28 | <0.001 |
| Other | 1.02 | 0.98 | 1.06 | 0.309 | 1.07 | 1.03 | 1.11 | <0.001 | 1.08 | 1.03 | 1.13 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 1.01 | 1.01 | 1.01 | <0.001 | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.01 | 1.01 | <0.001 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.92 | 0.90 | 0.93 | <0.001 | 0.82 | 0.81 | 0.83 | <0.001 | 0.76 | 0.75 | 0.77 | <0.001 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.12 | 1.06 | 1.18 | <0.001 | 1.10 | 1.04 | 1.15 | <0.001 | 1.07 | 1.02 | 1.13 | 0.001 |
| 2011 to 2015 | 1.25 | 1.17 | 1.32 | <0.001 | 1.19 | 1.12 | 1.26 | <0.001 | 1.14 | 1.08 | 1.22 | <0.001 |
| 2016 to 2020 | 1.30 | 1.22 | 1.39 | <0.001 | 1.13 | 1.06 | 1.20 | <0.001 | 0.98 | 0.91 | 1.04 | 0.339 |
| Coronary heart disease | 1.12 | 1.09 | 1.16 | <0.001 | 1.17 | 1.13 | 1.22 | <0.001 | 1.24 | 1.18 | 1.30 | <0.001 |
| Stroke | 1.11 | 1.07 | 1.15 | <0.001 | 1.17 | 1.12 | 1.22 | <0.001 | 1.21 | 1.16 | 1.27 | <0.001 |
| Diabetes | 1.07 | 1.04 | 1.10 | <0.001 | 1.17 | 1.13 | 1.21 | <0.001 | 1.29 | 1.23 | 1.35 | <0.001 |
| Epilepsy | 1.07 | 1.01 | 1.12 | 0.001 | 1.15 | 1.10 | 1.21 | <0.001 | 1.23 | 1.16 | 1.30 | <0.001 |
| Hypothyroidism | 1.02 | 0.99 | 1.05 | 0.089 | 1.07 | 1.03 | 1.10 | <0.001 | 1.10 | 1.06 | 1.14 | <0.001 |
| Arthritis | 1.10 | 1.07 | 1.13 | <0.001 | 1.21 | 1.18 | 1.24 | <0.001 | 1.27 | 1.23 | 1.31 | <0.001 |
| Anxiety | 1.52 | 1.47 | 1.56 | <0.001 | 1.57 | 1.53 | 1.61 | <0.001 | 1.59 | 1.54 | 1.63 | <0.001 |
| Migraine | 1.13 | 1.10 | 1.16 | <0.001 | 1.23 | 1.20 | 1.26 | <0.001 | 1.31 | 1.27 | 1.34 | <0.001 |
| Cancer | 1.13 | 1.10 | 1.15 | <0.001 | 1.20 | 1.17 | 1.23 | <0.001 | 1.28 | 1.25 | 1.32 | <0.001 |
| Asthma | 1.26 | 1.23 | 1.28 | <0.001 | 1.43 | 1.40 | 1.45 | <0.001 | 1.56 | 1.52 | 1.59 | <0.001 |
| Renal failure | 1.38 | 1.27 | 1.51 | <0.001 | 1.44 | 1.31 | 1.59 | <0.001 | 1.62 | 1.44 | 1.82 | <0.001 |
| Liver failure | 1.10 | 1.03 | 1.17 | <0.001 | 1.24 | 1.17 | 1.32 | <0.001 | 1.29 | 1.20 | 1.38 | <0.001 |
| Osteoporosis | 1.12 | 1.07 | 1.18 | <0.001 | 1.20 | 1.14 | 1.26 | <0.001 | 1.31 | 1.23 | 1.39 | <0.001 |
| Suicidality | 1.15 | 1.11 | 1.20 | <0.001 | 1.20 | 1.15 | 1.25 | <0.001 | 1.19 | 1.13 | 1.24 | <0.001 |
| Antihypertensive | 0.99 | 0.97 | 1.02 | 0.519 | 1.03 | 1.01 | 1.06 | 0.002 | 1.05 | 1.01 | 1.08 | <0.001 |
| Aspirin | 1.07 | 1.03 | 1.10 | <0.001 | 1.10 | 1.06 | 1.14 | <0.001 | 1.14 | 1.09 | 1.19 | <0.001 |
| Anticoagulants | 1.35 | 1.29 | 1.42 | <0.001 | 1.52 | 1.44 | 1.61 | <0.001 | 1.70 | 1.59 | 1.81 | <0.001 |
| NSAIDs | 1.11 | 1.07 | 1.14 | <0.001 | 1.17 | 1.13 | 1.20 | <0.001 | 1.21 | 1.17 | 1.25 | <0.001 |
| Anticonvulsants | 1.35 | 1.29 | 1.42 | <0.001 | 1.48 | 1.40 | 1.55 | <0.001 | 1.54 | 1.45 | 1.63 | <0.001 |
| Hypnotics | 1.21 | 1.18 | 1.25 | <0.001 | 1.17 | 1.14 | 1.20 | <0.001 | 1.15 | 1.12 | 1.18 | <0.001 |
| Bisphosphonates | 1.15 | 1.04 | 1.26 | <0.001 | 1.16 | 1.05 | 1.28 | <0.001 | 1.16 | 1.03 | 1.31 | 0.002 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Contraceptives | 1.01 | 0.98 | 1.04 | 0.380 | 1.08 | 1.05 | 1.11 | <0.001 | 1.12 | 1.09 | 1.15 | <0.001 |
| *Constant* | 0.20 | 0.17 | 0.23 | <0.001 | 0.45 | 0.39 | 0.51 | <0.001 | 0.72 | 0.62 | 0.84 | <0.001 |

***Table A4.6e*** *Regression analyses for adverse events (any psychiatric symptom) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Adverse events, any psychiatric symptom *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 0.97 | 0.86 | 1.09 | 0.494 | 0.94 | 0.84 | 1.04 | 0.117 | 0.92 | 0.83 | 1.02 | 0.045 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 3.61 | 3.24 | 4.03 | <0.001 | 2.88 | 2.62 | 3.16 | <0.001 | 2.50 | 2.30 | 2.71 | <0.001 |
| TCAs | 3.85 | 3.11 | 4.78 | <0.001 | 3.23 | 2.67 | 3.92 | <0.001 | 2.75 | 2.29 | 3.29 | <0.001 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | 3.48 | 2.90 | 4.17 | <0.001 | 2.93 | 2.52 | 3.42 | <0.001 | 2.62 | 2.28 | 3.02 | <0.001 |
| PHQ-9 baseline | 1.01 | 1.00 | 1.02 | <0.001 | 1.01 | 1.00 | 1.02 | <0.001 | 1.01 | 1.00 | 1.02 | 0.001 |
| BMI | 1.00 | 0.99 | 1.00 | 0.706 | 1.00 | 0.99 | 1.00 | 0.082 | 1.00 | 0.99 | 1.00 | 0.061 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 6.71 | 5.93 | 7.58 | <0.001 | 5.46 | 4.86 | 6.12 | <0.001 | 4.71 | 4.24 | 5.24 | <0.001 |
| Other | 0.91 | 0.67 | 1.23 | 0.423 | 0.92 | 0.73 | 1.16 | 0.369 | 0.98 | 0.81 | 1.19 | 0.831 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.98 | 0.90 | 1.06 | 0.548 | 0.99 | 0.92 | 1.06 | 0.639 | 0.99 | 0.93 | 1.06 | 0.728 |
| 3 | 1.01 | 0.92 | 1.12 | 0.750 | 1.03 | 0.94 | 1.12 | 0.422 | 1.04 | 0.96 | 1.14 | 0.200 |
| 4 | 0.97 | 0.87 | 1.09 | 0.521 | 1.08 | 0.97 | 1.20 | 0.064 | 1.11 | 1.00 | 1.22 | 0.012 |
| 5, most deprived | 1.13 | 0.98 | 1.30 | 0.026 | 1.21 | 1.06 | 1.37 | <0.001 | 1.24 | 1.11 | 1.40 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.94 | 0.56 | 1.59 | 0.779 | 0.85 | 0.54 | 1.33 | 0.351 | 0.88 | 0.57 | 1.34 | 0.430 |
| London | 0.97 | 0.59 | 1.58 | 0.856 | 0.95 | 0.63 | 1.43 | 0.738 | 0.98 | 0.67 | 1.43 | 0.880 |
| North East | 0.91 | 0.56 | 1.50 | 0.637 | 0.86 | 0.57 | 1.32 | 0.374 | 0.91 | 0.61 | 1.36 | 0.565 |
| North West | 1.04 | 0.64 | 1.67 | 0.842 | 1.00 | 0.67 | 1.50 | 0.993 | 1.03 | 0.71 | 1.49 | 0.856 |
| South Central | 0.90 | 0.55 | 1.47 | 0.584 | 0.84 | 0.56 | 1.27 | 0.276 | 0.86 | 0.59 | 1.26 | 0.309 |
| South East | 0.98 | 0.60 | 1.61 | 0.934 | 0.95 | 0.62 | 1.45 | 0.753 | 0.97 | 0.66 | 1.44 | 0.865 |
| South West | 1.01 | 0.62 | 1.64 | 0.953 | 0.95 | 0.63 | 1.43 | 0.729 | 0.97 | 0.66 | 1.43 | 0.839 |
| West Midlands | 0.68 | 0.42 | 1.10 | 0.040 | 0.69 | 0.46 | 1.05 | 0.022 | 0.74 | 0.50 | 1.08 | 0.041 |
| Yorkshire & Humber | 1.13 | 0.64 | 1.98 | 0.591 | 1.05 | 0.64 | 1.71 | 0.801 | 1.05 | 0.65 | 1.70 | 0.805 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.00 | 0.93 | 1.07 | 0.900 | 1.00 | 0.94 | 1.06 | 0.964 | 1.01 | 0.95 | 1.07 | 0.645 |
| Light-smoker | 0.90 | 0.85 | 0.97 | <0.001 | 0.96 | 0.90 | 1.02 | 0.053 | 0.99 | 0.93 | 1.05 | 0.608 |
| Moderate-smoker | 0.98 | 0.78 | 1.24 | 0.830 | 0.98 | 0.78 | 1.22 | 0.778 | 1.07 | 0.89 | 1.30 | 0.332 |
| Heavy-smoker | 0.97 | 0.71 | 1.35 | 0.835 | 1.00 | 0.74 | 1.36 | 0.984 | 1.02 | 0.76 | 1.37 | 0.841 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.02 | 0.96 | 1.08 | 0.439 | 0.98 | 0.93 | 1.04 | 0.359 | 0.95 | 0.90 | 1.00 | 0.017 |
| Medium | 0.98 | 0.89 | 1.08 | 0.623 | 0.98 | 0.89 | 1.07 | 0.495 | 0.98 | 0.90 | 1.06 | 0.511 |
| Heavy | 1.04 | 0.82 | 1.33 | 0.636 | 0.96 | 0.78 | 1.19 | 0.655 | 1.00 | 0.82 | 1.21 | 0.991 |
| Very heavy | 0.85 | 0.68 | 1.06 | 0.056 | 0.86 | 0.71 | 1.04 | 0.045 | 0.88 | 0.73 | 1.06 | 0.070 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.88 | 0.72 | 1.09 | 0.132 | 0.95 | 0.78 | 1.15 | 0.475 | 1.04 | 0.88 | 1.23 | 0.547 |
| Asian | 0.89 | 0.74 | 1.07 | 0.104 | 0.97 | 0.84 | 1.12 | 0.613 | 0.99 | 0.87 | 1.13 | 0.855 |
| Other | 1.03 | 0.88 | 1.22 | 0.584 | 1.03 | 0.90 | 1.19 | 0.558 | 1.04 | 0.91 | 1.18 | 0.486 |
| | | | | | | | | | | | | |
| Age | 1.00 | 1.00 | 1.00 | 0.503 | 1.00 | 1.00 | 1.00 | 0.577 | 1.00 | 1.00 | 1.00 | 0.735 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Male | 1.05 | 0.99 | 1.11 | 0.027 | 1.03 | 0.98 | 1.09 | 0.122 | 1.00 | 0.95 | 1.05 | 0.798 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 2.01 | 0.60 | 6.74 | 0.135 | 2.10 | 0.59 | 7.54 | 0.134 | 1.94 | 0.61 | 6.18 | 0.140 |
| 2011 to 2015 | 2.06 | 0.61 | 6.90 | 0.124 | 2.12 | 0.59 | 7.60 | 0.129 | 1.98 | 0.62 | 6.32 | 0.128 |
| 2016 to 2020 | 2.24 | 0.67 | 7.52 | 0.087 | 2.30 | 0.64 | 8.25 | 0.092 | 2.08 | 0.65 | 6.63 | 0.102 |
| Coronary heart disease | 0.89 | 0.75 | 1.06 | 0.095 | 0.96 | 0.82 | 1.11 | 0.444 | 1.00 | 0.87 | 1.15 | 0.987 |
| Stroke | 1.01 | 0.82 | 1.23 | 0.919 | 1.06 | 0.88 | 1.27 | 0.456 | 1.11 | 0.94 | 1.31 | 0.106 |
| Diabetes | 0.92 | 0.80 | 1.05 | 0.104 | 0.98 | 0.88 | 1.11 | 0.727 | 1.00 | 0.90 | 1.11 | 0.929 |
| Epilepsy | 1.11 | 0.86 | 1.45 | 0.289 | 1.21 | 0.96 | 1.51 | 0.032 | 1.20 | 0.97 | 1.48 | 0.027 |
| Hypothyroidism | 1.06 | 0.92 | 1.22 | 0.266 | 1.06 | 0.93 | 1.19 | 0.257 | 1.02 | 0.90 | 1.15 | 0.688 |
| Arthritis | 0.94 | 0.84 | 1.06 | 0.202 | 0.96 | 0.87 | 1.07 | 0.352 | 1.00 | 0.91 | 1.11 | 0.979 |
| Anxiety | - | - | - | - | - | - | - | - | - | - | - | - |
| Migraine | 1.11 | 1.01 | 1.23 | 0.006 | 1.15 | 1.05 | 1.26 | <0.001 | 1.17 | 1.08 | 1.28 | <0.001 |
| Cancer | 1.00 | 0.91 | 1.10 | 0.961 | 1.03 | 0.94 | 1.12 | 0.454 | 1.04 | 0.96 | 1.13 | 0.161 |
| Asthma | 1.02 | 0.95 | 1.09 | 0.443 | 1.05 | 0.99 | 1.12 | 0.039 | 1.07 | 1.01 | 1.13 | 0.001 |
| Renal failure | 1.26 | 0.78 | 2.04 | 0.222 | 1.33 | 0.88 | 2.01 | 0.078 | 1.41 | 0.96 | 2.08 | 0.020 |
| Liver failure | 0.95 | 0.72 | 1.25 | 0.617 | 1.10 | 0.87 | 1.40 | 0.295 | 1.12 | 0.90 | 1.39 | 0.201 |
| Osteoporosis | 0.88 | 0.64 | 1.21 | 0.305 | 0.92 | 0.69 | 1.22 | 0.438 | 1.00 | 0.77 | 1.30 | 0.999 |
| Suicidality | 1.33 | 1.13 | 1.58 | <0.001 | 1.34 | 1.15 | 1.56 | <0.001 | 1.38 | 1.18 | 1.61 | <0.001 |
| Antihypertensive | 0.97 | 0.87 | 1.09 | 0.557 | 1.00 | 0.90 | 1.10 | 0.950 | 0.99 | 0.90 | 1.09 | 0.792 |
| Aspirin | 1.11 | 0.94 | 1.31 | 0.114 | 1.08 | 0.93 | 1.25 | 0.171 | 1.13 | 0.98 | 1.29 | 0.024 |
| Anticoagulants | 1.01 | 0.78 | 1.31 | 0.918 | 1.09 | 0.87 | 1.37 | 0.340 | 1.10 | 0.89 | 1.35 | 0.255 |
| NSAIDs | 0.98 | 0.83 | 1.15 | 0.748 | 0.99 | 0.85 | 1.14 | 0.811 | 1.01 | 0.88 | 1.16 | 0.809 |
| Anticonvulsants | 0.91 | 0.68 | 1.21 | 0.378 | 0.93 | 0.72 | 1.20 | 0.438 | 0.92 | 0.73 | 1.17 | 0.382 |
| Hypnotics | 1.03 | 0.92 | 1.15 | 0.498 | 1.07 | 0.97 | 1.18 | 0.092 | 1.10 | 1.01 | 1.21 | 0.005 |
| Bisphosphonates | 0.86 | 0.47 | 1.58 | 0.528 | 0.86 | 0.49 | 1.50 | 0.477 | 1.05 | 0.66 | 1.67 | 0.769 |
| Contraceptives | 1.02 | 0.92 | 1.12 | 0.664 | 1.02 | 0.94 | 1.11 | 0.559 | 1.02 | 0.94 | 1.11 | 0.444 |
| *Constant* | 0.01 | 0.00 | 0.04 | <0.001 | 0.02 | 0.01 | 0.09 | <0.001 | 0.04 | 0.01 | 0.13 | <0.001 |

| | Adverse events, any psychiatric symptom *(FSA, N= 1,050,105)* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 0.98 | 0.95 | 1.02 | 0.172 | 0.98 | 0.95 | 1.01 | 0.100 | 0.98 | 0.95 | 1.01 | 0.124 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 4.56 | 4.32 | 4.82 | <0.001 | 3.44 | 3.29 | 3.60 | <0.001 | 2.86 | 2.75 | 2.97 | <0.001 |
| TCAs | 5.87 | 5.45 | 6.33 | <0.001 | 4.27 | 4.00 | 4.56 | <0.001 | 3.46 | 3.27 | 3.67 | <0.001 |
| MAOIs | 3.08 | 1.24 | 7.68 | 0.002 | 2.30 | 1.06 | 4.99 | 0.006 | 2.12 | 1.03 | 4.33 | 0.007 |
| Other antidepressants | 4.72 | 4.42 | 5.04 | <0.001 | 3.63 | 3.43 | 3.83 | <0.001 | 3.03 | 2.89 | 3.19 | <0.001 |
| PHQ-9 baseline | 1.00 | 1.00 | 1.00 | 0.021 | 1.00 | 1.00 | 1.01 | 0.003 | 1.00 | 1.00 | 1.01 | 0.002 |
| BMI | 1.00 | 1.00 | 1.00 | 0.006 | 1.00 | 1.00 | 1.00 | 0.027 | 1.00 | 1.00 | 1.00 | 0.005 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 5.39 | 5.03 | 5.77 | <0.001 | 4.45 | 4.19 | 4.74 | <0.001 | 3.82 | 3.61 | 4.04 | <0.001 |
| Other | 0.50 | 0.43 | 0.58 | <0.001 | 0.66 | 0.60 | 0.74 | <0.001 | 0.75 | 0.69 | 0.83 | <0.001 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.99 | 0.96 | 1.03 | 0.562 | 1.01 | 0.98 | 1.05 | 0.404 | 1.02 | 0.99 | 1.06 | 0.102 |
| 3 | 0.97 | 0.93 | 1.02 | 0.164 | 1.02 | 0.97 | 1.07 | 0.293 | 1.05 | 1.00 | 1.10 | 0.006 |
| 4 | 0.95 | 0.89 | 1.02 | 0.059 | 1.03 | 0.97 | 1.09 | 0.274 | 1.07 | 1.01 | 1.13 | 0.004 |
| 5, most deprived | 1.06 | 0.97 | 1.15 | 0.087 | 1.14 | 1.05 | 1.23 | <0.001 | 1.18 | 1.10 | 1.28 | <0.001 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.82 | 0.59 | 1.13 | 0.114 | 0.81 | 0.60 | 1.10 | 0.076 | 0.81 | 0.61 | 1.08 | 0.058 |
| London | 0.84 | 0.63 | 1.12 | 0.116 | 0.86 | 0.67 | 1.11 | 0.139 | 0.87 | 0.69 | 1.10 | 0.130 |
| North East | 1.01 | 0.69 | 1.46 | 0.965 | 1.01 | 0.72 | 1.43 | 0.925 | 1.03 | 0.75 | 1.41 | 0.813 |
| North West | 0.88 | 0.67 | 1.16 | 0.243 | 0.90 | 0.70 | 1.16 | 0.286 | 0.92 | 0.73 | 1.16 | 0.353 |
| South Central | 0.80 | 0.60 | 1.07 | 0.051 | 0.80 | 0.61 | 1.05 | 0.032 | 0.80 | 0.62 | 1.03 | 0.023 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South East | 0.81 | 0.59 | 1.12 | 0.095 | 0.83 | 0.62 | 1.12 | 0.111 | 0.84 | 0.64 | 1.10 | 0.100 |
| South West | 1.01 | 0.74 | 1.38 | 0.904 | 1.00 | 0.75 | 1.32 | 0.968 | 0.99 | 0.76 | 1.28 | 0.901 |
| West Midlands | 0.68 | 0.51 | 0.91 | 0.001 | 0.70 | 0.54 | 0.91 | <0.001 | 0.73 | 0.57 | 0.93 | 0.001 |
| Yorkshire & Humber | 0.98 | 0.71 | 1.36 | 0.902 | 0.95 | 0.71 | 1.28 | 0.671 | 0.94 | 0.71 | 1.26 | 0.606 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.00 | 0.97 | 1.03 | 0.952 | 0.99 | 0.97 | 1.02 | 0.545 | 1.00 | 0.97 | 1.02 | 0.804 |
| Light-smoker | 0.95 | 0.92 | 0.98 | <0.001 | 0.98 | 0.95 | 1.01 | 0.044 | 1.00 | 0.97 | 1.02 | 0.883 |
| Moderate-smoker | 0.96 | 0.88 | 1.04 | 0.153 | 0.96 | 0.89 | 1.04 | 0.186 | 0.97 | 0.91 | 1.04 | 0.341 |
| Heavy-smoker | 0.89 | 0.78 | 1.00 | 0.011 | 0.95 | 0.85 | 1.05 | 0.169 | 0.97 | 0.88 | 1.07 | 0.438 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.99 | 0.97 | 1.02 | 0.513 | 0.98 | 0.96 | 1.01 | 0.077 | 0.98 | 0.96 | 1.00 | 0.010 |
| Medium | 1.00 | 0.96 | 1.03 | 0.867 | 0.99 | 0.96 | 1.02 | 0.329 | 0.98 | 0.95 | 1.02 | 0.192 |
| Heavy | 1.00 | 0.93 | 1.07 | 0.899 | 0.99 | 0.93 | 1.06 | 0.813 | 1.00 | 0.94 | 1.06 | 0.981 |
| Very heavy | 0.97 | 0.89 | 1.06 | 0.339 | 0.98 | 0.91 | 1.06 | 0.464 | 0.98 | 0.92 | 1.05 | 0.436 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.96 | 0.91 | 1.01 | 0.024 | 0.99 | 0.95 | 1.03 | 0.555 | 1.01 | 0.97 | 1.05 | 0.527 |
| Asian | 0.95 | 0.88 | 1.01 | 0.041 | 1.02 | 0.96 | 1.08 | 0.478 | 1.06 | 1.00 | 1.13 | 0.012 |
| Other | 0.99 | 0.93 | 1.04 | 0.498 | 1.04 | 0.99 | 1.09 | 0.047 | 1.06 | 1.01 | 1.11 | 0.001 |
| | | | | | | | | | | | | |
| Age | 1.00 | 1.00 | 1.00 | 0.989 | 1.00 | 1.00 | 1.00 | 0.103 | 1.00 | 1.00 | 1.00 | 0.215 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.03 | 1.02 | 1.05 | <0.001 | 1.01 | 0.99 | 1.02 | 0.337 | 0.97 | 0.96 | 0.99 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.85 | 0.78 | 0.92 | <0.001 | 0.89 | 0.83 | 0.96 | <0.001 | 0.92 | 0.85 | 0.98 | 0.002 |
| 2011 to 2015 | 0.83 | 0.76 | 0.91 | <0.001 | 0.89 | 0.81 | 0.97 | <0.001 | 0.93 | 0.85 | 1.01 | 0.023 |
| 2016 to 2020 | 0.78 | 0.70 | 0.88 | <0.001 | 0.82 | 0.74 | 0.91 | <0.001 | 0.83 | 0.76 | 0.92 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Coronary heart disease | 0.97 | 0.92 | 1.02 | 0.090 | 1.00 | 0.96 | 1.04 | 0.910 | 1.03 | 0.99 | 1.07 | 0.109 |
| Stroke | 0.98 | 0.93 | 1.03 | 0.322 | 1.07 | 1.03 | 1.12 | <0.001 | 1.11 | 1.06 | 1.16 | <0.001 |
| Diabetes | 0.92 | 0.88 | 0.96 | <0.001 | 0.94 | 0.91 | 0.98 | <0.001 | 0.96 | 0.93 | 1.00 | 0.010 |
| Epilepsy | 1.02 | 0.96 | 1.10 | 0.370 | 1.04 | 0.98 | 1.11 | 0.098 | 1.06 | 1.00 | 1.12 | 0.010 |
| Hypothyroidism | 0.97 | 0.93 | 1.01 | 0.050 | 0.99 | 0.95 | 1.02 | 0.308 | 1.00 | 0.96 | 1.03 | 0.821 |
| Arthritis | 1.02 | 0.98 | 1.05 | 0.208 | 1.04 | 1.01 | 1.07 | 0.001 | 1.05 | 1.02 | 1.09 | <0.001 |
| Anxiety | | | | | | | | | | | | |
| Migraine | 1.08 | 1.05 | 1.12 | <0.001 | 1.11 | 1.07 | 1.14 | <0.001 | 1.13 | 1.10 | 1.16 | <0.001 |
| Cancer | 0.99 | 0.96 | 1.02 | 0.502 | 1.00 | 0.97 | 1.03 | 0.887 | 1.01 | 0.99 | 1.04 | 0.235 |
| Asthma | 1.02 | 1.00 | 1.04 | 0.031 | 1.04 | 1.02 | 1.06 | <0.001 | 1.06 | 1.04 | 1.08 | <0.001 |
| Renal failure | 0.98 | 0.86 | 1.11 | 0.611 | 0.98 | 0.88 | 1.10 | 0.730 | 1.02 | 0.92 | 1.13 | 0.609 |
| Liver failure | 1.06 | 0.98 | 1.15 | 0.065 | 1.12 | 1.04 | 1.20 | <0.001 | 1.12 | 1.05 | 1.19 | <0.001 |
| Osteoporosis | 0.97 | 0.91 | 1.04 | 0.298 | 1.02 | 0.96 | 1.08 | 0.428 | 1.03 | 0.97 | 1.09 | 0.167 |
| Suicidality | 1.15 | 1.07 | 1.24 | <0.001 | 1.24 | 1.16 | 1.33 | <0.001 | 1.28 | 1.19 | 1.37 | <0.001 |
| Antihypertensive | 0.95 | 0.92 | 0.99 | <0.001 | 0.97 | 0.94 | 1.00 | 0.009 | 0.97 | 0.95 | 1.00 | 0.012 |
| Aspirin | 0.95 | 0.91 | 0.99 | 0.003 | 0.96 | 0.92 | 1.00 | 0.009 | 0.97 | 0.94 | 1.01 | 0.069 |
| Anticoagulants | 0.96 | 0.89 | 1.03 | 0.108 | 0.99 | 0.93 | 1.05 | 0.614 | 1.00 | 0.95 | 1.06 | 0.876 |
| NSAIDs | 1.00 | 0.95 | 1.04 | 0.883 | 1.03 | 0.99 | 1.07 | 0.042 | 1.05 | 1.01 | 1.09 | 0.002 |
| Anticonvulsants | 1.06 | 0.99 | 1.13 | 0.020 | 1.06 | 1.00 | 1.13 | 0.009 | 1.08 | 1.02 | 1.14 | 0.001 |
| Hypnotics | 1.11 | 1.07 | 1.15 | <0.001 | 1.13 | 1.10 | 1.17 | <0.001 | 1.14 | 1.10 | 1.17 | <0.001 |
| Bisphosphonates | 0.98 | 0.87 | 1.12 | 0.759 | 1.01 | 0.90 | 1.13 | 0.831 | 1.05 | 0.95 | 1.17 | 0.212 |
| Contraceptives | 0.99 | 0.96 | 1.03 | 0.555 | 1.01 | 0.98 | 1.04 | 0.269 | 1.02 | 0.99 | 1.05 | 0.103 |
| *Constant* | 0.04 | 0.03 | 0.05 | <0.001 | 0.07 | 0.05 | 0.09 | <0.001 | 0.10 | 0.08 | 0.13 | <0.001 |

***Table A4.6f*** *Regression analyses for adverse events (anxiety) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Adverse events, anxiety *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.07 | 0.92 | 1.23 | 0.243 | 1.07 | 0.93 | 1.22 | 0.208 | 1.05 | 0.92 | 1.20 | 0.339 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 3.43 | 3.02 | 3.90 | <0.001 | 2.54 | 2.26 | 2.86 | <0.001 | 2.21 | 1.99 | 2.46 | <0.001 |
| TCAs | 2.79 | 2.09 | 3.71 | <0.001 | 2.05 | 1.57 | 2.69 | <0.001 | 1.78 | 1.38 | 2.30 | <0.001 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | 3.56 | 2.99 | 4.24 | <0.001 | 2.61 | 2.23 | 3.06 | <0.001 | 2.32 | 2.01 | 2.67 | <0.001 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.00 | 0.99 | 1.01 | 0.557 | 1.00 | 0.99 | 1.01 | 0.821 | 1.00 | 0.99 | 1.01 | 0.782 |
| BMI | 0.99 | 0.99 | 1.00 | 0.007 | 0.99 | 0.99 | 1.00 | 0.005 | 0.99 | 0.99 | 1.00 | 0.001 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.31 | 0.27 | 0.35 | <0.001 | 0.34 | 0.31 | 0.38 | <0.001 | 0.38 | 0.35 | 0.42 | <0.001 |
| Other | 0.35 | 0.25 | 0.49 | <0.001 | 0.41 | 0.32 | 0.54 | <0.001 | 0.46 | 0.37 | 0.57 | <0.001 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.01 | 0.92 | 1.10 | 0.838 | 1.01 | 0.92 | 1.10 | 0.879 | 1.01 | 0.93 | 1.10 | 0.750 |
| 3 | 1.00 | 0.89 | 1.11 | 0.910 | 1.01 | 0.90 | 1.12 | 0.856 | 1.02 | 0.92 | 1.13 | 0.688 |
| 4 | 1.06 | 0.93 | 1.22 | 0.250 | 1.08 | 0.95 | 1.24 | 0.116 | 1.09 | 0.96 | 1.24 | 0.073 |
| 5, most deprived | 1.01 | 0.85 | 1.20 | 0.877 | 1.05 | 0.89 | 1.23 | 0.479 | 1.08 | 0.92 | 1.27 | 0.214 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.48 | 0.27 | 0.86 | 0.001 | 0.49 | 0.28 | 0.85 | 0.001 | 0.48 | 0.28 | 0.84 | 0.001 |
| London | 0.59 | 0.39 | 0.90 | 0.001 | 0.60 | 0.40 | 0.91 | 0.002 | 0.60 | 0.39 | 0.90 | 0.001 |
| North East | 0.67 | 0.35 | 1.28 | 0.114 | 0.65 | 0.35 | 1.19 | 0.067 | 0.66 | 0.37 | 1.18 | 0.066 |
| North West | 0.66 | 0.43 | 1.01 | 0.011 | 0.66 | 0.43 | 1.00 | 0.011 | 0.67 | 0.44 | 1.02 | 0.014 |
| South Central | 0.48 | 0.31 | 0.76 | <0.001 | 0.47 | 0.30 | 0.74 | <0.001 | 0.48 | 0.31 | 0.75 | <0.001 |
| South East | 0.67 | 0.43 | 1.07 | 0.027 | 0.71 | 0.45 | 1.12 | 0.052 | 0.70 | 0.44 | 1.10 | 0.042 |
| South West | 0.54 | 0.33 | 0.86 | 0.001 | 0.52 | 0.32 | 0.85 | 0.001 | 0.52 | 0.33 | 0.84 | <0.001 |
| West Midlands | 0.72 | 0.43 | 1.21 | 0.106 | 0.74 | 0.45 | 1.23 | 0.125 | 0.74 | 0.45 | 1.22 | 0.120 |
| Yorkshire & Humber | 0.80 | 0.46 | 1.38 | 0.287 | 0.82 | 0.46 | 1.47 | 0.379 | 0.82 | 0.45 | 1.48 | 0.382 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.01 | 0.94 | 1.09 | 0.706 | 0.98 | 0.91 | 1.05 | 0.432 | 0.97 | 0.91 | 1.04 | 0.325 |
| Light-smoker | 0.89 | 0.83 | 0.97 | <0.001 | 0.91 | 0.84 | 0.99 | 0.003 | 0.93 | 0.86 | 1.00 | 0.015 |
| Moderate-smoker | 0.78 | 0.59 | 1.03 | 0.023 | 0.82 | 0.63 | 1.05 | 0.040 | 0.84 | 0.67 | 1.07 | 0.061 |
| Heavy-smoker | 0.86 | 0.61 | 1.21 | 0.260 | 0.84 | 0.61 | 1.15 | 0.145 | 0.78 | 0.58 | 1.07 | 0.041 |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.04 | 0.97 | 1.11 | 0.116 | 1.05 | 0.98 | 1.11 | 0.064 | 1.04 | 0.98 | 1.10 | 0.078 |
| Medium | 1.05 | 0.94 | 1.16 | 0.259 | 1.04 | 0.94 | 1.16 | 0.290 | 1.05 | 0.95 | 1.16 | 0.211 |
| Heavy | 1.08 | 0.86 | 1.36 | 0.373 | 1.08 | 0.88 | 1.33 | 0.314 | 1.08 | 0.88 | 1.31 | 0.345 |
| Very heavy | 0.97 | 0.77 | 1.22 | 0.703 | 1.05 | 0.86 | 1.28 | 0.568 | 1.08 | 0.90 | 1.31 | 0.276 |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.70 | 0.56 | 0.88 | <0.001 | 0.77 | 0.63 | 0.95 | 0.001 | 0.79 | 0.64 | 0.97 | 0.004 |
| Asian | 0.75 | 0.63 | 0.89 | <0.001 | 0.78 | 0.66 | 0.93 | <0.001 | 0.79 | 0.67 | 0.93 | <0.001 |
| Other | 0.80 | 0.68 | 0.95 | 0.001 | 0.84 | 0.72 | 0.99 | 0.007 | 0.85 | 0.73 | 0.99 | 0.005 |
| Age | 1.00 | 0.99 | 1.00 | <0.001 | 0.99 | 0.99 | 1.00 | <0.001 | 0.99 | 0.99 | 1.00 | <0.001 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.97 | 0.91 | 1.03 | 0.161 | 0.95 | 0.90 | 1.01 | 0.037 | 0.94 | 0.89 | 1.00 | 0.007 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.65 | 0.25 | 1.68 | 0.248 | 0.77 | 0.36 | 1.68 | 0.394 | 0.87 | 0.45 | 1.69 | 0.591 |
| 2011 to 2015 | 1.13 | 0.44 | 2.91 | 0.740 | 1.27 | 0.59 | 2.77 | 0.422 | 1.43 | 0.73 | 2.78 | 0.169 |
| 2016 to 2020 | 2.23 | 0.86 | 5.74 | 0.029 | 2.44 | 1.12 | 5.31 | 0.003 | 2.62 | 1.35 | 5.11 | <0.001 |
| Coronary heart disease | 0.80 | 0.65 | 0.97 | 0.003 | 0.79 | 0.66 | 0.94 | 0.001 | 0.82 | 0.69 | 0.98 | 0.004 |
| Stroke | 0.78 | 0.62 | 1.00 | 0.009 | 0.80 | 0.64 | 0.99 | 0.008 | 0.82 | 0.66 | 1.01 | 0.016 |
| Diabetes | 0.73 | 0.64 | 0.85 | <0.001 | 0.74 | 0.65 | 0.84 | <0.001 | 0.73 | 0.64 | 0.83 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Epilepsy | 0.94 | 0.72 | 1.23 | 0.546 | 0.94 | 0.73 | 1.21 | 0.541 | 0.93 | 0.72 | 1.20 | 0.458 |
| Hypothyroidism | 0.99 | 0.85 | 1.16 | 0.901 | 1.02 | 0.88 | 1.18 | 0.761 | 0.99 | 0.86 | 1.15 | 0.923 |
| Arthritis | 1.02 | 0.90 | 1.16 | 0.627 | 1.01 | 0.89 | 1.14 | 0.878 | 0.98 | 0.87 | 1.11 | 0.704 |
| Anxiety | - | - | - | - | - | - | - | - | - | - | - | - |
| Migraine | 1.09 | 0.98 | 1.22 | 0.044 | 1.06 | 0.95 | 1.17 | 0.177 | 1.03 | 0.94 | 1.14 | 0.398 |
| Cancer | 0.94 | 0.85 | 1.05 | 0.156 | 0.95 | 0.86 | 1.05 | 0.196 | 0.95 | 0.86 | 1.04 | 0.135 |
| Asthma | 1.00 | 0.93 | 1.07 | 0.856 | 1.00 | 0.94 | 1.07 | 0.855 | 1.00 | 0.94 | 1.07 | 0.952 |
| Renal failure | 0.45 | 0.21 | 0.95 | 0.006 | 0.43 | 0.21 | 0.87 | 0.002 | 0.44 | 0.22 | 0.85 | 0.001 |
| Liver failure | 0.86 | 0.63 | 1.17 | 0.204 | 0.89 | 0.67 | 1.18 | 0.296 | 0.95 | 0.73 | 1.24 | 0.642 |
| Osteoporosis | 1.14 | 0.82 | 1.57 | 0.314 | 1.14 | 0.84 | 1.56 | 0.273 | 1.17 | 0.86 | 1.59 | 0.193 |
| Suicidality | 1.03 | 0.87 | 1.22 | 0.678 | 1.06 | 0.91 | 1.23 | 0.333 | 1.09 | 0.94 | 1.26 | 0.145 |
| Antihypertensive | 0.99 | 0.88 | 1.13 | 0.901 | 1.03 | 0.91 | 1.15 | 0.573 | 1.04 | 0.93 | 1.17 | 0.325 |
| Aspirin | 0.88 | 0.72 | 1.07 | 0.092 | 0.87 | 0.72 | 1.06 | 0.063 | 0.86 | 0.71 | 1.05 | 0.052 |
| Anticoagulants | 0.88 | 0.64 | 1.21 | 0.307 | 0.88 | 0.65 | 1.20 | 0.283 | 0.89 | 0.67 | 1.19 | 0.302 |
| NSAIDs | 0.81 | 0.68 | 0.96 | 0.002 | 0.89 | 0.76 | 1.04 | 0.052 | 0.92 | 0.79 | 1.07 | 0.158 |
| Anticonvulsants | 0.90 | 0.64 | 1.27 | 0.446 | 0.98 | 0.70 | 1.37 | 0.870 | 0.96 | 0.70 | 1.33 | 0.763 |
| Hypnotics | 1.64 | 1.47 | 1.82 | <0.001 | 1.59 | 1.44 | 1.76 | <0.001 | 1.58 | 1.43 | 1.74 | <0.001 |
| Bisphosphonates | 0.76 | 0.42 | 1.37 | 0.233 | 0.76 | 0.43 | 1.33 | 0.207 | 0.82 | 0.49 | 1.39 | 0.341 |
| Contraceptives | 0.98 | 0.87 | 1.11 | 0.688 | 0.96 | 0.86 | 1.07 | 0.348 | 0.95 | 0.85 | 1.06 | 0.205 |
| *Constant* | 0.17 | 0.06 | 0.49 | <0.001 | 0.26 | 0.11 | 0.65 | <0.001 | 0.31 | 0.14 | 0.70 | <0.001 |

| | **Adverse events, anxiety *(FSA, N= 1,050,105)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.04 | 0.99 | 1.09 | 0.059 | 1.03 | 0.98 | 1.08 | 0.117 | 1.02 | 0.98 | 1.07 | 0.227 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 3.92 | 3.73 | 4.12 | <0.001 | 2.71 | 2.60 | 2.82 | <0.001 | 2.26 | 2.18 | 2.34 | <0.001 |
| TCAs | 4.02 | 3.74 | 4.33 | <0.001 | 2.75 | 2.58 | 2.93 | <0.001 | 2.31 | 2.18 | 2.45 | <0.001 |
| MAOIs | 2.26 | 0.80 | 6.39 | 0.044 | 3.38 | 1.46 | 7.81 | <0.001 | 2.44 | 1.06 | 5.62 | 0.006 |
| Other antidepressants | 3.70 | 3.46 | 3.96 | <0.001 | 2.61 | 2.47 | 2.76 | <0.001 | 2.21 | 2.10 | 2.32 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PHQ-9 baseline | 1.00 | 1.00 | 1.00 | 0.600 | 1.00 | 1.00 | 1.00 | 0.447 | 1.00 | 1.00 | 1.00 | 0.343 |
| BMI | 1.00 | 0.99 | 1.00 | <0.001 | 1.00 | 0.99 | 1.00 | <0.001 | 1.00 | 0.99 | 1.00 | <0.001 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.21 | 0.19 | 0.23 | <0.001 | 0.26 | 0.25 | 0.28 | <0.001 | 0.31 | 0.29 | 0.33 | <0.001 |
| Other | 0.22 | 0.18 | 0.28 | <0.001 | 0.27 | 0.23 | 0.31 | <0.001 | 0.29 | 0.26 | 0.34 | <0.001 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.98 | 0.94 | 1.03 | 0.303 | 0.99 | 0.95 | 1.04 | 0.763 | 1.00 | 0.96 | 1.04 | 0.916 |
| 3 | 0.94 | 0.89 | 0.99 | 0.003 | 0.97 | 0.93 | 1.02 | 0.182 | 1.00 | 0.95 | 1.05 | 0.872 |
| 4 | 0.93 | 0.86 | 0.99 | 0.004 | 0.98 | 0.91 | 1.05 | 0.408 | 1.01 | 0.94 | 1.08 | 0.791 |
| 5, most deprived | 0.93 | 0.85 | 1.01 | 0.022 | 0.99 | 0.91 | 1.07 | 0.664 | 1.01 | 0.94 | 1.10 | 0.674 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.71 | 0.45 | 1.12 | 0.055 | 0.71 | 0.46 | 1.09 | 0.038 | 0.72 | 0.47 | 1.09 | 0.042 |
| London | 0.65 | 0.52 | 0.83 | <0.001 | 0.66 | 0.52 | 0.84 | <0.001 | 0.68 | 0.54 | 0.86 | <0.001 |
| North East | 0.75 | 0.54 | 1.05 | 0.028 | 0.74 | 0.54 | 1.03 | 0.020 | 0.76 | 0.56 | 1.05 | 0.029 |
| North West | 0.82 | 0.64 | 1.06 | 0.044 | 0.83 | 0.65 | 1.06 | 0.052 | 0.86 | 0.68 | 1.09 | 0.109 |
| South Central | 0.56 | 0.43 | 0.74 | <0.001 | 0.56 | 0.43 | 0.74 | <0.001 | 0.58 | 0.44 | 0.76 | <0.001 |
| South East | 0.63 | 0.48 | 0.84 | <0.001 | 0.65 | 0.50 | 0.85 | <0.001 | 0.67 | 0.51 | 0.88 | <0.001 |
| South West | 0.67 | 0.51 | 0.88 | <0.001 | 0.66 | 0.50 | 0.86 | <0.001 | 0.68 | 0.52 | 0.88 | <0.001 |
| West Midlands | 0.73 | 0.55 | 0.97 | 0.004 | 0.74 | 0.56 | 0.98 | 0.006 | 0.77 | 0.59 | 1.01 | 0.014 |
| Yorkshire & Humber | 0.80 | 0.57 | 1.12 | 0.088 | 0.78 | 0.56 | 1.09 | 0.058 | 0.78 | 0.56 | 1.08 | 0.052 |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.98 | 0.95 | 1.02 | 0.214 | 0.99 | 0.96 | 1.02 | 0.390 | 0.99 | 0.97 | 1.02 | 0.448 |
| Light-smoker | 0.89 | 0.86 | 0.92 | <0.001 | 0.92 | 0.89 | 0.95 | <0.001 | 0.94 | 0.91 | 0.97 | <0.001 |
| Moderate-smoker | 0.85 | 0.78 | 0.93 | <0.001 | 0.87 | 0.80 | 0.94 | <0.001 | 0.90 | 0.83 | 0.97 | <0.001 |
| Heavy-smoker | 0.92 | 0.81 | 1.04 | 0.075 | 0.96 | 0.85 | 1.08 | 0.340 | 0.96 | 0.86 | 1.07 | 0.338 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.01 | 0.98 | 1.04 | 0.463 | 1.01 | 0.98 | 1.03 | 0.438 | 1.01 | 0.99 | 1.03 | 0.377 |
| Medium | 1.02 | 0.98 | 1.07 | 0.150 | 1.03 | 0.99 | 1.07 | 0.040 | 1.03 | 1.00 | 1.07 | 0.022 |
| Heavy | 1.00 | 0.91 | 1.11 | 0.957 | 1.01 | 0.92 | 1.11 | 0.755 | 1.02 | 0.93 | 1.11 | 0.625 |
| Very heavy | 1.00 | 0.91 | 1.10 | 0.946 | 1.00 | 0.92 | 1.09 | 0.916 | 1.02 | 0.93 | 1.11 | 0.590 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.77 | 0.72 | 0.81 | <0.001 | 0.78 | 0.73 | 0.82 | <0.001 | 0.77 | 0.73 | 0.82 | <0.001 |
| Asian | 0.79 | 0.72 | 0.86 | <0.001 | 0.82 | 0.76 | 0.89 | <0.001 | 0.83 | 0.77 | 0.89 | <0.001 |
| Other | 0.84 | 0.78 | 0.89 | <0.001 | 0.87 | 0.82 | 0.92 | <0.001 | 0.87 | 0.83 | 0.92 | <0.001 |
| | | | | | | | | | | | | |
| Age | 0.99 | 0.99 | 1.00 | <0.001 | 0.99 | 0.99 | 0.99 | <0.001 | 0.99 | 0.99 | 0.99 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.96 | 0.94 | 0.98 | <0.001 | 0.94 | 0.92 | 0.96 | <0.001 | 0.92 | 0.90 | 0.94 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.43 | 1.31 | 1.56 | <0.001 | 1.36 | 1.25 | 1.48 | <0.001 | 1.30 | 1.20 | 1.41 | <0.001 |
| 2011 to 2015 | 2.23 | 2.02 | 2.46 | <0.001 | 2.06 | 1.88 | 2.25 | <0.001 | 1.94 | 1.78 | 2.11 | <0.001 |
| 2016 to 2020 | 3.35 | 3.02 | 3.71 | <0.001 | 3.02 | 2.74 | 3.32 | <0.001 | 2.77 | 2.53 | 3.04 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.85 | 0.80 | 0.91 | <0.001 | 0.85 | 0.80 | 0.90 | <0.001 | 0.87 | 0.82 | 0.92 | <0.001 |
| Stroke | 0.73 | 0.68 | 0.79 | <0.001 | 0.75 | 0.70 | 0.80 | <0.001 | 0.76 | 0.71 | 0.80 | <0.001 |
| Diabetes | 0.73 | 0.69 | 0.77 | <0.001 | 0.72 | 0.69 | 0.76 | <0.001 | 0.73 | 0.69 | 0.76 | <0.001 |
| Epilepsy | 0.92 | 0.85 | 1.00 | 0.011 | 0.92 | 0.86 | 0.99 | 0.005 | 0.97 | 0.90 | 1.04 | 0.255 |
| Hypothyroidism | 1.00 | 0.94 | 1.05 | 0.828 | 1.00 | 0.95 | 1.05 | 0.993 | 1.00 | 0.96 | 1.04 | 0.952 |
| Arthritis | 0.94 | 0.90 | 0.98 | <0.001 | 0.94 | 0.90 | 0.98 | <0.001 | 0.95 | 0.91 | 0.98 | <0.001 |
| Anxiety | - | - | - | - | - | - | - | - | - | - | - | - |
| Migraine | 1.07 | 1.03 | 1.11 | <0.001 | 1.06 | 1.02 | 1.10 | <0.001 | 1.07 | 1.03 | 1.10 | <0.001 |
| Cancer | 0.92 | 0.89 | 0.96 | <0.001 | 0.92 | 0.89 | 0.95 | <0.001 | 0.93 | 0.90 | 0.96 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Asthma | 0.99 | 0.96 | 1.02 | 0.403 | 1.00 | 0.97 | 1.03 | 0.986 | 1.01 | 0.98 | 1.03 | 0.450 |
| Renal failure | 0.63 | 0.51 | 0.76 | <0.001 | 0.65 | 0.55 | 0.78 | <0.001 | 0.67 | 0.57 | 0.78 | <0.001 |
| Liver failure | 0.88 | 0.79 | 0.97 | 0.001 | 0.92 | 0.84 | 1.00 | 0.015 | 0.93 | 0.86 | 1.02 | 0.038 |
| Osteoporosis | 0.88 | 0.79 | 0.98 | 0.002 | 0.89 | 0.81 | 0.98 | 0.002 | 0.90 | 0.83 | 0.99 | 0.003 |
| Suicidality | 1.01 | 0.94 | 1.10 | 0.639 | 1.06 | 0.99 | 1.14 | 0.037 | 1.08 | 1.01 | 1.16 | 0.002 |
| Antihypertensive | 1.02 | 0.98 | 1.07 | 0.247 | 1.03 | 0.99 | 1.07 | 0.082 | 1.02 | 0.98 | 1.06 | 0.152 |
| Aspirin | 0.90 | 0.84 | 0.96 | <0.001 | 0.91 | 0.86 | 0.97 | <0.001 | 0.91 | 0.85 | 0.96 | <0.001 |
| Anticoagulants | 0.83 | 0.75 | 0.91 | <0.001 | 0.82 | 0.75 | 0.90 | <0.001 | 0.83 | 0.77 | 0.91 | <0.001 |
| NSAIDs | 0.85 | 0.80 | 0.90 | <0.001 | 0.88 | 0.84 | 0.93 | <0.001 | 0.91 | 0.87 | 0.96 | <0.001 |
| Anticonvulsants | 0.85 | 0.78 | 0.92 | <0.001 | 0.89 | 0.82 | 0.96 | <0.001 | 0.89 | 0.83 | 0.96 | <0.001 |
| Hypnotics | 1.64 | 1.57 | 1.71 | <0.001 | 1.61 | 1.55 | 1.67 | <0.001 | 1.58 | 1.52 | 1.63 | <0.001 |
| Bisphosphonates | 0.79 | 0.65 | 0.95 | 0.001 | 0.79 | 0.66 | 0.94 | 0.001 | 0.80 | 0.68 | 0.94 | <0.001 |
| Contraceptives | 0.96 | 0.92 | 0.99 | 0.003 | 0.95 | 0.92 | 0.99 | 0.001 | 0.95 | 0.92 | 0.98 | <0.001 |
| *Constant* | 0.08 | 0.07 | 0.11 | <0.001 | 0.16 | 0.12 | 0.20 | <0.001 | 0.22 | 0.17 | 0.27 | <0.001 |

***Table A4.6g*** *Regression analyses for adverse events (sleep disturbance) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Adverse events, sleep disturbance *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.16 | 0.76 | 1.77 | 0.361 | 1.05 | 0.73 | 1.50 | 0.753 | 1.13 | 0.85 | 1.50 | 0.254 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 1.63 | 1.18 | 2.25 | <0.001 | 1.21 | 0.96 | 1.52 | 0.032 | 1.11 | 0.92 | 1.34 | 0.138 |
| TCAs | 4.81 | 2.81 | 8.23 | <0.001 | 2.99 | 1.91 | 4.69 | <0.001 | 2.31 | 1.54 | 3.46 | <0.001 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | 2.74 | 1.65 | 4.54 | <0.001 | 2.20 | 1.52 | 3.19 | <0.001 | 2.10 | 1.56 | 2.84 | <0.001 |
| PHQ-9 baseline | 1.02 | 0.99 | 1.04 | 0.064 | 1.02 | 1.00 | 1.03 | 0.019 | 1.01 | 1.00 | 1.03 | 0.043 |
| BMI | 0.98 | 0.95 | 1.01 | 0.048 | 0.98 | 0.96 | 1.00 | 0.001 | 0.98 | 0.97 | 1.00 | 0.002 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.71 | 1.14 | 2.56 | 0.001 | 1.50 | 1.10 | 2.05 | 0.001 | 1.39 | 1.08 | 1.78 | 0.001 |
| Other | 0.97 | 0.47 | 2.03 | 0.927 | 0.86 | 0.50 | 1.49 | 0.475 | 0.82 | 0.51 | 1.31 | 0.273 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.74 | 0.51 | 1.09 | 0.045 | 0.85 | 0.64 | 1.12 | 0.130 | 0.88 | 0.71 | 1.10 | 0.141 |
| 3 | 0.92 | 0.64 | 1.31 | 0.531 | 1.02 | 0.77 | 1.35 | 0.883 | 1.14 | 0.91 | 1.42 | 0.130 |
| 4 | 0.98 | 0.66 | 1.46 | 0.890 | 1.22 | 0.90 | 1.66 | 0.094 | 1.29 | 1.01 | 1.65 | 0.008 |
| 5, most deprived | 1.07 | 0.71 | 1.60 | 0.684 | 1.26 | 0.92 | 1.71 | 0.059 | 1.36 | 1.06 | 1.74 | 0.002 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.90 | 0.24 | 3.37 | 0.832 | 0.79 | 0.30 | 2.09 | 0.531 | 0.81 | 0.37 | 1.81 | 0.508 |
| London | 1.99 | 0.89 | 4.48 | 0.028 | 1.21 | 0.53 | 2.72 | 0.554 | 1.11 | 0.62 | 2.01 | 0.645 |
| North East | 2.97 | 1.01 | 8.71 | 0.009 | 1.16 | 0.39 | 3.48 | 0.722 | 1.22 | 0.56 | 2.65 | 0.514 |
| North West | 1.87 | 0.79 | 4.45 | 0.062 | 1.24 | 0.55 | 2.82 | 0.493 | 1.15 | 0.63 | 2.12 | 0.541 |
| South Central | 1.89 | 0.77 | 4.63 | 0.068 | 0.97 | 0.41 | 2.28 | 0.927 | 1.11 | 0.58 | 2.14 | 0.675 |
| South East | 3.37 | 1.22 | 9.29 | 0.002 | 1.94 | 0.76 | 4.95 | 0.069 | 1.73 | 0.83 | 3.61 | 0.054 |
| South West | 1.80 | 0.74 | 4.37 | 0.086 | 1.14 | 0.49 | 2.65 | 0.691 | 1.09 | 0.58 | 2.06 | 0.718 |
| West Midlands | 1.88 | 0.79 | 4.51 | 0.061 | 1.11 | 0.49 | 2.50 | 0.752 | 1.16 | 0.62 | 2.16 | 0.546 |
| Yorkshire & Humber | 2.17 | 0.79 | 5.96 | 0.049 | 0.99 | 0.38 | 2.61 | 0.981 | 1.02 | 0.47 | 2.24 | 0.944 |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.87 | 0.65 | 1.16 | 0.198 | 0.98 | 0.79 | 1.21 | 0.784 | 0.98 | 0.82 | 1.17 | 0.764 |
| Light-smoker | 0.91 | 0.65 | 1.27 | 0.452 | 0.98 | 0.77 | 1.24 | 0.813 | 0.98 | 0.81 | 1.19 | 0.798 |
| Moderate-smoker | 1.24 | 0.56 | 2.71 | 0.488 | 0.83 | 0.42 | 1.66 | 0.496 | 1.06 | 0.65 | 1.73 | 0.752 |
| Heavy-smoker | 0.45 | 0.07 | 2.86 | 0.268 | 0.64 | 0.19 | 2.10 | 0.334 | 0.60 | 0.22 | 1.64 | 0.191 |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.93 | 0.72 | 1.21 | 0.495 | 1.03 | 0.85 | 1.24 | 0.721 | 1.00 | 0.85 | 1.17 | 0.954 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medium | 1.22 | 0.87 | 1.71 | 0.136 | 1.14 | 0.86 | 1.50 | 0.227 | 1.08 | 0.86 | 1.37 | 0.371 |
| Heavy | 1.09 | 0.47 | 2.50 | 0.797 | 1.16 | 0.62 | 2.16 | 0.549 | 1.30 | 0.80 | 2.11 | 0.171 |
| Very heavy | 0.96 | 0.41 | 2.25 | 0.901 | 1.13 | 0.65 | 1.97 | 0.579 | 1.09 | 0.67 | 1.77 | 0.636 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.86 | 0.38 | 1.97 | 0.642 | 0.89 | 0.51 | 1.57 | 0.606 | 1.12 | 0.74 | 1.69 | 0.473 |
| Asian | 1.23 | 0.70 | 2.17 | 0.344 | 1.24 | 0.82 | 1.88 | 0.184 | 1.25 | 0.90 | 1.74 | 0.085 |
| Other | 1.12 | 0.63 | 1.98 | 0.620 | 1.14 | 0.77 | 1.70 | 0.394 | 1.26 | 0.91 | 1.75 | 0.070 |
| | | | | | | | | | | | | |
| Age | 1.01 | 0.99 | 1.02 | 0.262 | 1.00 | 0.99 | 1.01 | 0.355 | 1.01 | 1.00 | 1.01 | 0.067 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.17 | 0.91 | 1.50 | 0.110 | 1.11 | 0.92 | 1.35 | 0.141 | 1.07 | 0.91 | 1.26 | 0.261 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.27 | 0.73 | 2.22 | 0.272 | 1.30 | 0.85 | 1.99 | 0.108 | 3.42 | 0.43 | 27.02 | 0.126 |
| 2011 to 2015 | 1.03 | 0.69 | 1.54 | 0.835 | 1.00 | 0.74 | 1.35 | 0.988 | 2.58 | 0.33 | 20.27 | 0.236 |
| 2016 to 2020 | 1.00 | | | | 1.00 | | | | 2.34 | 0.29 | 18.71 | 0.290 |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.40 | 0.80 | 2.46 | 0.120 | 1.38 | 0.92 | 2.05 | 0.040 | 1.21 | 0.87 | 1.69 | 0.142 |
| Stroke | 0.99 | 0.46 | 2.16 | 0.986 | 0.91 | 0.52 | 1.59 | 0.647 | 1.06 | 0.69 | 1.62 | 0.740 |
| Diabetes | 1.17 | 0.72 | 1.88 | 0.404 | 1.14 | 0.80 | 1.64 | 0.338 | 1.10 | 0.82 | 1.47 | 0.398 |
| Epilepsy | 1.19 | 0.42 | 3.39 | 0.674 | 1.31 | 0.65 | 2.67 | 0.323 | 1.04 | 0.58 | 1.88 | 0.848 |
| Hypothyroidism | 0.99 | 0.53 | 1.86 | 0.973 | 0.97 | 0.61 | 1.55 | 0.878 | 0.99 | 0.69 | 1.43 | 0.964 |
| Arthritis | 1.33 | 0.89 | 1.99 | 0.064 | 1.24 | 0.91 | 1.69 | 0.078 | 1.29 | 1.01 | 1.65 | 0.008 |
| Anxiety | 1.09 | 0.80 | 1.49 | 0.463 | 1.12 | 0.90 | 1.40 | 0.173 | 1.22 | 1.03 | 1.45 | 0.002 |
| Migraine | 0.89 | 0.56 | 1.41 | 0.505 | 1.16 | 0.84 | 1.59 | 0.242 | 1.14 | 0.87 | 1.49 | 0.222 |
| Cancer | 1.10 | 0.75 | 1.61 | 0.535 | 1.11 | 0.82 | 1.48 | 0.378 | 1.05 | 0.81 | 1.35 | 0.624 |
| Asthma | 1.05 | 0.78 | 1.41 | 0.683 | 1.12 | 0.92 | 1.38 | 0.139 | 1.14 | 0.97 | 1.35 | 0.041 |
| Renal failure | 1.80 | 0.48 | 6.76 | 0.253 | 1.65 | 0.61 | 4.49 | 0.193 | 1.29 | 0.55 | 3.04 | 0.448 |
| Liver failure | 1.28 | 0.49 | 3.32 | 0.505 | 0.93 | 0.42 | 2.09 | 0.829 | 0.82 | 0.42 | 1.62 | 0.452 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Osteoporosis | 0.51 | 0.11 | 2.31 | 0.251 | 0.60 | 0.24 | 1.54 | 0.164 | 0.87 | 0.44 | 1.75 | 0.616 |
| Suicidality | 1.72 | 0.95 | 3.14 | 0.019 | 1.68 | 1.18 | 2.38 | <0.001 | 1.62 | 1.16 | 2.25 | <0.001 |
| Antihypertensive | 0.98 | 0.67 | 1.44 | 0.893 | 1.02 | 0.74 | 1.41 | 0.861 | 0.98 | 0.76 | 1.27 | 0.853 |
| Aspirin | 0.89 | 0.51 | 1.54 | 0.573 | 1.15 | 0.76 | 1.75 | 0.391 | 1.13 | 0.83 | 1.55 | 0.313 |
| Anticoagulants | 0.67 | 0.22 | 2.05 | 0.359 | 1.13 | 0.57 | 2.23 | 0.641 | 1.09 | 0.62 | 1.90 | 0.697 |
| NSAIDs | 1.25 | 0.70 | 2.23 | 0.315 | 1.41 | 0.91 | 2.17 | 0.043 | 1.39 | 0.98 | 1.96 | 0.016 |
| Anticonvulsants | 0.78 | 0.23 | 2.60 | 0.597 | 0.77 | 0.34 | 1.73 | 0.409 | 1.21 | 0.70 | 2.08 | 0.371 |
| Hypnotics | 3.12 | 2.28 | 4.26 | <0.001 | 2.90 | 2.28 | 3.69 | <0.001 | 3.03 | 2.52 | 3.65 | <0.001 |
| Bisphosphonates | 1.00 | | | | 0.76 | 0.13 | 4.41 | 0.684 | 0.59 | 0.13 | 2.64 | 0.368 |
| Contraceptives | 0.75 | 0.35 | 1.61 | 0.328 | 0.84 | 0.54 | 1.29 | 0.293 | 0.80 | 0.57 | 1.14 | 0.106 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.01 | 0.00 | 0.02 | <0.001 | 0.00 | 0.00 | 0.03 | <0.001 |

| | **Adverse events, sleep disturbance *(FSA, N= 1,050,105)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.02 | 0.88 | 1.18 | 0.761 | 0.95 | 0.85 | 1.06 | 0.192 | 0.98 | 0.89 | 1.07 | 0.496 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 1.94 | 1.74 | 2.16 | <0.001 | 1.47 | 1.36 | 1.58 | <0.001 | 1.28 | 1.20 | 1.37 | <0.001 |
| TCAs | 4.95 | 4.27 | 5.72 | <0.001 | 3.23 | 2.88 | 3.62 | <0.001 | 2.65 | 2.40 | 2.92 | <0.001 |
| MAOIs | 7.57 | 1.67 | 34.29 | 0.001 | 4.18 | 1.11 | 15.79 | 0.006 | 3.04 | 0.91 | 10.16 | 0.018 |
| Other antidepressants | 3.30 | 2.82 | 3.86 | <0.001 | 2.44 | 2.18 | 2.74 | <0.001 | 2.13 | 1.92 | 2.37 | <0.001 |
| PHQ-9 baseline | 1.01 | 0.99 | 1.02 | 0.253 | 1.00 | 1.00 | 1.01 | 0.144 | 1.00 | 1.00 | 1.01 | 0.188 |
| BMI | 0.99 | 0.98 | 1.00 | 0.002 | 0.99 | 0.99 | 1.00 | <0.001 | 0.99 | 0.99 | 1.00 | <0.001 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.57 | 1.35 | 1.81 | <0.001 | 1.40 | 1.25 | 1.56 | <0.001 | 1.33 | 1.21 | 1.45 | <0.001 |
| Other | 0.93 | 0.76 | 1.12 | 0.314 | 0.88 | 0.76 | 1.01 | 0.021 | 0.84 | 0.74 | 0.95 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.05 | 0.93 | 1.18 | 0.329 | 1.09 | 0.98 | 1.21 | 0.035 | 1.07 | 0.98 | 1.17 | 0.053 |
| 3 | 1.09 | 0.93 | 1.27 | 0.156 | 1.15 | 1.01 | 1.31 | 0.005 | 1.19 | 1.06 | 1.33 | <0.001 |
| 4 | 1.19 | 1.02 | 1.40 | 0.003 | 1.29 | 1.12 | 1.48 | <0.001 | 1.30 | 1.15 | 1.48 | <0.001 |
| 5, most deprived | 1.26 | 1.04 | 1.52 | 0.002 | 1.37 | 1.17 | 1.61 | <0.001 | 1.41 | 1.22 | 1.63 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.86 | 0.50 | 1.46 | 0.457 | 0.87 | 0.57 | 1.33 | 0.399 | 0.85 | 0.58 | 1.25 | 0.271 |
| London | 0.97 | 0.69 | 1.35 | 0.788 | 0.96 | 0.70 | 1.30 | 0.719 | 0.97 | 0.74 | 1.28 | 0.776 |
| North East | 0.97 | 0.45 | 2.09 | 0.929 | 0.88 | 0.45 | 1.73 | 0.624 | 0.86 | 0.49 | 1.53 | 0.506 |
| North West | 0.94 | 0.64 | 1.37 | 0.653 | 0.99 | 0.71 | 1.39 | 0.954 | 0.99 | 0.73 | 1.34 | 0.906 |
| South Central | 0.87 | 0.60 | 1.25 | 0.321 | 0.81 | 0.58 | 1.14 | 0.113 | 0.81 | 0.60 | 1.08 | 0.058 |
| South East | 1.30 | 0.84 | 2.02 | 0.116 | 1.20 | 0.79 | 1.83 | 0.267 | 1.13 | 0.77 | 1.65 | 0.415 |
| South West | 1.10 | 0.77 | 1.56 | 0.506 | 1.05 | 0.76 | 1.47 | 0.689 | 1.01 | 0.74 | 1.37 | 0.964 |
| West Midlands | 1.05 | 0.74 | 1.48 | 0.738 | 1.00 | 0.73 | 1.37 | 0.978 | 1.01 | 0.76 | 1.34 | 0.927 |
| Yorkshire & Humber | 0.97 | 0.57 | 1.63 | 0.862 | 0.94 | 0.58 | 1.51 | 0.728 | 0.96 | 0.59 | 1.55 | 0.817 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.93 | 0.84 | 1.03 | 0.083 | 0.97 | 0.90 | 1.05 | 0.331 | 0.97 | 0.91 | 1.04 | 0.240 |
| Light-smoker | 0.97 | 0.88 | 1.06 | 0.364 | 1.06 | 0.99 | 1.13 | 0.042 | 1.06 | 1.00 | 1.13 | 0.007 |
| Moderate-smoker | 1.01 | 0.78 | 1.31 | 0.894 | 1.06 | 0.87 | 1.28 | 0.450 | 1.02 | 0.86 | 1.21 | 0.768 |
| Heavy-smoker | 0.94 | 0.64 | 1.38 | 0.701 | 1.14 | 0.88 | 1.47 | 0.196 | 1.05 | 0.84 | 1.32 | 0.561 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.00 | 0.90 | 1.11 | 0.988 | 1.01 | 0.94 | 1.09 | 0.653 | 1.00 | 0.95 | 1.06 | 0.855 |
| Medium | 1.04 | 0.89 | 1.21 | 0.537 | 1.02 | 0.90 | 1.15 | 0.653 | 1.02 | 0.93 | 1.13 | 0.498 |
| Heavy | 0.92 | 0.68 | 1.25 | 0.481 | 0.96 | 0.77 | 1.21 | 0.670 | 1.00 | 0.81 | 1.23 | 0.965 |
| Very heavy | 0.83 | 0.57 | 1.20 | 0.186 | 1.00 | 0.80 | 1.25 | 0.993 | 1.00 | 0.84 | 1.19 | 0.980 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| African/Caribbean | 1.15 | 0.93 | 1.41 | 0.086 | 1.11 | 0.94 | 1.31 | 0.084 | 1.07 | 0.94 | 1.22 | 0.162 |
| Asian | 1.32 | 1.12 | 1.57 | <0.001 | 1.35 | 1.18 | 1.54 | <0.001 | 1.32 | 1.19 | 1.47 | <0.001 |
| Other | 1.36 | 1.15 | 1.62 | <0.001 | 1.34 | 1.16 | 1.55 | <0.001 | 1.26 | 1.12 | 1.42 | <0.001 |
| Age | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.01 | 1.01 | <0.001 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.26 | 1.17 | 1.35 | <0.001 | 1.16 | 1.10 | 1.23 | <0.001 | 1.11 | 1.06 | 1.17 | <0.001 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.86 | 0.72 | 1.03 | 0.027 | 0.88 | 0.76 | 1.01 | 0.013 | 0.87 | 0.77 | 0.97 | 0.002 |
| 2011 to 2015 | 0.65 | 0.53 | 0.79 | <0.001 | 0.68 | 0.58 | 0.79 | <0.001 | 0.67 | 0.59 | 0.77 | <0.001 |
| 2016 to 2020 | 0.56 | 0.45 | 0.70 | <0.001 | 0.57 | 0.48 | 0.67 | <0.001 | 0.55 | 0.47 | 0.63 | <0.001 |
| Coronary heart disease | 1.06 | 0.89 | 1.26 | 0.403 | 1.13 | 1.00 | 1.27 | 0.010 | 1.16 | 1.05 | 1.28 | <0.001 |
| Stroke | 0.86 | 0.71 | 1.04 | 0.042 | 1.03 | 0.91 | 1.17 | 0.551 | 1.08 | 0.98 | 1.20 | 0.051 |
| Diabetes | 0.98 | 0.85 | 1.15 | 0.796 | 1.04 | 0.93 | 1.16 | 0.424 | 0.97 | 0.89 | 1.06 | 0.381 |
| Epilepsy | 1.09 | 0.83 | 1.43 | 0.437 | 1.02 | 0.84 | 1.24 | 0.777 | 1.03 | 0.87 | 1.20 | 0.683 |
| Hypothyroidism | 1.02 | 0.86 | 1.20 | 0.794 | 1.00 | 0.89 | 1.12 | 0.941 | 1.04 | 0.95 | 1.14 | 0.296 |
| Arthritis | 1.17 | 1.06 | 1.29 | <0.001 | 1.18 | 1.10 | 1.27 | <0.001 | 1.20 | 1.13 | 1.27 | <0.001 |
| Anxiety | 1.10 | 0.98 | 1.24 | 0.040 | 1.14 | 1.04 | 1.24 | <0.001 | 1.16 | 1.08 | 1.25 | <0.001 |
| Migraine | 1.03 | 0.88 | 1.19 | 0.656 | 1.09 | 0.98 | 1.20 | 0.034 | 1.11 | 1.02 | 1.20 | 0.002 |
| Cancer | 1.02 | 0.91 | 1.15 | 0.594 | 1.11 | 1.02 | 1.20 | 0.001 | 1.11 | 1.04 | 1.19 | <0.001 |
| Asthma | 0.99 | 0.91 | 1.09 | 0.881 | 1.08 | 1.01 | 1.15 | 0.003 | 1.10 | 1.05 | 1.16 | <0.001 |
| Renal failure | 1.14 | 0.74 | 1.76 | 0.426 | 1.10 | 0.81 | 1.49 | 0.424 | 1.06 | 0.84 | 1.35 | 0.518 |
| Liver failure | 1.01 | 0.72 | 1.43 | 0.928 | 1.14 | 0.90 | 1.43 | 0.155 | 1.15 | 0.96 | 1.39 | 0.048 |
| Osteoporosis | 0.98 | 0.75 | 1.27 | 0.829 | 1.07 | 0.90 | 1.28 | 0.311 | 1.06 | 0.91 | 1.23 | 0.349 |
| Suicidality | 1.58 | 1.30 | 1.93 | <0.001 | 1.56 | 1.35 | 1.80 | <0.001 | 1.54 | 1.37 | 1.73 | <0.001 |
| Antihypertensive | 0.94 | 0.82 | 1.07 | 0.203 | 0.96 | 0.87 | 1.06 | 0.267 | 0.99 | 0.92 | 1.07 | 0.791 |
| Aspirin | 1.00 | 0.85 | 1.18 | 0.987 | 1.05 | 0.94 | 1.18 | 0.276 | 1.03 | 0.94 | 1.13 | 0.416 |
| Anticoagulants | 1.17 | 0.91 | 1.52 | 0.107 | 1.21 | 1.02 | 1.44 | 0.005 | 1.15 | 1.00 | 1.31 | 0.009 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NSAIDs | 1.07 | 0.91 | 1.26 | 0.312 | 1.15 | 1.02 | 1.29 | 0.002 | 1.19 | 1.08 | 1.30 | <0.001 |
| Anticonvulsants | 0.93 | 0.71 | 1.20 | 0.453 | 1.01 | 0.83 | 1.21 | 0.939 | 1.05 | 0.91 | 1.22 | 0.400 |
| Hypnotics | 3.04 | 2.77 | 3.34 | <0.001 | 2.84 | 2.64 | 3.06 | <0.001 | 2.73 | 2.56 | 2.92 | <0.001 |
| Bisphosphonates | 0.87 | 0.53 | 1.44 | 0.487 | 0.90 | 0.64 | 1.27 | 0.443 | 0.84 | 0.63 | 1.12 | 0.117 |
| Contraceptives | 0.95 | 0.80 | 1.12 | 0.389 | 0.98 | 0.88 | 1.10 | 0.721 | 0.94 | 0.86 | 1.03 | 0.083 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.01 | <0.001 | 0.01 | 0.01 | 0.01 | <0.001 |

***Table A4.6h*** *Regression analyses for adverse events (memory impairment) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Adverse events, memory impairment *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.32 | 0.79 | 2.20 | 0.159 | 0.89 | 0.61 | 1.31 | 0.448 | 0.98 | 0.73 | 1.31 | 0.841 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 0.75 | 0.46 | 1.22 | 0.127 | 1.03 | 0.74 | 1.45 | 0.798 | 1.11 | 0.85 | 1.47 | 0.312 |
| TCAs | 0.25 | 0.02 | 3.55 | 0.181 | 0.88 | 0.29 | 2.64 | 0.769 | 1.27 | 0.61 | 2.63 | 0.406 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | 0.68 | 0.25 | 1.85 | 0.320 | 1.24 | 0.70 | 2.22 | 0.335 | 1.23 | 0.75 | 2.03 | 0.280 |
| PHQ-9 baseline | 1.01 | 0.96 | 1.05 | 0.628 | 1.02 | 0.99 | 1.05 | 0.140 | 1.00 | 0.98 | 1.03 | 0.574 |
| BMI | 0.99 | 0.94 | 1.03 | 0.405 | 0.96 | 0.94 | 0.99 | 0.001 | 0.97 | 0.95 | 0.99 | <0.001 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.01 | 0.63 | 1.60 | 0.964 | 1.18 | 0.85 | 1.64 | 0.187 | 1.15 | 0.91 | 1.46 | 0.117 |
| Other | 0.55 | 0.14 | 2.11 | 0.254 | 0.72 | 0.29 | 1.79 | 0.357 | 0.59 | 0.28 | 1.26 | 0.075 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.42 | 0.77 | 2.60 | 0.138 | 1.24 | 0.85 | 1.83 | 0.145 | 1.13 | 0.85 | 1.50 | 0.264 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 1.48 | 0.80 | 2.76 | 0.102 | 1.15 | 0.75 | 1.76 | 0.412 | 0.99 | 0.70 | 1.40 | 0.946 |
| 4 | 2.13 | 1.09 | 4.14 | 0.003 | 1.66 | 1.08 | 2.55 | 0.003 | 1.43 | 1.00 | 2.05 | 0.010 |
| 5, most deprived | 1.42 | 0.53 | 3.79 | 0.354 | 1.34 | 0.76 | 2.36 | 0.182 | 1.14 | 0.73 | 1.77 | 0.463 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.60 | 0.08 | 4.42 | 0.511 | 0.97 | 0.26 | 3.54 | 0.948 | 1.17 | 0.35 | 3.86 | 0.740 |
| London | 0.54 | 0.14 | 2.14 | 0.253 | 0.68 | 0.25 | 1.89 | 0.336 | 0.90 | 0.35 | 2.34 | 0.780 |
| North East | 0.29 | 0.03 | 2.62 | 0.146 | 0.87 | 0.23 | 3.34 | 0.787 | 1.40 | 0.45 | 4.30 | 0.445 |
| North West | 0.49 | 0.13 | 1.91 | 0.180 | 0.77 | 0.27 | 2.15 | 0.506 | 1.01 | 0.39 | 2.64 | 0.968 |
| South Central | 0.87 | 0.24 | 3.22 | 0.786 | 0.93 | 0.34 | 2.56 | 0.857 | 1.11 | 0.42 | 2.95 | 0.783 |
| South East | 0.97 | 0.26 | 3.59 | 0.960 | 0.92 | 0.33 | 2.56 | 0.838 | 0.99 | 0.38 | 2.60 | 0.978 |
| South West | 0.65 | 0.17 | 2.57 | 0.423 | 0.96 | 0.34 | 2.74 | 0.924 | 1.18 | 0.44 | 3.15 | 0.664 |
| West Midlands | 1.06 | 0.27 | 4.15 | 0.907 | 1.33 | 0.47 | 3.77 | 0.479 | 1.60 | 0.60 | 4.26 | 0.219 |
| Yorkshire & Humber | 1.11 | 0.27 | 4.58 | 0.845 | 1.22 | 0.39 | 3.87 | 0.652 | 1.22 | 0.43 | 3.46 | 0.624 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.94 | 0.56 | 1.58 | 0.761 | 1.00 | 0.72 | 1.37 | 0.968 | 1.09 | 0.85 | 1.41 | 0.358 |
| Light-smoker | 0.95 | 0.52 | 1.77 | 0.843 | 0.82 | 0.55 | 1.21 | 0.187 | 0.95 | 0.70 | 1.30 | 0.686 |
| Moderate-smoker | 2.11 | 0.31 | 14.54 | 0.319 | 1.05 | 0.14 | 7.77 | 0.952 | 0.99 | 0.23 | 4.25 | 0.990 |
| Heavy-smoker | 1.00 | - | - | - | 1.79 | 0.39 | 8.26 | 0.329 | 1.13 | 0.25 | 5.10 | 0.838 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.82 | 0.50 | 1.35 | 0.307 | 0.92 | 0.66 | 1.27 | 0.484 | 0.87 | 0.67 | 1.12 | 0.155 |
| Medium | 1.25 | 0.64 | 2.44 | 0.380 | 1.00 | 0.62 | 1.63 | 0.980 | 1.13 | 0.78 | 1.64 | 0.405 |
| Heavy | 2.58 | 0.78 | 8.49 | 0.041 | 1.69 | 0.66 | 4.33 | 0.154 | 1.12 | 0.47 | 2.68 | 0.736 |
| Very heavy | 0.46 | 0.03 | 6.69 | 0.458 | 0.58 | 0.13 | 2.68 | 0.361 | 0.82 | 0.30 | 2.27 | 0.619 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.59 | 0.46 | 5.49 | 0.338 | 2.56 | 1.07 | 6.13 | 0.006 | 1.75 | 0.78 | 3.89 | 0.073 |
| Asian | 1.55 | 0.48 | 5.06 | 0.340 | 1.52 | 0.61 | 3.75 | 0.237 | 1.55 | 0.79 | 3.01 | 0.093 |
| Other | 1.54 | 0.47 | 5.00 | 0.349 | 1.34 | 0.55 | 3.27 | 0.404 | 1.40 | 0.68 | 2.88 | 0.227 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 1.08 | 1.06 | 1.09 | <0.001 | 1.07 | 1.06 | 1.09 | <0.001 | 1.07 | 1.07 | 1.08 | <0.001 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.56 | 0.96 | 2.52 | 0.018 | 1.21 | 0.90 | 1.64 | 0.100 | 1.12 | 0.89 | 1.42 | 0.195 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.22 | 0.12 | 0.40 | <0.001 | 0.24 | 0.16 | 0.36 | <0.001 | 0.26 | 0.18 | 0.36 | <0.001 |
| 2011 to 2015 | 0.57 | 0.34 | 0.95 | 0.005 | 0.68 | 0.48 | 0.95 | 0.003 | 0.75 | 0.57 | 0.97 | 0.005 |
| 2016 to 2020 | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Coronary heart disease | 1.12 | 0.58 | 2.17 | 0.658 | 1.05 | 0.65 | 1.72 | 0.783 | 1.05 | 0.72 | 1.53 | 0.756 |
| Stroke | 1.01 | 0.48 | 2.15 | 0.962 | 1.27 | 0.76 | 2.14 | 0.230 | 1.39 | 0.94 | 2.08 | 0.031 |
| Diabetes | 0.66 | 0.33 | 1.30 | 0.114 | 1.09 | 0.71 | 1.68 | 0.602 | 1.02 | 0.74 | 1.42 | 0.852 |
| Epilepsy | 0.96 | 0.20 | 4.71 | 0.947 | 1.20 | 0.41 | 3.46 | 0.662 | 1.26 | 0.54 | 2.97 | 0.480 |
| Hypothyroidism | 1.43 | 0.60 | 3.40 | 0.292 | 1.04 | 0.58 | 1.88 | 0.848 | 1.08 | 0.69 | 1.67 | 0.667 |
| Arthritis | 1.31 | 0.74 | 2.32 | 0.225 | 1.08 | 0.71 | 1.65 | 0.644 | 1.05 | 0.75 | 1.47 | 0.710 |
| Anxiety | 1.01 | 0.58 | 1.75 | 0.968 | 1.17 | 0.81 | 1.67 | 0.278 | 1.18 | 0.89 | 1.57 | 0.125 |
| Migraine | 1.31 | 0.51 | 3.37 | 0.469 | 1.24 | 0.69 | 2.22 | 0.338 | 1.19 | 0.74 | 1.91 | 0.354 |
| Cancer | 1.17 | 0.69 | 1.98 | 0.452 | 0.96 | 0.66 | 1.39 | 0.771 | 0.95 | 0.72 | 1.25 | 0.640 |
| Asthma | 1.12 | 0.68 | 1.86 | 0.557 | 1.16 | 0.83 | 1.63 | 0.252 | 1.01 | 0.76 | 1.35 | 0.904 |
| Renal failure | 0.50 | 0.03 | 7.17 | 0.501 | 0.20 | 0.01 | 2.77 | 0.116 | 0.82 | 0.26 | 2.54 | 0.646 |
| Liver failure | 1.15 | 0.17 | 7.66 | 0.853 | 2.11 | 0.83 | 5.38 | 0.040 | 1.72 | 0.79 | 3.76 | 0.073 |
| Osteoporosis | 0.69 | 0.17 | 2.79 | 0.492 | 1.03 | 0.51 | 2.07 | 0.919 | 1.09 | 0.65 | 1.85 | 0.665 |
| Suicidality | 0.53 | 0.12 | 2.29 | 0.260 | 0.60 | 0.18 | 2.04 | 0.280 | 0.89 | 0.41 | 1.93 | 0.687 |
| Antihypertensive | 0.80 | 0.48 | 1.33 | 0.259 | 0.92 | 0.64 | 1.31 | 0.525 | 0.84 | 0.63 | 1.11 | 0.103 |
| Aspirin | 1.18 | 0.60 | 2.35 | 0.527 | 1.09 | 0.67 | 1.76 | 0.646 | 1.04 | 0.73 | 1.50 | 0.763 |
| Anticoagulants | 1.30 | 0.52 | 3.22 | 0.463 | 1.34 | 0.73 | 2.46 | 0.220 | 1.19 | 0.73 | 1.94 | 0.372 |
| NSAIDs | 0.19 | 0.01 | 2.56 | 0.098 | 0.48 | 0.16 | 1.42 | 0.081 | 0.88 | 0.45 | 1.70 | 0.611 |
| Anticonvulsants | 2.00 | 0.61 | 6.49 | 0.131 | 1.36 | 0.56 | 3.31 | 0.372 | 1.07 | 0.49 | 2.34 | 0.813 |
| Hypnotics | 0.44 | 0.15 | 1.28 | 0.048 | 0.60 | 0.32 | 1.10 | 0.030 | 0.70 | 0.45 | 1.10 | 0.042 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bisphosphonates | 1.00 | - | - | - | 0.76 | 0.16 | 3.65 | 0.652 | 0.89 | 0.30 | 2.64 | 0.778 |
| Contraceptives | 1.00 | - | - | - | 0.33 | 0.05 | 2.05 | 0.117 | 0.29 | 0.07 | 1.26 | 0.030 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 |

| | **Adverse events, memory impairment *(FSA, N= 1,050,105)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.15 | 0.99 | 1.34 | 0.013 | 1.09 | 0.98 | 1.21 | 0.037 | 1.13 | 1.04 | 1.23 | <0.001 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 1.21 | 1.05 | 1.39 | 0.001 | 1.18 | 1.07 | 1.30 | <0.001 | 1.18 | 1.09 | 1.27 | <0.001 |
| TCAs | 1.21 | 0.90 | 1.64 | 0.098 | 1.20 | 0.97 | 1.48 | 0.028 | 1.18 | 1.00 | 1.40 | 0.011 |
| MAOIs | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Other antidepressants | 1.25 | 1.01 | 1.54 | 0.008 | 1.20 | 1.03 | 1.39 | 0.002 | 1.12 | 0.99 | 1.27 | 0.018 |
| PHQ-9 baseline | 1.00 | 0.98 | 1.01 | 0.774 | 1.00 | 0.99 | 1.01 | 0.705 | 1.00 | 0.99 | 1.01 | 0.772 |
| BMI | 0.99 | 0.98 | 1.00 | 0.032 | 0.99 | 0.98 | 1.00 | <0.001 | 0.99 | 0.98 | 1.00 | <0.001 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.11 | 0.97 | 1.26 | 0.051 | 1.07 | 0.97 | 1.18 | 0.059 | 1.08 | 1.00 | 1.17 | 0.013 |
| Other | 0.53 | 0.39 | 0.73 | <0.001 | 0.58 | 0.46 | 0.73 | <0.001 | 0.63 | 0.51 | 0.77 | <0.001 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.02 | 0.88 | 1.19 | 0.704 | 0.99 | 0.89 | 1.10 | 0.818 | 1.02 | 0.94 | 1.11 | 0.499 |
| 3 | 1.13 | 0.95 | 1.35 | 0.063 | 1.06 | 0.94 | 1.20 | 0.215 | 1.07 | 0.97 | 1.18 | 0.064 |
| 4 | 1.23 | 1.02 | 1.48 | 0.004 | 1.13 | 0.99 | 1.29 | 0.018 | 1.11 | 0.99 | 1.23 | 0.017 |
| 5, most deprived | 1.12 | 0.90 | 1.40 | 0.176 | 1.11 | 0.94 | 1.30 | 0.099 | 1.08 | 0.95 | 1.24 | 0.114 |
| Region of England (East Midlands) | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| East of England | 0.73 | 0.39 | 1.36 | 0.191 | 0.81 | 0.47 | 1.40 | 0.319 | 0.85 | 0.51 | 1.41 | 0.414 |
| London | 1.02 | 0.62 | 1.68 | 0.919 | 1.07 | 0.68 | 1.69 | 0.696 | 1.09 | 0.73 | 1.62 | 0.585 |
| North East | 1.03 | 0.50 | 2.11 | 0.913 | 1.12 | 0.59 | 2.11 | 0.651 | 1.19 | 0.69 | 2.06 | 0.400 |
| North West | 1.10 | 0.67 | 1.82 | 0.612 | 1.14 | 0.73 | 1.79 | 0.455 | 1.17 | 0.79 | 1.73 | 0.298 |
| South Central | 0.74 | 0.45 | 1.22 | 0.123 | 0.86 | 0.55 | 1.37 | 0.412 | 0.88 | 0.59 | 1.31 | 0.403 |
| South East | 0.91 | 0.54 | 1.53 | 0.638 | 0.98 | 0.61 | 1.57 | 0.910 | 0.97 | 0.65 | 1.45 | 0.857 |
| South West | 1.16 | 0.68 | 1.96 | 0.471 | 1.23 | 0.77 | 1.96 | 0.253 | 1.22 | 0.81 | 1.83 | 0.205 |
| West Midlands | 1.13 | 0.67 | 1.88 | 0.552 | 1.18 | 0.74 | 1.87 | 0.351 | 1.24 | 0.83 | 1.85 | 0.174 |
| Yorkshire & Humber | 1.09 | 0.59 | 2.01 | 0.727 | 1.21 | 0.72 | 2.03 | 0.336 | 1.23 | 0.78 | 1.94 | 0.233 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.02 | 0.90 | 1.16 | 0.670 | 1.02 | 0.94 | 1.11 | 0.515 | 1.02 | 0.95 | 1.10 | 0.435 |
| Light-smoker | 0.93 | 0.79 | 1.09 | 0.226 | 0.93 | 0.83 | 1.04 | 0.096 | 0.92 | 0.84 | 1.01 | 0.017 |
| Moderate-smoker | 0.77 | 0.39 | 1.55 | 0.343 | 0.77 | 0.47 | 1.25 | 0.159 | 0.77 | 0.52 | 1.14 | 0.087 |
| Heavy-smoker | 0.96 | 0.41 | 2.29 | 0.915 | 0.95 | 0.51 | 1.77 | 0.844 | 0.91 | 0.55 | 1.51 | 0.630 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.97 | 0.85 | 1.12 | 0.621 | 0.96 | 0.86 | 1.06 | 0.261 | 0.97 | 0.90 | 1.05 | 0.356 |
| Medium | 0.91 | 0.70 | 1.18 | 0.340 | 0.93 | 0.79 | 1.10 | 0.286 | 0.96 | 0.84 | 1.10 | 0.457 |
| Heavy | 0.95 | 0.54 | 1.66 | 0.808 | 0.96 | 0.64 | 1.44 | 0.816 | 1.00 | 0.70 | 1.42 | 0.974 |
| Very heavy | 0.91 | 0.53 | 1.57 | 0.653 | 0.87 | 0.60 | 1.26 | 0.348 | 0.90 | 0.67 | 1.23 | 0.392 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.35 | 1.00 | 1.82 | 0.011 | 1.23 | 0.99 | 1.54 | 0.014 | 1.15 | 0.96 | 1.38 | 0.044 |
| Asian | 1.63 | 1.26 | 2.11 | <0.001 | 1.46 | 1.20 | 1.76 | <0.001 | 1.50 | 1.29 | 1.75 | <0.001 |
| Other | 1.55 | 1.09 | 2.21 | 0.002 | 1.48 | 1.15 | 1.91 | <0.001 | 1.39 | 1.13 | 1.70 | <0.001 |
| | | | | | | | | | | | | |
| Age | 1.07 | 1.06 | 1.07 | <0.001 | 1.07 | 1.06 | 1.07 | <0.001 | 1.06 | 1.06 | 1.07 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.18 | 1.05 | 1.33 | <0.001 | 1.10 | 1.01 | 1.19 | 0.003 | 1.06 | 0.99 | 1.13 | 0.028 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.47 | 1.14 | 1.91 | <0.001 | 1.35 | 1.12 | 1.63 | <0.001 | 1.33 | 1.14 | 1.55 | <0.001 |
| 2011 to 2015 | 2.79 | 2.19 | 3.56 | <0.001 | 2.97 | 2.47 | 3.55 | <0.001 | 3.19 | 2.75 | 3.70 | <0.001 |
| 2016 to 2020 | 3.69 | 2.85 | 4.77 | <0.001 | 3.47 | 2.87 | 4.19 | <0.001 | 3.35 | 2.88 | 3.91 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.97 | 0.82 | 1.14 | 0.616 | 1.03 | 0.92 | 1.16 | 0.522 | 1.03 | 0.94 | 1.13 | 0.458 |
| Stroke | 1.04 | 0.88 | 1.24 | 0.524 | 1.09 | 0.97 | 1.23 | 0.053 | 1.12 | 1.02 | 1.24 | 0.003 |
| Diabetes | 0.99 | 0.84 | 1.17 | 0.898 | 0.99 | 0.87 | 1.12 | 0.789 | 1.02 | 0.92 | 1.14 | 0.633 |
| Epilepsy | 1.36 | 0.96 | 1.92 | 0.023 | 1.43 | 1.11 | 1.86 | <0.001 | 1.36 | 1.10 | 1.66 | <0.001 |
| Hypothyroidism | 0.99 | 0.81 | 1.19 | 0.852 | 1.05 | 0.93 | 1.19 | 0.322 | 1.05 | 0.95 | 1.16 | 0.213 |
| Arthritis | 1.09 | 0.93 | 1.28 | 0.173 | 1.07 | 0.95 | 1.21 | 0.138 | 1.09 | 0.99 | 1.19 | 0.024 |
| Anxiety | 1.21 | 1.07 | 1.38 | <0.001 | 1.21 | 1.11 | 1.32 | <0.001 | 1.17 | 1.09 | 1.25 | <0.001 |
| Migraine | 1.16 | 0.89 | 1.50 | 0.148 | 0.97 | 0.81 | 1.18 | 0.722 | 1.06 | 0.93 | 1.22 | 0.262 |
| Cancer | 0.99 | 0.87 | 1.12 | 0.785 | 0.99 | 0.90 | 1.09 | 0.814 | 0.98 | 0.91 | 1.05 | 0.492 |
| Asthma | 0.98 | 0.86 | 1.13 | 0.765 | 1.02 | 0.92 | 1.12 | 0.651 | 1.05 | 0.97 | 1.14 | 0.091 |
| Renal failure | 0.57 | 0.32 | 1.00 | 0.010 | 0.64 | 0.44 | 0.94 | 0.003 | 0.71 | 0.54 | 0.94 | 0.001 |
| Liver failure | 1.55 | 1.09 | 2.21 | 0.001 | 1.40 | 1.09 | 1.82 | 0.001 | 1.27 | 1.03 | 1.56 | 0.004 |
| Osteoporosis | 1.04 | 0.85 | 1.28 | 0.624 | 1.00 | 0.86 | 1.17 | 0.997 | 0.99 | 0.87 | 1.12 | 0.795 |
| Suicidality | 0.98 | 0.64 | 1.49 | 0.904 | 1.07 | 0.81 | 1.42 | 0.518 | 1.06 | 0.86 | 1.31 | 0.448 |
| Antihypertensive | 0.91 | 0.79 | 1.05 | 0.080 | 0.97 | 0.88 | 1.07 | 0.460 | 0.96 | 0.89 | 1.04 | 0.239 |
| Aspirin | 1.01 | 0.87 | 1.17 | 0.883 | 0.99 | 0.89 | 1.10 | 0.780 | 0.98 | 0.89 | 1.07 | 0.463 |
| Anticoagulants | 0.92 | 0.75 | 1.15 | 0.350 | 0.98 | 0.85 | 1.13 | 0.701 | 0.96 | 0.86 | 1.08 | 0.414 |
| NSAIDs | 0.69 | 0.49 | 0.96 | 0.004 | 0.87 | 0.71 | 1.07 | 0.090 | 1.01 | 0.86 | 1.18 | 0.887 |
| Anticonvulsants | 1.18 | 0.91 | 1.53 | 0.100 | 1.06 | 0.86 | 1.30 | 0.487 | 1.04 | 0.88 | 1.23 | 0.552 |
| Hypnotics | 0.73 | 0.58 | 0.91 | <0.001 | 0.73 | 0.62 | 0.87 | <0.001 | 0.73 | 0.64 | 0.82 | <0.001 |
| Bisphosphonates | 1.22 | 0.83 | 1.80 | 0.192 | 1.27 | 0.97 | 1.67 | 0.021 | 1.29 | 1.03 | 1.60 | 0.003 |
| Contraceptives | 0.42 | 0.19 | 0.94 | 0.006 | 0.49 | 0.31 | 0.77 | <0.001 | 0.51 | 0.37 | 0.71 | <0.001 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 |

***Table A4.6i*** *Regression analyses for adverse events (self-harm) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Adverse events, self-harm *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 0.24 | 0.05 | 1.24 | 0.025 | 0.25 | 0.06 | 1.01 | 0.011 | 0.25 | 0.09 | 0.73 | 0.001 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 3.35 | 1.65 | 6.83 | <0.001 | 2.85 | 1.71 | 4.76 | <0.001 | 2.49 | 1.70 | 3.65 | <0.001 |
| TCAs | 3.58 | 0.68 | 18.99 | 0.049 | 3.25 | 1.00 | 10.62 | 0.010 | 2.33 | 0.81 | 6.68 | 0.039 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | 3.92 | 1.46 | 10.49 | <0.001 | 3.54 | 1.71 | 7.31 | <0.001 | 2.90 | 1.60 | 5.24 | <0.001 |
| PHQ-9 baseline | 1.08 | 1.03 | 1.13 | <0.001 | 1.07 | 1.03 | 1.11 | <0.001 | 1.06 | 1.03 | 1.09 | <0.001 |
| BMI | 0.98 | 0.93 | 1.02 | 0.162 | 0.98 | 0.95 | 1.01 | 0.136 | 0.97 | 0.94 | 1.00 | 0.002 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.89 | 0.58 | 1.37 | 0.494 | 0.96 | 0.71 | 1.30 | 0.734 | 0.95 | 0.74 | 1.23 | 0.630 |
| Other | 1.73 | 0.49 | 6.08 | 0.261 | 0.85 | 0.25 | 2.93 | 0.737 | 0.67 | 0.22 | 2.03 | 0.356 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.87 | 0.47 | 1.64 | 0.581 | 0.96 | 0.61 | 1.53 | 0.841 | 1.09 | 0.73 | 1.62 | 0.566 |
| 3 | 0.78 | 0.40 | 1.51 | 0.325 | 0.93 | 0.58 | 1.50 | 0.706 | 1.06 | 0.71 | 1.57 | 0.729 |
| 4 | 0.87 | 0.44 | 1.71 | 0.596 | 1.09 | 0.66 | 1.81 | 0.655 | 1.35 | 0.88 | 2.07 | 0.069 |
| 5, most deprived | 0.85 | 0.41 | 1.80 | 0.587 | 0.92 | 0.53 | 1.59 | 0.693 | 1.09 | 0.69 | 1.74 | 0.613 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.33 | 0.05 | 2.41 | 0.153 | 0.37 | 0.09 | 1.44 | 0.059 | 0.29 | 0.08 | 1.09 | 0.016 |
| London | 0.61 | 0.21 | 1.77 | 0.231 | 0.64 | 0.31 | 1.35 | 0.124 | 0.69 | 0.36 | 1.30 | 0.129 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| North East | 0.32 | 0.07 | 1.52 | 0.060 | 0.63 | 0.24 | 1.64 | 0.214 | 0.92 | 0.45 | 1.89 | 0.761 |
| North West | 0.73 | 0.25 | 2.16 | 0.459 | 0.65 | 0.30 | 1.38 | 0.140 | 0.75 | 0.39 | 1.43 | 0.251 |
| South Central | 0.93 | 0.31 | 2.76 | 0.855 | 1.06 | 0.52 | 2.19 | 0.822 | 1.22 | 0.66 | 2.24 | 0.412 |
| South East | 0.92 | 0.32 | 2.65 | 0.839 | 0.85 | 0.41 | 1.78 | 0.580 | 0.87 | 0.45 | 1.68 | 0.590 |
| South West | 0.75 | 0.23 | 2.44 | 0.534 | 0.80 | 0.35 | 1.87 | 0.503 | 0.86 | 0.42 | 1.78 | 0.594 |
| West Midlands | 0.49 | 0.15 | 1.63 | 0.126 | 0.60 | 0.26 | 1.38 | 0.113 | 0.76 | 0.39 | 1.50 | 0.303 |
| Yorkshire & Humber | 1.08 | 0.36 | 3.30 | 0.853 | 0.89 | 0.40 | 1.95 | 0.697 | 1.00 | 0.52 | 1.90 | 0.992 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.11 | 0.65 | 1.91 | 0.606 | 0.99 | 0.65 | 1.51 | 0.962 | 1.09 | 0.78 | 1.54 | 0.497 |
| Light-smoker | 1.24 | 0.77 | 2.01 | 0.250 | 1.37 | 0.99 | 1.89 | 0.013 | 1.44 | 1.09 | 1.88 | 0.001 |
| Moderate-smoker | 1.61 | 0.48 | 5.40 | 0.307 | 1.51 | 0.62 | 3.68 | 0.229 | 1.96 | 1.00 | 3.88 | 0.010 |
| Heavy-smoker | 2.94 | 0.72 | 11.97 | 0.048 | 2.05 | 0.60 | 7.02 | 0.134 | 1.78 | 0.58 | 5.44 | 0.183 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.48 | 0.97 | 2.27 | 0.018 | 1.41 | 1.03 | 1.93 | 0.005 | 1.40 | 1.06 | 1.83 | 0.002 |
| Medium | 2.63 | 1.59 | 4.35 | <0.001 | 2.00 | 1.32 | 3.03 | <0.001 | 2.27 | 1.59 | 3.24 | <0.001 |
| Heavy | 2.41 | 0.68 | 8.59 | 0.074 | 2.20 | 0.86 | 5.62 | 0.030 | 2.08 | 0.94 | 4.62 | 0.018 |
| Very heavy | 2.09 | 0.72 | 6.10 | 0.075 | 2.09 | 1.00 | 4.38 | 0.010 | 1.87 | 0.98 | 3.59 | 0.013 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.69 | 0.60 | 4.76 | 0.194 | 1.37 | 0.63 | 2.96 | 0.292 | 1.08 | 0.51 | 2.29 | 0.804 |
| Asian | 1.06 | 0.37 | 3.07 | 0.890 | 0.93 | 0.44 | 1.98 | 0.810 | 1.05 | 0.52 | 2.11 | 0.850 |
| Other | 0.92 | 0.32 | 2.66 | 0.845 | 1.12 | 0.57 | 2.21 | 0.670 | 1.08 | 0.61 | 1.94 | 0.721 |
| | | | | | | | | | | | | |
| Age | 0.97 | 0.95 | 0.99 | 0.001 | 0.96 | 0.94 | 0.98 | <0.001 | 0.97 | 0.95 | 0.98 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.19 | 0.77 | 1.83 | 0.301 | 1.25 | 0.90 | 1.73 | 0.075 | 1.08 | 0.83 | 1.41 | 0.466 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2006 to 2010 | 0.12 | 0.02 | 0.91 | 0.007 | 0.27 | 0.04 | 1.82 | 0.078 | 0.42 | 0.07 | 2.67 | 0.224 |
| 2011 to 2015 | 0.14 | 0.02 | 1.06 | 0.012 | 0.27 | 0.04 | 1.87 | 0.081 | 0.40 | 0.06 | 2.62 | 0.209 |
| 2016 to 2020 | 0.23 | 0.03 | 1.89 | 0.073 | 0.43 | 0.06 | 3.01 | 0.262 | 0.54 | 0.08 | 3.62 | 0.407 |
| | | | | | | | | | | | | |
| Coronary heart disease | 5.48 | 1.41 | 21.32 | 0.001 | 2.69 | 0.63 | 11.56 | 0.081 | 2.26 | 0.58 | 8.86 | 0.123 |
| Stroke | 1.26 | 0.17 | 9.31 | 0.765 | 0.82 | 0.12 | 5.33 | 0.780 | 1.19 | 0.32 | 4.40 | 0.726 |
| Diabetes | 0.77 | 0.19 | 3.13 | 0.637 | 0.87 | 0.31 | 2.43 | 0.729 | 1.10 | 0.50 | 2.41 | 0.750 |
| Epilepsy | 2.20 | 0.59 | 8.22 | 0.122 | 1.73 | 0.60 | 4.96 | 0.179 | 1.48 | 0.64 | 3.41 | 0.225 |
| Hypothyroidism | 1.26 | 0.32 | 5.04 | 0.666 | 1.22 | 0.43 | 3.44 | 0.621 | 0.96 | 0.37 | 2.48 | 0.904 |
| Arthritis | 1.74 | 0.66 | 4.57 | 0.142 | 1.62 | 0.76 | 3.48 | 0.103 | 1.10 | 0.52 | 2.33 | 0.738 |
| Anxiety | 0.93 | 0.54 | 1.61 | 0.739 | 0.97 | 0.67 | 1.43 | 0.861 | 1.00 | 0.72 | 1.39 | 0.985 |
| Migraine | 0.81 | 0.36 | 1.82 | 0.499 | 1.27 | 0.73 | 2.21 | 0.274 | 1.19 | 0.75 | 1.91 | 0.336 |
| Cancer | 0.80 | 0.30 | 2.13 | 0.563 | 1.05 | 0.54 | 2.07 | 0.839 | 0.96 | 0.55 | 1.69 | 0.856 |
| Asthma | 1.07 | 0.65 | 1.74 | 0.733 | 0.93 | 0.65 | 1.33 | 0.603 | 1.07 | 0.80 | 1.42 | 0.564 |
| Renal failure | 5.43 | 0.65 | 45.70 | 0.041 | 5.65 | 1.14 | 28.09 | 0.005 | 3.79 | 0.76 | 18.74 | 0.032 |
| Liver failure | 0.69 | 0.06 | 8.25 | 0.697 | 1.56 | 0.41 | 5.92 | 0.386 | 1.67 | 0.55 | 5.06 | 0.232 |
| Osteoporosis | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Suicidality | 6.57 | 3.82 | 11.32 | <0.001 | 5.95 | 4.02 | 8.83 | <0.001 | 5.87 | 4.22 | 8.15 | <0.001 |
| Antihypertensive | 1.29 | 0.52 | 3.20 | 0.465 | 1.10 | 0.50 | 2.45 | 0.752 | 1.20 | 0.60 | 2.40 | 0.505 |
| Aspirin | 0.45 | 0.06 | 3.50 | 0.313 | 1.79 | 0.40 | 8.09 | 0.319 | 1.71 | 0.52 | 5.64 | 0.250 |
| Anticoagulants | 2.07 | 0.32 | 13.44 | 0.315 | 1.80 | 0.30 | 10.66 | 0.394 | 1.22 | 0.20 | 7.36 | 0.771 |
| NSAIDs | 1.42 | 0.47 | 4.25 | 0.413 | 1.23 | 0.53 | 2.86 | 0.529 | 0.96 | 0.43 | 2.13 | 0.901 |
| Anticonvulsants | 0.35 | 0.03 | 4.62 | 0.292 | 0.63 | 0.12 | 3.21 | 0.464 | 0.99 | 0.33 | 2.95 | 0.983 |
| Hypnotics | 2.72 | 1.59 | 4.63 | <0.001 | 2.08 | 1.37 | 3.16 | <0.001 | 2.02 | 1.43 | 2.84 | <0.001 |
| Bisphosphonates | 1.00 | | | | 8.62 | 0.60 | 122.90 | 0.037 | 6.17 | 0.43 | 87.70 | 0.078 |
| Contraceptives | 1.28 | 0.63 | 2.62 | 0.374 | 1.12 | 0.65 | 1.93 | 0.603 | 1.06 | 0.67 | 1.67 | 0.741 |
| *Constant* | 0.01 | 0.00 | 0.08 | <0.001 | 0.01 | 0.00 | 0.08 | <0.001 | 0.01 | 0.00 | 0.08 | <0.001 |

| **Adverse events, self-harm *(FSA, N= 1,050,105)*** | | |
|---|---|---|
| *2 months* | *6 months* | *12 months* |

| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Statin** | 0.76 | 0.50 | 1.15 | 0.086 | 0.78 | 0.56 | 1.07 | 0.044 | 0.82 | 0.62 | 1.08 | 0.063 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 1.91 | 1.63 | 2.25 | <0.001 | 1.90 | 1.69 | 2.14 | <0.001 | 1.71 | 1.55 | 1.88 | <0.001 |
| TCAs | 2.29 | 1.74 | 3.03 | <0.001 | 2.12 | 1.72 | 2.62 | <0.001 | 1.83 | 1.53 | 2.20 | <0.001 |
| MAOIs | 1.00 | - | - | - | 4.61 | 0.32 | 67.20 | 0.142 | 3.10 | 0.21 | 44.78 | 0.276 |
| Other antidepressants | 2.66 | 2.11 | 3.36 | <0.001 | 2.72 | 2.27 | 3.26 | <0.001 | 2.44 | 2.10 | 2.84 | <0.001 |
| PHQ-9 baseline | 1.01 | 1.00 | 1.03 | 0.013 | 1.01 | 1.00 | 1.03 | 0.004 | 1.01 | 1.00 | 1.02 | <0.001 |
| BMI | 0.99 | 0.98 | 1.00 | 0.014 | 0.99 | 0.98 | 1.00 | 0.007 | 0.99 | 0.98 | 1.00 | 0.002 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.83 | 0.72 | 0.97 | 0.002 | 0.82 | 0.73 | 0.91 | <0.001 | 0.84 | 0.76 | 0.92 | <0.001 |
| Other | 0.65 | 0.47 | 0.89 | 0.001 | 0.69 | 0.55 | 0.87 | <0.001 | 0.71 | 0.59 | 0.86 | <0.001 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.05 | 0.88 | 1.27 | 0.463 | 1.07 | 0.93 | 1.23 | 0.230 | 1.10 | 0.97 | 1.24 | 0.055 |
| 3 | 1.16 | 0.96 | 1.39 | 0.044 | 1.26 | 1.09 | 1.45 | <0.001 | 1.30 | 1.15 | 1.46 | <0.001 |
| 4 | 1.19 | 0.97 | 1.45 | 0.027 | 1.33 | 1.14 | 1.55 | <0.001 | 1.39 | 1.21 | 1.59 | <0.001 |
| 5, most deprived | 1.41 | 1.12 | 1.77 | <0.001 | 1.44 | 1.22 | 1.71 | <0.001 | 1.54 | 1.33 | 1.78 | <0.001 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.02 | 0.64 | 1.63 | 0.913 | 0.93 | 0.63 | 1.36 | 0.605 | 0.86 | 0.61 | 1.20 | 0.233 |
| London | 0.64 | 0.44 | 0.92 | 0.002 | 0.60 | 0.46 | 0.78 | <0.001 | 0.59 | 0.48 | 0.72 | <0.001 |
| North East | 1.00 | 0.68 | 1.47 | 0.981 | 0.97 | 0.73 | 1.29 | 0.782 | 1.00 | 0.80 | 1.25 | 0.991 |
| North West | 0.81 | 0.58 | 1.12 | 0.093 | 0.79 | 0.62 | 1.01 | 0.012 | 0.78 | 0.64 | 0.94 | <0.001 |
| South Central | 0.85 | 0.58 | 1.26 | 0.287 | 0.82 | 0.63 | 1.08 | 0.064 | 0.86 | 0.69 | 1.07 | 0.074 |
| South East | 1.02 | 0.70 | 1.49 | 0.871 | 0.90 | 0.68 | 1.21 | 0.378 | 0.89 | 0.70 | 1.13 | 0.204 |
| South West | 0.97 | 0.65 | 1.43 | 0.814 | 0.91 | 0.70 | 1.19 | 0.368 | 0.90 | 0.72 | 1.12 | 0.220 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| West Midlands | 0.69 | 0.48 | 1.00 | 0.011 | 0.64 | 0.49 | 0.84 | <0.001 | 0.66 | 0.53 | 0.81 | <0.001 |
| Yorkshire & Humber | 0.89 | 0.59 | 1.34 | 0.478 | 0.87 | 0.64 | 1.18 | 0.242 | 0.90 | 0.70 | 1.14 | 0.250 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.93 | 0.79 | 1.10 | 0.277 | 0.92 | 0.80 | 1.05 | 0.112 | 0.89 | 0.79 | 1.01 | 0.014 |
| Light-smoker | 1.23 | 1.09 | 1.39 | <0.001 | 1.28 | 1.16 | 1.41 | <0.001 | 1.33 | 1.23 | 1.45 | <0.001 |
| Moderate-smoker | 1.48 | 1.10 | 1.99 | 0.001 | 1.52 | 1.20 | 1.93 | <0.001 | 1.56 | 1.27 | 1.91 | <0.001 |
| Heavy-smoker | 1.27 | 0.77 | 2.08 | 0.220 | 1.41 | 0.98 | 2.04 | 0.014 | 1.61 | 1.19 | 2.18 | <0.001 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.01 | 0.87 | 1.17 | 0.844 | 1.04 | 0.93 | 1.15 | 0.381 | 1.06 | 0.97 | 1.16 | 0.096 |
| Medium | 1.16 | 0.95 | 1.42 | 0.054 | 1.19 | 1.03 | 1.37 | 0.001 | 1.20 | 1.04 | 1.38 | 0.001 |
| Heavy | 1.39 | 0.94 | 2.04 | 0.029 | 1.40 | 1.04 | 1.87 | 0.003 | 1.49 | 1.14 | 1.95 | <0.001 |
| Very heavy | 1.47 | 0.99 | 2.16 | 0.011 | 1.55 | 1.16 | 2.09 | <0.001 | 1.59 | 1.22 | 2.07 | <0.001 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.95 | 0.70 | 1.28 | 0.633 | 0.94 | 0.73 | 1.22 | 0.532 | 0.91 | 0.72 | 1.14 | 0.252 |
| Asian | 0.97 | 0.76 | 1.24 | 0.749 | 0.89 | 0.73 | 1.09 | 0.148 | 0.92 | 0.79 | 1.09 | 0.204 |
| Other | 0.92 | 0.70 | 1.22 | 0.459 | 1.02 | 0.83 | 1.26 | 0.763 | 1.00 | 0.84 | 1.20 | 0.980 |
| | | | | | | | | | | | | |
| Age | 0.97 | 0.96 | 0.97 | <0.001 | 0.96 | 0.96 | 0.97 | <0.001 | 0.96 | 0.96 | 0.97 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.31 | 1.16 | 1.48 | <0.001 | 1.22 | 1.12 | 1.33 | <0.001 | 1.15 | 1.06 | 1.25 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.82 | 0.65 | 1.03 | 0.024 | 0.83 | 0.70 | 1.00 | 0.009 | 0.82 | 0.71 | 0.95 | 0.001 |
| 2011 to 2015 | 0.94 | 0.74 | 1.19 | 0.469 | 0.95 | 0.78 | 1.15 | 0.452 | 0.93 | 0.79 | 1.10 | 0.268 |
| 2016 to 2020 | 1.15 | 0.89 | 1.49 | 0.165 | 1.15 | 0.94 | 1.41 | 0.080 | 1.10 | 0.93 | 1.31 | 0.134 |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.21 | 0.70 | 2.09 | 0.367 | 1.28 | 0.85 | 1.95 | 0.123 | 1.29 | 0.90 | 1.85 | 0.070 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stroke | 0.85 | 0.48 | 1.48 | 0.441 | 1.13 | 0.74 | 1.73 | 0.451 | 1.13 | 0.79 | 1.62 | 0.370 |
| Diabetes | 1.21 | 0.86 | 1.72 | 0.152 | 1.18 | 0.91 | 1.55 | 0.102 | 1.19 | 0.94 | 1.50 | 0.053 |
| Epilepsy | 1.08 | 0.73 | 1.59 | 0.624 | 0.98 | 0.72 | 1.34 | 0.860 | 1.03 | 0.79 | 1.36 | 0.745 |
| Hypothyroidism | 0.88 | 0.57 | 1.36 | 0.445 | 0.90 | 0.65 | 1.25 | 0.400 | 0.94 | 0.71 | 1.23 | 0.527 |
| Arthritis | 1.44 | 1.05 | 1.96 | 0.003 | 1.33 | 1.03 | 1.71 | 0.004 | 1.21 | 0.97 | 1.52 | 0.026 |
| Anxiety | 1.02 | 0.87 | 1.20 | 0.760 | 0.99 | 0.87 | 1.12 | 0.777 | 1.00 | 0.90 | 1.10 | 0.905 |
| Migraine | 0.82 | 0.65 | 1.04 | 0.028 | 0.88 | 0.74 | 1.05 | 0.064 | 0.87 | 0.75 | 1.01 | 0.017 |
| Cancer | 0.94 | 0.72 | 1.21 | 0.509 | 0.97 | 0.80 | 1.18 | 0.671 | 0.93 | 0.79 | 1.11 | 0.294 |
| Asthma | 0.99 | 0.86 | 1.13 | 0.781 | 1.04 | 0.94 | 1.14 | 0.352 | 1.09 | 1.01 | 1.19 | 0.006 |
| Renal failure | 1.07 | 0.36 | 3.16 | 0.869 | 1.09 | 0.47 | 2.50 | 0.801 | 1.24 | 0.63 | 2.43 | 0.413 |
| Liver failure | 0.99 | 0.55 | 1.78 | 0.953 | 1.29 | 0.86 | 1.91 | 0.103 | 1.22 | 0.85 | 1.74 | 0.150 |
| Osteoporosis | 1.26 | 0.60 | 2.64 | 0.430 | 1.18 | 0.63 | 2.21 | 0.491 | 1.15 | 0.66 | 2.00 | 0.506 |
| Suicidality | 7.73 | 6.44 | 9.28 | <0.001 | 6.94 | 6.06 | 7.94 | <0.001 | 6.31 | 5.64 | 7.06 | <0.001 |
| Antihypertensive | 1.14 | 0.85 | 1.53 | 0.236 | 1.12 | 0.88 | 1.43 | 0.229 | 1.09 | 0.88 | 1.35 | 0.313 |
| Aspirin | 0.79 | 0.46 | 1.36 | 0.270 | 0.94 | 0.63 | 1.40 | 0.671 | 0.90 | 0.63 | 1.27 | 0.421 |
| Anticoagulants | 1.00 | 0.48 | 2.10 | 0.996 | 0.86 | 0.45 | 1.62 | 0.534 | 0.96 | 0.56 | 1.65 | 0.849 |
| NSAIDs | 0.81 | 0.57 | 1.13 | 0.101 | 1.01 | 0.81 | 1.25 | 0.952 | 1.01 | 0.83 | 1.22 | 0.904 |
| Anticonvulsants | 1.61 | 1.11 | 2.35 | 0.001 | 1.59 | 1.16 | 2.17 | <0.001 | 1.52 | 1.17 | 1.99 | <0.001 |
| Hypnotics | 2.14 | 1.82 | 2.51 | <0.001 | 1.92 | 1.69 | 2.18 | <0.001 | 1.83 | 1.64 | 2.04 | <0.001 |
| Bisphosphonates | 1.35 | 0.35 | 5.19 | 0.565 | 1.32 | 0.43 | 4.06 | 0.526 | 0.99 | 0.33 | 2.99 | 0.987 |
| Contraceptives | 0.95 | 0.75 | 1.20 | 0.567 | 0.90 | 0.77 | 1.05 | 0.077 | 0.88 | 0.77 | 1.00 | 0.010 |
| *Constant* | 0.00 | 0.00 | 0.01 | <0.001 | 0.01 | 0.01 | 0.01 | <0.001 | 0.01 | 0.01 | 0.02 | <0.001 |

***Table A4.6l*** *Regression analyses for adverse events (suicidality) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Adverse events, suicidality *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.11 | 0.75 | 1.63 | 0.504 | 0.98 | 0.68 | 1.41 | 0.891 | 0.95 | 0.69 | 1.32 | 0.708 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 3.71 | 2.61 | 5.26 | <0.001 | 2.86 | 2.21 | 3.72 | <0.001 | 2.47 | 1.95 | 3.13 | <0.001 |
| TCAs | 5.29 | 2.87 | 9.75 | <0.001 | 4.26 | 2.62 | 6.92 | <0.001 | 3.30 | 2.06 | 5.29 | <0.001 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | 3.85 | 2.40 | 6.19 | <0.001 | 2.95 | 1.97 | 4.42 | <0.001 | 2.65 | 1.82 | 3.84 | <0.001 |
| PHQ-9 baseline | 1.03 | 1.00 | 1.05 | 0.003 | 1.03 | 1.00 | 1.05 | 0.003 | 1.03 | 1.00 | 1.05 | 0.002 |
| BMI | 0.99 | 0.97 | 1.01 | 0.120 | 0.99 | 0.98 | 1.01 | 0.118 | 0.99 | 0.98 | 1.01 | 0.214 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.49 | 0.82 | 2.70 | 0.083 | 1.42 | 0.81 | 2.49 | 0.104 | 1.42 | 0.84 | 2.40 | 0.084 |
| Other | 1.16 | 0.66 | 2.01 | 0.503 | 0.82 | 0.50 | 1.37 | 0.327 | 0.80 | 0.50 | 1.27 | 0.208 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.92 | 0.64 | 1.30 | 0.523 | 0.92 | 0.66 | 1.29 | 0.529 | 0.91 | 0.67 | 1.25 | 0.465 |
| 3 | 1.14 | 0.72 | 1.81 | 0.464 | 1.16 | 0.76 | 1.78 | 0.368 | 1.13 | 0.74 | 1.71 | 0.452 |
| 4 | 1.74 | 1.06 | 2.88 | 0.004 | 1.82 | 1.12 | 2.96 | 0.001 | 1.75 | 1.10 | 2.79 | 0.002 |
| 5, most deprived | 2.51 | 1.47 | 4.30 | <0.001 | 2.50 | 1.56 | 4.02 | <0.001 | 2.44 | 1.54 | 3.88 | <0.001 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.46 | 0.14 | 1.53 | 0.098 | 0.30 | 0.10 | 0.92 | 0.006 | 0.39 | 0.13 | 1.18 | 0.028 |
| London | 1.38 | 0.45 | 4.25 | 0.460 | 1.33 | 0.47 | 3.81 | 0.482 | 1.30 | 0.49 | 3.47 | 0.486 |
| North East | 0.19 | 0.05 | 0.78 | 0.002 | 0.27 | 0.07 | 0.99 | 0.009 | 0.29 | 0.09 | 0.94 | 0.007 |
| North West | 0.48 | 0.14 | 1.62 | 0.120 | 0.45 | 0.15 | 1.36 | 0.064 | 0.43 | 0.15 | 1.18 | 0.031 |
| South Central | 0.59 | 0.16 | 2.21 | 0.302 | 0.48 | 0.14 | 1.65 | 0.126 | 0.46 | 0.15 | 1.41 | 0.073 |
| South East | 1.99 | 0.57 | 6.97 | 0.158 | 1.91 | 0.59 | 6.25 | 0.158 | 1.73 | 0.57 | 5.29 | 0.203 |
| South West | 0.41 | 0.11 | 1.51 | 0.077 | 0.49 | 0.14 | 1.70 | 0.140 | 0.49 | 0.15 | 1.54 | 0.109 |
| West Midlands | 0.30 | 0.09 | 0.98 | 0.009 | 0.38 | 0.13 | 1.11 | 0.020 | 0.44 | 0.17 | 1.18 | 0.033 |
| Yorkshire & Humber | 1.80 | 0.21 | 15.48 | 0.482 | 1.64 | 0.22 | 12.51 | 0.530 | 1.54 | 0.21 | 11.09 | 0.576 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.96 | 0.76 | 1.21 | 0.646 | 1.02 | 0.85 | 1.23 | 0.768 | 0.99 | 0.83 | 1.17 | 0.826 |
| Light-smoker | 0.89 | 0.70 | 1.14 | 0.241 | 0.96 | 0.80 | 1.16 | 0.583 | 0.97 | 0.81 | 1.16 | 0.654 |
| Moderate-smoker | 0.83 | 0.39 | 1.75 | 0.519 | 0.79 | 0.43 | 1.46 | 0.327 | 0.87 | 0.53 | 1.44 | 0.486 |
| Heavy-smoker | 1.04 | 0.45 | 2.41 | 0.895 | 0.87 | 0.38 | 1.99 | 0.658 | 1.02 | 0.48 | 2.16 | 0.939 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.90 | 0.74 | 1.10 | 0.180 | 0.95 | 0.79 | 1.13 | 0.431 | 0.93 | 0.80 | 1.08 | 0.185 |
| Medium | 0.92 | 0.68 | 1.25 | 0.494 | 0.97 | 0.73 | 1.28 | 0.767 | 1.02 | 0.81 | 1.29 | 0.823 |
| Heavy | 1.17 | 0.67 | 2.04 | 0.475 | 1.13 | 0.69 | 1.85 | 0.518 | 1.22 | 0.78 | 1.90 | 0.247 |
| Very heavy | 0.94 | 0.50 | 1.74 | 0.781 | 1.02 | 0.65 | 1.62 | 0.895 | 1.20 | 0.82 | 1.76 | 0.216 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.89 | 0.57 | 1.38 | 0.492 | 1.00 | 0.68 | 1.47 | 0.994 | 0.95 | 0.68 | 1.34 | 0.704 |
| Asian | 1.06 | 0.66 | 1.72 | 0.746 | 1.07 | 0.72 | 1.59 | 0.656 | 1.09 | 0.77 | 1.54 | 0.540 |
| Other | 0.91 | 0.62 | 1.34 | 0.522 | 0.86 | 0.61 | 1.20 | 0.238 | 0.85 | 0.63 | 1.16 | 0.185 |
| | | | | | | | | | | | | |
| Age | 1.00 | 0.98 | 1.01 | 0.264 | 0.99 | 0.98 | 1.00 | 0.051 | 0.99 | 0.98 | 1.00 | 0.032 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.22 | 1.02 | 1.45 | 0.004 | 1.25 | 1.08 | 1.46 | <0.001 | 1.27 | 1.10 | 1.48 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.74 | 0.12 | 4.66 | 0.672 | 0.94 | 0.15 | 5.88 | 0.936 | 0.70 | 0.20 | 2.40 | 0.453 |
| 2011 to 2015 | 0.72 | 0.11 | 4.50 | 0.639 | 0.79 | 0.13 | 4.81 | 0.734 | 0.61 | 0.18 | 2.00 | 0.281 |
| 2016 to 2020 | 0.78 | 0.13 | 4.79 | 0.729 | 0.89 | 0.15 | 5.29 | 0.864 | 0.63 | 0.20 | 2.00 | 0.300 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.69 | 0.36 | 1.32 | 0.141 | 0.81 | 0.50 | 1.33 | 0.278 | 1.02 | 0.66 | 1.59 | 0.896 |
| Stroke | 0.61 | 0.25 | 1.54 | 0.171 | 0.85 | 0.39 | 1.83 | 0.576 | 0.93 | 0.51 | 1.71 | 0.769 |
| Diabetes | 0.91 | 0.62 | 1.34 | 0.532 | 1.03 | 0.73 | 1.44 | 0.828 | 1.01 | 0.75 | 1.37 | 0.908 |
| Epilepsy | 0.72 | 0.29 | 1.80 | 0.358 | 0.71 | 0.36 | 1.43 | 0.209 | 0.80 | 0.45 | 1.45 | 0.343 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hypothyroidism | 0.88 | 0.54 | 1.44 | 0.511 | 0.91 | 0.58 | 1.43 | 0.599 | 0.86 | 0.56 | 1.34 | 0.392 |
| Arthritis | 0.73 | 0.42 | 1.27 | 0.148 | 0.91 | 0.62 | 1.36 | 0.562 | 0.93 | 0.64 | 1.35 | 0.636 |
| Anxiety | 0.98 | 0.80 | 1.20 | 0.814 | 1.03 | 0.87 | 1.21 | 0.703 | 1.04 | 0.88 | 1.21 | 0.562 |
| Migraine | 0.94 | 0.64 | 1.37 | 0.656 | 0.98 | 0.73 | 1.30 | 0.835 | 0.95 | 0.72 | 1.25 | 0.624 |
| Cancer | 0.84 | 0.61 | 1.16 | 0.158 | 0.82 | 0.62 | 1.08 | 0.061 | 0.83 | 0.64 | 1.08 | 0.065 |
| Asthma | 1.03 | 0.82 | 1.31 | 0.724 | 1.09 | 0.90 | 1.32 | 0.251 | 1.12 | 0.95 | 1.32 | 0.077 |
| Renal failure | 2.36 | 0.79 | 7.01 | 0.043 | 1.83 | 0.67 | 5.02 | 0.123 | 2.08 | 0.91 | 4.79 | 0.023 |
| Liver failure | 1.13 | 0.55 | 2.31 | 0.665 | 1.10 | 0.59 | 2.04 | 0.696 | 1.13 | 0.67 | 1.91 | 0.547 |
| Osteoporosis | 1.00 | 0.38 | 2.66 | 0.999 | 0.93 | 0.37 | 2.30 | 0.831 | 0.95 | 0.46 | 1.99 | 0.866 |
| Suicidality | 4.18 | 3.11 | 5.61 | <0.001 | 3.85 | 2.94 | 5.05 | <0.001 | 3.76 | 2.91 | 4.87 | <0.001 |
| Antihypertensive | 1.06 | 0.75 | 1.50 | 0.674 | 1.05 | 0.78 | 1.42 | 0.658 | 1.00 | 0.76 | 1.32 | 0.982 |
| Aspirin | 1.31 | 0.75 | 2.29 | 0.217 | 1.05 | 0.65 | 1.68 | 0.794 | 1.06 | 0.71 | 1.59 | 0.706 |
| Anticoagulants | 0.89 | 0.33 | 2.45 | 0.775 | 0.76 | 0.31 | 1.88 | 0.433 | 1.02 | 0.46 | 2.26 | 0.942 |
| NSAIDs | 1.28 | 0.82 | 1.99 | 0.149 | 1.29 | 0.92 | 1.83 | 0.054 | 1.30 | 0.95 | 1.77 | 0.033 |
| Anticonvulsants | 0.69 | 0.24 | 1.99 | 0.365 | 1.12 | 0.57 | 2.19 | 0.660 | 0.96 | 0.51 | 1.79 | 0.871 |
| Hypnotics | 1.07 | 0.73 | 1.55 | 0.660 | 1.03 | 0.76 | 1.40 | 0.787 | 0.98 | 0.74 | 1.30 | 0.853 |
| Bisphosphonates | 2.54 | 0.74 | 8.69 | 0.050 | 2.23 | 0.61 | 8.12 | 0.109 | 1.74 | 0.47 | 6.49 | 0.279 |
| Contraceptives | 0.98 | 0.72 | 1.34 | 0.861 | 1.04 | 0.82 | 1.31 | 0.696 | 1.00 | 0.83 | 1.22 | 0.952 |
| *Constant* | 0.00 | 0.00 | 0.03 | <0.001 | 0.01 | 0.00 | 0.05 | <0.001 | 0.01 | 0.00 | 0.05 | <0.001 |

| | **Adverse events, suicidality *(FSA, N= 1,050,105)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 1.02 | 0.84 | 1.23 | 0.827 | 1.04 | 0.89 | 1.21 | 0.546 | 1.00 | 0.88 | 1.15 | 0.940 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 3.58 | 3.07 | 4.18 | <0.001 | 2.48 | 2.21 | 2.78 | <0.001 | 2.09 | 1.88 | 2.33 | <0.001 |
| TCAs | 4.72 | 3.60 | 6.17 | <0.001 | 3.04 | 2.49 | 3.71 | <0.001 | 2.38 | 2.00 | 2.83 | <0.001 |
| MAOIs | 1.00 | - | - | - | 2.80 | 0.22 | 36.19 | 0.301 | 1.77 | 0.14 | 22.96 | 0.565 |
| Other antidepressants | 4.08 | 3.28 | 5.07 | <0.001 | 2.99 | 2.53 | 3.55 | <0.001 | 2.55 | 2.19 | 2.97 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PHQ-9 baseline | 1.01 | 1.00 | 1.02 | <0.001 | 1.01 | 1.00 | 1.02 | <0.001 | 1.01 | 1.01 | 1.02 | <0.001 |
| BMI | 1.00 | 0.99 | 1.00 | 0.092 | 1.00 | 0.99 | 1.00 | 0.104 | 1.00 | 0.99 | 1.00 | 0.525 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.14 | 0.87 | 1.49 | 0.214 | 1.05 | 0.83 | 1.33 | 0.608 | 1.02 | 0.82 | 1.25 | 0.843 |
| Other | 0.86 | 0.66 | 1.12 | 0.146 | 0.80 | 0.64 | 0.99 | 0.008 | 0.83 | 0.67 | 1.02 | 0.022 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.04 | 0.88 | 1.22 | 0.549 | 1.03 | 0.88 | 1.20 | 0.650 | 1.01 | 0.88 | 1.17 | 0.794 |
| 3 | 1.12 | 0.92 | 1.36 | 0.140 | 1.16 | 0.97 | 1.39 | 0.032 | 1.18 | 1.00 | 1.39 | 0.008 |
| 4 | 1.39 | 1.11 | 1.76 | <0.001 | 1.45 | 1.16 | 1.80 | <0.001 | 1.46 | 1.20 | 1.78 | <0.001 |
| 5, most deprived | 2.11 | 1.62 | 2.76 | <0.001 | 2.07 | 1.61 | 2.65 | <0.001 | 2.07 | 1.65 | 2.60 | <0.001 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.53 | 0.21 | 1.32 | 0.072 | 0.51 | 0.21 | 1.23 | 0.049 | 0.51 | 0.22 | 1.16 | 0.035 |
| London | 1.16 | 0.58 | 2.34 | 0.573 | 1.17 | 0.57 | 2.40 | 0.577 | 1.14 | 0.59 | 2.23 | 0.605 |
| North East | 0.53 | 0.24 | 1.19 | 0.043 | 0.60 | 0.26 | 1.38 | 0.117 | 0.64 | 0.29 | 1.42 | 0.149 |
| North West | 0.66 | 0.30 | 1.46 | 0.176 | 0.64 | 0.30 | 1.39 | 0.139 | 0.64 | 0.32 | 1.28 | 0.098 |
| South Central | 0.42 | 0.20 | 0.88 | 0.002 | 0.43 | 0.21 | 0.89 | 0.003 | 0.45 | 0.23 | 0.89 | 0.003 |
| South East | 1.23 | 0.49 | 3.07 | 0.557 | 1.21 | 0.48 | 3.01 | 0.595 | 1.14 | 0.49 | 2.65 | 0.682 |
| South West | 0.58 | 0.28 | 1.22 | 0.060 | 0.57 | 0.27 | 1.21 | 0.054 | 0.59 | 0.30 | 1.18 | 0.051 |
| West Midlands | 0.40 | 0.20 | 0.83 | 0.001 | 0.45 | 0.22 | 0.93 | 0.005 | 0.47 | 0.24 | 0.92 | 0.004 |
| Yorkshire & Humber | 0.75 | 0.21 | 2.72 | 0.561 | 0.72 | 0.21 | 2.51 | 0.496 | 0.72 | 0.22 | 2.35 | 0.480 |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.95 | 0.85 | 1.07 | 0.276 | 0.96 | 0.87 | 1.05 | 0.220 | 0.95 | 0.87 | 1.04 | 0.141 |
| Light-smoker | 0.96 | 0.87 | 1.07 | 0.370 | 1.00 | 0.91 | 1.10 | 0.964 | 1.03 | 0.95 | 1.12 | 0.342 |
| Moderate-smoker | 0.87 | 0.63 | 1.20 | 0.259 | 0.86 | 0.66 | 1.13 | 0.154 | 0.88 | 0.70 | 1.10 | 0.129 |
| Heavy-smoker | 0.86 | 0.54 | 1.36 | 0.402 | 0.98 | 0.69 | 1.38 | 0.876 | 1.01 | 0.76 | 1.36 | 0.895 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.97 | 0.89 | 1.07 | 0.436 | 0.97 | 0.90 | 1.05 | 0.384 | 0.97 | 0.91 | 1.04 | 0.299 |
| Medium | 1.02 | 0.89 | 1.17 | 0.712 | 1.01 | 0.90 | 1.14 | 0.746 | 1.01 | 0.91 | 1.13 | 0.749 |
| Heavy | 1.19 | 0.92 | 1.55 | 0.082 | 1.13 | 0.88 | 1.44 | 0.201 | 1.15 | 0.94 | 1.41 | 0.072 |
| Very heavy | 1.25 | 0.95 | 1.64 | 0.033 | 1.26 | 1.02 | 1.56 | 0.004 | 1.29 | 1.07 | 1.54 | <0.001 |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.90 | 0.76 | 1.08 | 0.138 | 0.93 | 0.80 | 1.08 | 0.187 | 0.90 | 0.79 | 1.03 | 0.052 |
| Asian | 1.37 | 1.10 | 1.71 | <0.001 | 1.33 | 1.08 | 1.63 | <0.001 | 1.33 | 1.08 | 1.65 | <0.001 |
| Other | 1.09 | 0.91 | 1.29 | 0.229 | 1.12 | 0.97 | 1.28 | 0.037 | 1.12 | 0.98 | 1.28 | 0.035 |
| Age | 0.99 | 0.98 | 0.99 | <0.001 | 0.99 | 0.98 | 0.99 | <0.001 | 0.99 | 0.98 | 0.99 | <0.001 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.33 | 1.22 | 1.46 | <0.001 | 1.31 | 1.20 | 1.42 | <0.001 | 1.29 | 1.20 | 1.39 | <0.001 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 3.25 | 2.19 | 4.82 | <0.001 | 3.03 | 2.18 | 4.23 | <0.001 | 2.62 | 1.96 | 3.49 | <0.001 |
| 2011 to 2015 | 2.98 | 1.84 | 4.83 | <0.001 | 2.62 | 1.79 | 3.85 | <0.001 | 2.34 | 1.69 | 3.24 | <0.001 |
| 2016 to 2020 | 2.90 | 1.75 | 4.80 | <0.001 | 2.57 | 1.69 | 3.91 | <0.001 | 2.25 | 1.58 | 3.20 | <0.001 |
| Coronary heart disease | 0.93 | 0.72 | 1.19 | 0.434 | 0.89 | 0.73 | 1.08 | 0.121 | 0.98 | 0.84 | 1.15 | 0.805 |
| Stroke | 0.85 | 0.64 | 1.12 | 0.122 | 0.98 | 0.80 | 1.20 | 0.781 | 0.98 | 0.81 | 1.19 | 0.791 |
| Diabetes | 0.95 | 0.81 | 1.12 | 0.421 | 0.98 | 0.86 | 1.13 | 0.766 | 0.99 | 0.87 | 1.13 | 0.866 |
| Epilepsy | 0.87 | 0.66 | 1.16 | 0.222 | 0.81 | 0.65 | 1.02 | 0.018 | 0.85 | 0.70 | 1.03 | 0.030 |
| Hypothyroidism | 1.01 | 0.84 | 1.21 | 0.879 | 0.94 | 0.80 | 1.10 | 0.292 | 0.93 | 0.81 | 1.07 | 0.206 |
| Arthritis | 0.80 | 0.65 | 0.98 | 0.004 | 0.88 | 0.76 | 1.02 | 0.029 | 0.96 | 0.85 | 1.10 | 0.473 |
| Anxiety | 1.15 | 1.05 | 1.27 | <0.001 | 1.18 | 1.09 | 1.28 | <0.001 | 1.19 | 1.11 | 1.28 | <0.001 |
| Migraine | 1.00 | 0.88 | 1.15 | 0.966 | 0.98 | 0.89 | 1.09 | 0.691 | 0.99 | 0.90 | 1.09 | 0.842 |
| Cancer | 0.95 | 0.82 | 1.09 | 0.324 | 0.91 | 0.81 | 1.03 | 0.059 | 0.91 | 0.82 | 1.01 | 0.020 |
| Asthma | 1.00 | 0.90 | 1.10 | 0.915 | 1.03 | 0.95 | 1.11 | 0.304 | 1.05 | 0.98 | 1.12 | 0.078 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Renal failure | 0.72 | 0.38 | 1.39 | 0.200 | 0.89 | 0.56 | 1.41 | 0.507 | 0.98 | 0.66 | 1.45 | 0.883 |
| Liver failure | 0.84 | 0.59 | 1.20 | 0.215 | 0.89 | 0.66 | 1.19 | 0.303 | 0.87 | 0.66 | 1.14 | 0.178 |
| Osteoporosis | 0.97 | 0.67 | 1.40 | 0.815 | 0.89 | 0.66 | 1.22 | 0.348 | 0.99 | 0.75 | 1.31 | 0.952 |
| Suicidality | 3.93 | 3.36 | 4.60 | <0.001 | 4.02 | 3.46 | 4.67 | <0.001 | 4.00 | 3.41 | 4.68 | <0.001 |
| Antihypertensive | 1.12 | 0.96 | 1.30 | 0.061 | 1.07 | 0.94 | 1.22 | 0.168 | 1.05 | 0.94 | 1.17 | 0.265 |
| Aspirin | 0.99 | 0.78 | 1.25 | 0.917 | 0.96 | 0.79 | 1.17 | 0.611 | 0.95 | 0.80 | 1.12 | 0.399 |
| Anticoagulants | 0.74 | 0.48 | 1.14 | 0.074 | 0.69 | 0.48 | 0.98 | 0.007 | 0.76 | 0.58 | 1.02 | 0.015 |
| NSAIDs | 1.03 | 0.89 | 1.19 | 0.650 | 1.12 | 1.00 | 1.26 | 0.012 | 1.15 | 1.03 | 1.28 | 0.001 |
| Anticonvulsants | 1.47 | 1.18 | 1.82 | <0.001 | 1.55 | 1.29 | 1.86 | <0.001 | 1.46 | 1.23 | 1.72 | <0.001 |
| Hypnotics | 1.34 | 1.18 | 1.52 | <0.001 | 1.26 | 1.13 | 1.41 | <0.001 | 1.24 | 1.13 | 1.37 | <0.001 |
| Bisphosphonates | 1.28 | 0.68 | 2.42 | 0.322 | 1.43 | 0.88 | 2.35 | 0.060 | 1.31 | 0.84 | 2.03 | 0.119 |
| Contraceptives | 0.84 | 0.72 | 0.97 | 0.002 | 0.87 | 0.78 | 0.97 | 0.001 | 0.85 | 0.77 | 0.93 | <0.001 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.01 | <0.001 | 0.00 | 0.00 | 0.01 | <0.001 |

***Table A4.6m*** *Regression analyses for adverse events (completed suicide) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Adverse events, completed suicide *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 0.83 | 0.01 | 68.14 | 0.911 | 0.37 | 0.01 | 13.43 | 0.479 | 0.33 | 0.01 | 9.89 | 0.399 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 3.87 | 0.43 | 34.98 | 0.113 | 5.81 | 0.78 | 43.01 | 0.024 | 5.19 | 0.99 | 27.27 | 0.011 |
| TCAs | 1.00 | - | - | - | 1.00 | - | - | - | 6.00 | 0.29 | 125.51 | 0.129 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 1.00 | - | - | - | 2.93 | 0.13 | 64.38 | 0.370 | 4.14 | 0.37 | 46.45 | 0.130 |
| PHQ-9 baseline | 0.96 | 0.79 | 1.16 | 0.604 | 1.02 | 0.88 | 1.19 | 0.670 | 1.02 | 0.88 | 1.18 | 0.723 |
| BMI | 0.98 | 0.88 | 1.08 | 0.561 | 0.99 | 0.93 | 1.06 | 0.786 | 1.01 | 0.95 | 1.08 | 0.647 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.87 | 0.44 | 8.01 | 0.266 | 1.36 | 0.48 | 3.80 | 0.446 | 1.58 | 0.64 | 3.90 | 0.189 |
| Other | 3.27 | 0.19 | 57.76 | 0.288 | 1.61 | 0.10 | 24.63 | 0.654 | 2.58 | 0.38 | 17.72 | 0.204 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.91 | 0.18 | 4.70 | 0.882 | 0.50 | 0.13 | 1.98 | 0.194 | 0.63 | 0.17 | 2.27 | 0.349 |
| 3 | 0.73 | 0.09 | 5.91 | 0.701 | 0.51 | 0.11 | 2.42 | 0.262 | 1.07 | 0.32 | 3.64 | 0.880 |
| 4 | 1.43 | 0.17 | 11.82 | 0.662 | 0.93 | 0.22 | 3.93 | 0.898 | 1.25 | 0.33 | 4.65 | 0.666 |
| 5, most deprived | 0.86 | 0.05 | 15.07 | 0.896 | 0.66 | 0.11 | 3.84 | 0.543 | 1.12 | 0.24 | 5.20 | 0.843 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.00 | - | - | - | 1.00 | - | - | - | 1.19 | 0.04 | 38.23 | 0.896 |
| London | 0.13 | 0.00 | 4.55 | 0.141 | 1.01 | 0.08 | 13.06 | 0.992 | 1.19 | 0.11 | 13.43 | 0.852 |
| North East | 0.78 | 0.02 | 26.45 | 0.855 | 1.53 | 0.08 | 30.69 | 0.713 | 1.40 | 0.07 | 26.58 | 0.766 |
| North West | 0.21 | 0.01 | 7.01 | 0.250 | 0.55 | 0.03 | 10.56 | 0.599 | 0.72 | 0.05 | 11.07 | 0.755 |
| South Central | 1.90 | 0.19 | 18.66 | 0.471 | 1.70 | 0.13 | 22.00 | 0.596 | 2.23 | 0.18 | 28.29 | 0.415 |
| South East | 0.28 | 0.01 | 9.02 | 0.345 | 0.58 | 0.03 | 11.66 | 0.641 | 0.90 | 0.06 | 13.11 | 0.920 |
| South West | 0.84 | 0.05 | 14.63 | 0.878 | 2.39 | 0.18 | 31.34 | 0.383 | 2.35 | 0.19 | 29.71 | 0.385 |
| West Midlands | 1.04 | 0.08 | 13.35 | 0.967 | 1.21 | 0.08 | 17.23 | 0.855 | 1.46 | 0.11 | 18.74 | 0.704 |
| Yorkshire & Humber | 1.25 | 0.07 | 22.84 | 0.844 | 1.76 | 0.10 | 30.17 | 0.609 | 2.85 | 0.19 | 43.56 | 0.322 |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.73 | 0.13 | 4.07 | 0.636 | 1.70 | 0.56 | 5.16 | 0.220 | 1.00 | 0.36 | 2.76 | 0.996 |
| Light-smoker | 0.90 | 0.19 | 4.29 | 0.867 | 1.48 | 0.45 | 4.88 | 0.393 | 1.11 | 0.40 | 3.03 | 0.797 |
| Moderate-smoker | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Heavy-smoker | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.52 | 0.35 | 6.56 | 0.465 | 1.70 | 0.55 | 5.20 | 0.224 | 1.87 | 0.71 | 4.90 | 0.096 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Medium | 2.68 | 0.38 | 19.04 | 0.195 | 3.34 | 0.92 | 12.16 | 0.016 | 2.41 | 0.69 | 8.47 | 0.071 |
| Heavy | 5.64 | 0.31 | 103.51 | 0.126 | 5.61 | 0.76 | 41.26 | 0.026 | 4.04 | 0.59 | 27.66 | 0.061 |
| Very heavy | 7.67 | 0.93 | 63.03 | 0.013 | 5.26 | 0.88 | 31.47 | 0.017 | 5.54 | 1.26 | 24.45 | 0.003 |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Asian | 1.00 | - | - | - | 1.00 | - | - | - | 0.79 | 0.06 | 11.28 | 0.819 |
| Other | 2.67 | 0.14 | 51.27 | 0.392 | 0.97 | 0.06 | 15.57 | 0.978 | 1.43 | 0.21 | 9.99 | 0.632 |
| Age | 0.97 | 0.92 | 1.03 | 0.233 | 0.99 | 0.94 | 1.03 | 0.486 | 0.99 | 0.96 | 1.03 | 0.736 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 3.35 | 0.72 | 15.60 | 0.043 | 1.90 | 0.74 | 4.88 | 0.081 | 2.02 | 0.89 | 4.60 | 0.027 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| 2011 to 2015 | 1.37 | 0.20 | 9.33 | 0.676 | 1.92 | 0.38 | 9.70 | 0.298 | 2.69 | 0.56 | 12.98 | 0.106 |
| 2016 to 2020 | 1.78 | 0.26 | 12.42 | 0.442 | 1.80 | 0.36 | 9.12 | 0.350 | 2.68 | 0.55 | 13.04 | 0.107 |
| Coronary heart disease | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Stroke | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Diabetes | 3.95 | 0.23 | 66.64 | 0.210 | 3.80 | 0.47 | 30.80 | 0.100 | 2.72 | 0.40 | 18.77 | 0.181 |
| Epilepsy | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Hypothyroidism | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Arthritis | 1.66 | 0.08 | 33.15 | 0.663 | 0.70 | 0.04 | 12.72 | 0.752 | 0.52 | 0.03 | 8.45 | 0.542 |
| Anxiety | 0.84 | 0.12 | 6.11 | 0.820 | 0.86 | 0.21 | 3.62 | 0.790 | 1.28 | 0.43 | 3.81 | 0.567 |
| Migraine | 1.00 | | | | 0.50 | 0.04 | 6.53 | 0.490 | 0.38 | 0.03 | 4.73 | 0.319 |
| Cancer | 1.24 | 0.08 | 19.56 | 0.841 | 0.57 | 0.04 | 8.12 | 0.590 | 0.43 | 0.03 | 5.98 | 0.407 |
| Asthma | 0.54 | 0.08 | 3.84 | 0.421 | 0.75 | 0.22 | 2.61 | 0.557 | 0.85 | 0.30 | 2.41 | 0.682 |
| Renal failure | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Liver failure | 5.99 | 0.28 | 128.15 | 0.132 | 2.37 | 0.12 | 47.82 | 0.460 | 1.90 | 0.11 | 33.77 | 0.565 |
| Osteoporosis | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Suicidality | 5.68 | 1.05 | 30.84 | 0.008 | 4.37 | 1.13 | 16.84 | 0.005 | 3.07 | 0.84 | 11.20 | 0.026 |
| Antihypertensive | 0.68 | 0.03 | 16.27 | 0.751 | 0.91 | 0.09 | 8.75 | 0.913 | 0.68 | 0.08 | 5.91 | 0.650 |
| Aspirin | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Anticoagulants | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| NSAIDs | 2.21 | 0.13 | 36.52 | 0.466 | 1.06 | 0.07 | 15.42 | 0.953 | 1.62 | 0.24 | 10.84 | 0.511 |
| Anticonvulsants | 1.00 | - | - | | 6.76 | 0.33 | 138.95 | 0.104 | 4.57 | 0.29 | 72.04 | 0.156 |
| Hypnotics | 2.97 | 0.58 | 15.32 | 0.088 | 1.51 | 0.37 | 6.19 | 0.450 | 2.11 | 0.70 | 6.36 | 0.083 |
| Bisphosphonates | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| Contraceptives | 3.50 | 0.31 | 39.08 | 0.181 | 1.32 | 0.17 | 10.46 | 0.731 | 1.01 | 0.13 | 7.61 | 0.991 |
| *Constant* | 0.00 | 0.00 | 0.10 | 0.001 | 0.00 | 0.00 | 0.01 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 |

| | **Adverse events, completed suicide *(FSA, N= 1,050,105)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 0.72 | 0.18 | 2.87 | 0.542 | 0.54 | 0.18 | 1.58 | 0.138 | 0.819385 | 0.355293 | 1.889686 | 0.539 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 2.06 | 1.22 | 3.48 | <0.001 | 1.87 | 1.28 | 2.75 | <0.001 | 1.82 | 1.34 | 2.47 | <0.001 |
| TCAs | 1.38 | 0.48 | 3.97 | 0.427 | 1.64 | 0.78 | 3.44 | 0.087 | 1.71 | 0.95 | 3.07 | 0.019 |
| MAOIs | 1.00 | - | - | - | 1.00 | - | - | - | 20.82 | 1.43 | 302.30 | 0.003 |
| Other antidepressants | 2.72 | 1.25 | 5.95 | 0.001 | 2.63 | 1.50 | 4.60 | <0.001 | 3.04 | 1.94 | 4.75 | <0.001 |
| PHQ-9 baseline | 1.00 | 0.95 | 1.06 | 0.942 | 1.01 | 0.97 | 1.05 | 0.523 | 1.01 | 0.98 | 1.05 | 0.285 |
| BMI | 1.00 | 0.96 | 1.04 | 0.912 | 1.00 | 0.97 | 1.03 | 0.866 | 1.00 | 0.97 | 1.02 | 0.831 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.72 | 0.46 | 1.14 | 0.065 | 0.69 | 0.49 | 0.99 | 0.007 | 0.78 | 0.58 | 1.04 | 0.026 |
| Other | 0.55 | 0.20 | 1.55 | 0.136 | 0.70 | 0.34 | 1.45 | 0.208 | 0.80 | 0.44 | 1.43 | 0.316 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.07 | 0.58 | 1.97 | 0.772 | 0.83 | 0.52 | 1.34 | 0.319 | 0.94 | 0.63 | 1.40 | 0.676 |
| 3 | 1.25 | 0.70 | 2.25 | 0.322 | 1.20 | 0.77 | 1.87 | 0.296 | 1.43 | 0.99 | 2.05 | 0.012 |
| 4 | 1.40 | 0.75 | 2.63 | 0.169 | 1.19 | 0.74 | 1.90 | 0.356 | 1.32 | 0.87 | 2.00 | 0.083 |
| 5, most deprived | 1.04 | 0.53 | 2.06 | 0.869 | 0.98 | 0.57 | 1.70 | 0.935 | 1.24 | 0.78 | 2.00 | 0.233 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.94 | 0.28 | 3.21 | 0.898 | 1.35 | 0.47 | 3.89 | 0.470 | 1.65 | 0.66 | 4.13 | 0.164 |
| London | 0.87 | 0.33 | 2.29 | 0.710 | 1.07 | 0.50 | 2.29 | 0.812 | 1.25 | 0.61 | 2.53 | 0.424 |
| North East | 1.67 | 0.50 | 5.63 | 0.274 | 1.98 | 0.54 | 7.24 | 0.174 | 2.01 | 0.59 | 6.89 | 0.144 |
| North West | 1.14 | 0.42 | 3.10 | 0.730 | 1.24 | 0.55 | 2.82 | 0.499 | 1.54 | 0.73 | 3.24 | 0.133 |
| South Central | 1.35 | 0.49 | 3.70 | 0.439 | 1.40 | 0.62 | 3.17 | 0.289 | 1.76 | 0.82 | 3.78 | 0.056 |
| South East | 0.98 | 0.35 | 2.76 | 0.964 | 1.00 | 0.44 | 2.28 | 0.990 | 1.25 | 0.58 | 2.68 | 0.457 |
| South West | 1.41 | 0.51 | 3.91 | 0.390 | 1.57 | 0.69 | 3.59 | 0.156 | 1.88 | 0.88 | 3.99 | 0.032 |
| West Midlands | 0.76 | 0.24 | 2.37 | 0.534 | 0.89 | 0.37 | 2.15 | 0.740 | 0.92 | 0.40 | 2.12 | 0.807 |
| Yorkshire & Humber | 1.18 | 0.36 | 3.92 | 0.719 | 1.25 | 0.46 | 3.38 | 0.559 | 1.69 | 0.63 | 4.50 | 0.168 |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.16 | 0.65 | 2.09 | 0.511 | 1.22 | 0.79 | 1.89 | 0.229 | 0.96 | 0.66 | 1.41 | 0.799 |
| Light-smoker | 1.36 | 0.88 | 2.10 | 0.067 | 1.28 | 0.90 | 1.81 | 0.070 | 1.18 | 0.88 | 1.58 | 0.146 |
| Moderate-smoker | 2.50 | 0.98 | 6.42 | 0.012 | 1.62 | 0.69 | 3.83 | 0.149 | 1.56 | 0.76 | 3.19 | 0.108 |
| Heavy-smoker | 0.86 | 0.14 | 5.31 | 0.828 | 1.03 | 0.28 | 3.85 | 0.950 | 1.13 | 0.41 | 3.12 | 0.750 |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.01 | 0.63 | 1.64 | 0.936 | 1.07 | 0.71 | 1.62 | 0.643 | 1.08 | 0.78 | 1.49 | 0.516 |
| Medium | 1.17 | 0.61 | 2.27 | 0.529 | 1.13 | 0.63 | 2.02 | 0.583 | 1.09 | 0.66 | 1.82 | 0.640 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Heavy | 1.43 | 0.38 | 5.39 | 0.487 | 1.68 | 0.61 | 4.62 | 0.182 | 1.69 | 0.76 | 3.76 | 0.092 |
| Very heavy | 1.82 | 0.64 | 5.15 | 0.134 | 1.76 | 0.69 | 4.49 | 0.116 | 1.77 | 0.82 | 3.84 | 0.055 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.18 | 0.45 | 3.10 | 0.649 | 1.03 | 0.47 | 2.26 | 0.922 | 0.86 | 0.39 | 1.88 | 0.607 |
| Asian | 0.95 | 0.37 | 2.40 | 0.879 | 0.98 | 0.49 | 1.94 | 0.934 | 1.09 | 0.60 | 1.98 | 0.720 |
| Other | 1.11 | 0.37 | 3.32 | 0.802 | 1.12 | 0.51 | 2.49 | 0.708 | 1.14 | 0.59 | 2.19 | 0.618 |
| | | | | | | | | | | | | |
| Age | 0.97 | 0.96 | 0.99 | <0.001 | 0.98 | 0.97 | 0.99 | <0.001 | 0.98 | 0.97 | 0.99 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.90 | 1.30 | 2.78 | <0.001 | 1.72 | 1.29 | 2.30 | <0.001 | 1.65 | 1.29 | 2.11 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.80 | 0.42 | 1.52 | 0.376 | 0.72 | 0.45 | 1.16 | 0.074 | 0.69 | 0.47 | 1.01 | 0.011 |
| 2011 to 2015 | 0.45 | 0.22 | 0.93 | 0.005 | 0.48 | 0.28 | 0.82 | <0.001 | 0.42 | 0.27 | 0.66 | <0.001 |
| 2016 to 2020 | 0.23 | 0.11 | 0.48 | <0.001 | 0.28 | 0.16 | 0.50 | <0.001 | 0.27 | 0.17 | 0.43 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.97 | 0.21 | 4.58 | 0.962 | 0.75 | 0.23 | 2.43 | 0.525 | 0.77 | 0.28 | 2.16 | 0.518 |
| Stroke | 1.10 | 0.21 | 5.77 | 0.883 | 1.22 | 0.38 | 3.96 | 0.665 | 1.08 | 0.39 | 3.01 | 0.852 |
| Diabetes | 0.85 | 0.24 | 3.04 | 0.750 | 1.01 | 0.40 | 2.54 | 0.968 | 0.73 | 0.31 | 1.70 | 0.332 |
| Epilepsy | 0.98 | 0.25 | 3.81 | 0.971 | 0.78 | 0.22 | 2.72 | 0.604 | 1.21 | 0.45 | 3.28 | 0.618 |
| Hypothyroidism | 1.00 | - | - | - | 0.15 | 0.01 | 1.93 | 0.055 | 0.20 | 0.03 | 1.24 | 0.023 |
| Arthritis | 1.71 | 0.73 | 3.96 | 0.103 | 1.23 | 0.60 | 2.50 | 0.454 | 1.21 | 0.66 | 2.22 | 0.419 |
| Anxiety | 0.67 | 0.35 | 1.31 | 0.128 | 0.86 | 0.56 | 1.33 | 0.383 | 0.96 | 0.68 | 1.36 | 0.768 |
| Migraine | 0.25 | 0.06 | 1.11 | 0.016 | 0.39 | 0.16 | 0.95 | 0.006 | 0.55 | 0.30 | 1.03 | 0.013 |
| Cancer | 0.81 | 0.31 | 2.12 | 0.574 | 1.03 | 0.48 | 2.22 | 0.921 | 1.17 | 0.66 | 2.06 | 0.490 |
| Asthma | 1.03 | 0.64 | 1.67 | 0.874 | 1.21 | 0.83 | 1.75 | 0.198 | 1.10 | 0.80 | 1.52 | 0.421 |
| Renal failure | 1.00 | - | - | - | 1.00 | - | - | - | 0.75 | 0.05 | 10.16 | 0.773 |
| Liver failure | 2.68 | 0.72 | 10.03 | 0.054 | 1.49 | 0.40 | 5.47 | 0.433 | 1.32 | 0.41 | 4.29 | 0.544 |
| Osteoporosis | 0.82 | 0.03 | 19.58 | 0.874 | 1.04 | 0.13 | 8.59 | 0.960 | 1.09 | 0.21 | 5.65 | 0.898 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suicidality | 6.72 | 4.19 | 10.77 | <0.001 | 6.46 | 4.42 | 9.44 | <0.001 | 6.14 | 4.47 | 8.43 | <0.001 |
| Antihypertensive | 1.60 | 0.64 | 4.03 | 0.189 | 1.15 | 0.54 | 2.43 | 0.630 | 0.92 | 0.49 | 1.74 | 0.738 |
| Aspirin | 0.64 | 0.14 | 3.01 | 0.458 | 1.08 | 0.39 | 3.04 | 0.839 | 0.90 | 0.36 | 2.25 | 0.777 |
| Anticoagulants | 0.72 | 0.05 | 10.29 | 0.749 | 0.91 | 0.14 | 6.09 | 0.896 | 0.60 | 0.09 | 3.94 | 0.482 |
| NSAIDs | 1.02 | 0.42 | 2.47 | 0.945 | 1.17 | 0.61 | 2.24 | 0.533 | 0.99 | 0.56 | 1.76 | 0.967 |
| Anticonvulsants | 1.88 | 0.54 | 6.53 | 0.191 | 1.94 | 0.68 | 5.56 | 0.106 | 1.39 | 0.52 | 3.71 | 0.385 |
| Hypnotics | 2.06 | 1.29 | 3.26 | <0.001 | 2.17 | 1.52 | 3.09 | <0.001 | 2.19 | 1.62 | 2.97 | <0.001 |
| Bisphosphonates | 3.82 | 0.16 | 93.15 | 0.280 | 1.77 | 0.09 | 34.73 | 0.622 | 1.05 | 0.06 | 18.27 | 0.967 |
| Contraceptives | 1.00 | 0.44 | 2.26 | 0.992 | 0.66 | 0.32 | 1.37 | 0.144 | 0.67 | 0.37 | 1.22 | 0.085 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 |

***Table A4.6n*** *Regression analyses for adverse events (all-cause mortality) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis*

| | **Adverse events, all-cause mortality *(CCA, N= 88,227)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 0.70 | 0.41 | 1.19 | 0.083 | 0.70 | 0.41 | 1.19 | 0.083 | 0.78 | 0.60 | 1.02 | 0.016 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 0.95 | 0.54 | 1.67 | 0.818 | 0.95 | 0.54 | 1.67 | 0.818 | 1.25 | 0.93 | 1.69 | 0.050 |
| TCAs | 0.47 | 0.07 | 3.32 | 0.319 | 0.47 | 0.07 | 3.32 | 0.319 | 1.27 | 0.63 | 2.55 | 0.374 |
| MAOIs | - | - | - | - | - | - | - | - | - | - | - | - |
| Other antidepressants | 1.49 | 0.68 | 3.27 | 0.188 | 1.49 | 0.68 | 3.27 | 0.188 | 1.31 | 0.84 | 2.05 | 0.120 |
| PHQ-9 baseline | 1.07 | 1.03 | 1.12 | <0.001 | 1.07 | 1.03 | 1.12 | <0.001 | 1.05 | 1.03 | 1.07 | <0.001 |
| BMI | 0.95 | 0.91 | 0.99 | 0.002 | 0.95 | 0.91 | 0.99 | 0.002 | 0.96 | 0.94 | 0.98 | <0.001 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.79 | 0.50 | 1.24 | 0.174 | 0.79 | 0.50 | 1.24 | 0.174 | 0.91 | 0.71 | 1.15 | 0.297 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Other | 1.16 | 0.43 | 3.13 | 0.692 | 1.16 | 0.43 | 3.13 | 0.692 | 1.31 | 0.82 | 2.09 | 0.144 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.35 | 0.79 | 2.31 | 0.147 | 1.35 | 0.79 | 2.31 | 0.147 | 1.29 | 0.97 | 1.72 | 0.021 |
| 3 | 1.26 | 0.72 | 2.20 | 0.290 | 1.26 | 0.72 | 2.20 | 0.290 | 1.20 | 0.90 | 1.61 | 0.104 |
| 4 | 0.81 | 0.39 | 1.67 | 0.453 | 0.81 | 0.39 | 1.67 | 0.453 | 1.28 | 0.92 | 1.77 | 0.053 |
| 5, most deprived | 1.56 | 0.75 | 3.23 | 0.117 | 1.56 | 0.75 | 3.23 | 0.117 | 1.34 | 0.93 | 1.94 | 0.041 |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.94 | 0.17 | 5.27 | 0.931 | 0.94 | 0.17 | 5.27 | 0.931 | 0.76 | 0.35 | 1.67 | 0.372 |
| London | 0.97 | 0.24 | 3.80 | 0.947 | 0.97 | 0.24 | 3.80 | 0.947 | 0.96 | 0.54 | 1.68 | 0.838 |
| North East | 0.63 | 0.10 | 3.91 | 0.511 | 0.63 | 0.10 | 3.91 | 0.511 | 0.71 | 0.29 | 1.73 | 0.315 |
| North West | 0.97 | 0.25 | 3.77 | 0.950 | 0.97 | 0.25 | 3.77 | 0.950 | 1.01 | 0.59 | 1.75 | 0.945 |
| South Central | 1.03 | 0.26 | 4.11 | 0.953 | 1.03 | 0.26 | 4.11 | 0.953 | 0.91 | 0.51 | 1.61 | 0.672 |
| South East | 0.61 | 0.13 | 2.82 | 0.406 | 0.61 | 0.13 | 2.82 | 0.406 | 0.68 | 0.37 | 1.24 | 0.097 |
| South West | 0.79 | 0.17 | 3.72 | 0.701 | 0.79 | 0.17 | 3.72 | 0.701 | 0.77 | 0.42 | 1.43 | 0.280 |
| West Midlands | 1.43 | 0.37 | 5.55 | 0.493 | 1.43 | 0.37 | 5.55 | 0.493 | 1.04 | 0.59 | 1.86 | 0.846 |
| Yorkshire & Humber | 1.00 | 0.22 | 4.49 | 0.998 | 1.00 | 0.22 | 4.49 | 0.998 | 0.98 | 0.50 | 1.94 | 0.951 |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.29 | 0.80 | 2.09 | 0.166 | 1.29 | 0.80 | 2.09 | 0.166 | 1.27 | 1.00 | 1.63 | 0.011 |
| Light-smoker | 1.38 | 0.79 | 2.43 | 0.140 | 1.38 | 0.79 | 2.43 | 0.140 | 1.68 | 1.26 | 2.24 | <0.001 |
| Moderate-smoker | 0.69 | 0.05 | 10.29 | 0.726 | 0.69 | 0.05 | 10.29 | 0.726 | 0.92 | 0.26 | 3.21 | 0.864 |
| Heavy-smoker | 1.00 | - | - | - | 1.00 | - | - | - | 1.14 | 0.24 | 5.42 | 0.823 |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.97 | 0.60 | 1.55 | 0.852 | 0.97 | 0.60 | 1.55 | 0.852 | 1.11 | 0.87 | 1.42 | 0.260 |
| Medium | 0.81 | 0.39 | 1.69 | 0.468 | 0.81 | 0.39 | 1.69 | 0.468 | 1.30 | 0.93 | 1.80 | 0.044 |
| Heavy | 1.32 | 0.28 | 6.23 | 0.643 | 1.32 | 0.28 | 6.23 | 0.643 | 1.26 | 0.57 | 2.75 | 0.455 |
| Very heavy | 1.49 | 0.43 | 5.08 | 0.406 | 1.49 | 0.43 | 5.08 | 0.406 | 1.94 | 1.05 | 3.56 | 0.005 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.27 | 0.02 | 3.19 | 0.173 | 0.27 | 0.02 | 3.19 | 0.173 | 0.77 | 0.35 | 1.68 | 0.388 |
| Asian | 0.30 | 0.02 | 3.85 | 0.223 | 0.30 | 0.02 | 3.85 | 0.223 | 0.92 | 0.43 | 1.96 | 0.777 |
| Other | 1.59 | 0.38 | 6.61 | 0.400 | 1.59 | 0.38 | 6.61 | 0.400 | 0.90 | 0.36 | 2.29 | 0.782 |
| Age | 1.09 | 1.07 | 1.10 | <0.001 | 1.09 | 1.07 | 1.10 | <0.001 | 1.09 | 1.08 | 1.10 | <0.001 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.53 | 0.98 | 2.38 | 0.013 | 1.53 | 0.98 | 2.38 | 0.013 | 1.60 | 1.27 | 2.01 | <0.001 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.00 | - | - | - | 1.00 | - | - | - | 1.00 | - | - | - |
| 2011 to 2015 | 1.29 | 0.64 | 2.60 | 0.347 | 1.29 | 0.64 | 2.60 | 0.347 | 0.87 | 0.64 | 1.18 | 0.229 |
| 2016 to 2020 | 1.32 | 0.66 | 2.67 | 0.301 | 1.32 | 0.66 | 2.67 | 0.301 | 0.90 | 0.67 | 1.22 | 0.381 |
| Coronary heart disease | 1.11 | 0.61 | 2.01 | 0.647 | 1.11 | 0.61 | 2.01 | 0.647 | 1.33 | 1.00 | 1.77 | 0.010 |
| Stroke | 1.50 | 0.83 | 2.70 | 0.079 | 1.50 | 0.83 | 2.70 | 0.079 | 1.35 | 0.99 | 1.83 | 0.013 |
| Diabetes | 1.28 | 0.73 | 2.25 | 0.264 | 1.28 | 0.73 | 2.25 | 0.264 | 1.44 | 1.09 | 1.90 | 0.001 |
| Epilepsy | 2.28 | 0.48 | 10.85 | 0.175 | 2.28 | 0.48 | 10.85 | 0.175 | 1.00 | 0.41 | 2.39 | 0.992 |
| Hypothyroidism | 1.04 | 0.47 | 2.30 | 0.903 | 1.04 | 0.47 | 2.30 | 0.903 | 0.98 | 0.65 | 1.48 | 0.894 |
| Arthritis | 0.89 | 0.52 | 1.50 | 0.551 | 0.89 | 0.52 | 1.50 | 0.551 | 0.95 | 0.74 | 1.22 | 0.577 |
| Anxiety | 0.62 | 0.29 | 1.32 | 0.106 | 0.62 | 0.29 | 1.32 | 0.106 | 0.78 | 0.55 | 1.12 | 0.076 |
| Migraine | 0.65 | 0.19 | 2.18 | 0.357 | 0.65 | 0.19 | 2.18 | 0.357 | 1.25 | 0.82 | 1.91 | 0.169 |
| Cancer | 2.32 | 1.51 | 3.55 | <0.001 | 2.32 | 1.51 | 3.55 | <0.001 | 2.54 | 2.03 | 3.20 | <0.001 |
| Asthma | 1.11 | 0.68 | 1.81 | 0.587 | 1.11 | 0.68 | 1.81 | 0.587 | 1.27 | 1.00 | 1.63 | 0.011 |
| Renal failure | 3.23 | 1.12 | 9.32 | 0.004 | 3.23 | 1.12 | 9.32 | 0.004 | 3.15 | 1.77 | 5.63 | <0.001 |
| Liver failure | 2.11 | 0.65 | 6.87 | 0.105 | 2.11 | 0.65 | 6.87 | 0.105 | 2.11 | 1.17 | 3.83 | 0.001 |
| Osteoporosis | 0.77 | 0.24 | 2.46 | 0.566 | 0.77 | 0.24 | 2.46 | 0.566 | 1.06 | 0.64 | 1.75 | 0.760 |
| Suicidality | 1.29 | 0.33 | 5.06 | 0.637 | 1.29 | 0.33 | 5.06 | 0.637 | 1.12 | 0.56 | 2.24 | 0.675 |
| Antihypertensive | 1.12 | 0.67 | 1.84 | 0.575 | 1.12 | 0.67 | 1.84 | 0.575 | 1.17 | 0.90 | 1.51 | 0.130 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Aspirin | 1.11 | 0.61 | 2.02 | 0.645 | 1.11 | 0.61 | 2.02 | 0.645 | 1.10 | 0.81 | 1.48 | 0.430 |
| Anticoagulants | 2.18 | 1.06 | 4.49 | 0.005 | 2.18 | 1.06 | 4.49 | 0.005 | 1.82 | 1.23 | 2.69 | <0.001 |
| NSAIDs | 2.04 | 0.88 | 4.69 | 0.028 | 2.04 | 0.88 | 4.69 | 0.028 | 1.07 | 0.66 | 1.74 | 0.727 |
| Anticonvulsants | 0.58 | 0.10 | 3.32 | 0.419 | 0.58 | 0.10 | 3.32 | 0.419 | 1.20 | 0.57 | 2.53 | 0.534 |
| Hypnotics | 1.42 | 0.78 | 2.58 | 0.133 | 1.42 | 0.78 | 2.58 | 0.133 | 1.04 | 0.75 | 1.45 | 0.740 |
| Bisphosphonates | 0.45 | 0.03 | 7.43 | 0.463 | 0.45 | 0.03 | 7.43 | 0.463 | 0.69 | 0.24 | 1.99 | 0.366 |
| Contraceptives | 0.76 | 0.05 | 11.01 | 0.793 | 0.76 | 0.05 | 11.01 | 0.793 | 0.42 | 0.07 | 2.65 | 0.225 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 |

| | **Adverse events all-cause mortality *(FSA, N= 1,050,105)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *2 months* | | | | *6 months* | | | | *12 months* | | | |
| | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* | *OR* | *99% CI* | | *p* |
| **Statin** | 0.66 | 0.60 | 0.72 | <0.001 | 0.66 | 0.60 | 0.72 | <0.001 | 0.69 | 0.65 | 0.73 | <0.001 |
| Antidepressant category (None) | | | | | | | | | | | | |
| SSRIs | 1.13 | 1.02 | 1.24 | 0.002 | 1.13 | 1.02 | 1.24 | 0.002 | 1.36 | 1.28 | 1.44 | <0.001 |
| TCAs | 1.03 | 0.86 | 1.22 | 0.702 | 1.03 | 0.86 | 1.22 | 0.702 | 1.30 | 1.18 | 1.44 | <0.001 |
| MAOIs | 1.71 | 0.09 | 31.27 | 0.635 | 1.71 | 0.09 | 31.27 | 0.635 | 1.05 | 0.15 | 7.18 | 0.950 |
| Other antidepressants | 1.38 | 1.20 | 1.59 | <0.001 | 1.38 | 1.20 | 1.59 | <0.001 | 1.59 | 1.46 | 1.73 | <0.001 |
| PHQ-9 baseline | 1.01 | 1.00 | 1.02 | 0.019 | 1.01 | 1.00 | 1.02 | 0.019 | 1.01 | 1.00 | 1.01 | 0.004 |
| BMI | 0.98 | 0.97 | 0.99 | <0.001 | 0.98 | 0.97 | 0.99 | <0.001 | 0.98 | 0.98 | 0.99 | <0.001 |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.06 | 0.97 | 1.15 | 0.095 | 1.06 | 0.97 | 1.15 | 0.095 | 1.13 | 1.07 | 1.19 | <0.001 |
| Other | 0.61 | 0.48 | 0.76 | <0.001 | 0.61 | 0.48 | 0.76 | <0.001 | 0.88 | 0.77 | 1.01 | 0.017 |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.11 | 1.00 | 1.22 | 0.008 | 1.11 | 1.00 | 1.22 | 0.008 | 1.06 | 0.99 | 1.13 | 0.020 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 1.16 | 1.04 | 1.30 | <0.001 | 1.16 | 1.04 | 1.30 | <0.001 | 1.11 | 1.04 | 1.20 | <0.001 |
| 4 | 1.14 | 1.00 | 1.29 | 0.007 | 1.14 | 1.00 | 1.29 | 0.007 | 1.15 | 1.06 | 1.25 | <0.001 |
| 5, most deprived | 1.23 | 1.05 | 1.44 | 0.001 | 1.23 | 1.05 | 1.44 | 0.001 | 1.22 | 1.11 | 1.35 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.86 | 0.60 | 1.22 | 0.259 | 0.86 | 0.60 | 1.22 | 0.259 | 0.91 | 0.72 | 1.15 | 0.299 |
| London | 0.66 | 0.50 | 0.88 | <0.001 | 0.66 | 0.50 | 0.88 | <0.001 | 0.78 | 0.65 | 0.95 | 0.001 |
| North East | 0.82 | 0.60 | 1.12 | 0.100 | 0.82 | 0.60 | 1.12 | 0.100 | 0.96 | 0.77 | 1.20 | 0.650 |
| North West | 0.93 | 0.71 | 1.23 | 0.513 | 0.93 | 0.71 | 1.23 | 0.513 | 1.01 | 0.83 | 1.22 | 0.897 |
| South Central | 0.84 | 0.63 | 1.12 | 0.110 | 0.84 | 0.63 | 1.12 | 0.110 | 0.89 | 0.73 | 1.07 | 0.106 |
| South East | 0.78 | 0.58 | 1.06 | 0.036 | 0.78 | 0.58 | 1.06 | 0.036 | 0.82 | 0.67 | 1.01 | 0.013 |
| South West | 0.90 | 0.68 | 1.20 | 0.361 | 0.90 | 0.68 | 1.20 | 0.361 | 0.94 | 0.77 | 1.14 | 0.394 |
| West Midlands | 0.87 | 0.66 | 1.15 | 0.194 | 0.87 | 0.66 | 1.15 | 0.194 | 0.93 | 0.77 | 1.13 | 0.341 |
| Yorkshire & Humber | 0.82 | 0.60 | 1.13 | 0.107 | 0.82 | 0.60 | 1.13 | 0.107 | 0.92 | 0.74 | 1.14 | 0.330 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.00 | 0.91 | 1.09 | 0.883 | 1.00 | 0.91 | 1.09 | 0.883 | 1.04 | 0.99 | 1.10 | 0.028 |
| Light-smoker | 1.30 | 1.17 | 1.44 | <0.001 | 1.30 | 1.17 | 1.44 | <0.001 | 1.41 | 1.32 | 1.49 | <0.001 |
| Moderate-smoker | 1.51 | 1.07 | 2.14 | 0.002 | 1.51 | 1.07 | 2.14 | 0.002 | 1.42 | 1.15 | 1.74 | <0.001 |
| Heavy-smoker | 1.50 | 0.89 | 2.53 | 0.047 | 1.50 | 0.89 | 2.53 | 0.047 | 1.63 | 1.24 | 2.13 | <0.001 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.01 | 0.90 | 1.13 | 0.819 | 1.01 | 0.90 | 1.13 | 0.819 | 1.04 | 0.98 | 1.10 | 0.106 |
| Medium | 1.12 | 0.95 | 1.32 | 0.073 | 1.12 | 0.95 | 1.32 | 0.073 | 1.14 | 1.04 | 1.25 | <0.001 |
| Heavy | 1.24 | 0.88 | 1.75 | 0.107 | 1.24 | 0.88 | 1.75 | 0.107 | 1.15 | 0.95 | 1.39 | 0.062 |
| Very heavy | 1.22 | 0.76 | 1.94 | 0.257 | 1.22 | 0.76 | 1.94 | 0.257 | 1.40 | 1.16 | 1.70 | <0.001 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.26 | 0.93 | 1.70 | 0.047 | 1.26 | 0.93 | 1.70 | 0.047 | 1.26 | 1.08 | 1.47 | <0.001 |
| Asian | 0.78 | 0.59 | 1.02 | 0.019 | 0.78 | 0.59 | 1.02 | 0.019 | 0.76 | 0.65 | 0.88 | <0.001 |
| Other | 0.73 | 0.46 | 1.14 | 0.067 | 0.73 | 0.46 | 1.14 | 0.067 | 0.70 | 0.55 | 0.90 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 1.10 | 1.10 | 1.10 | <0.001 | 1.10 | 1.10 | 1.10 | <0.001 | 1.10 | 1.10 | 1.10 | <0.001 |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.67 | 1.54 | 1.80 | <0.001 | 1.67 | 1.54 | 1.80 | <0.001 | 1.64 | 1.57 | 1.72 | <0.001 |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.96 | 0.84 | 1.09 | 0.390 | 0.96 | 0.84 | 1.09 | 0.390 | 0.92 | 0.85 | 1.00 | 0.013 |
| 2011 to 2015 | 0.92 | 0.80 | 1.06 | 0.114 | 0.92 | 0.80 | 1.06 | 0.114 | 0.86 | 0.79 | 0.94 | <0.001 |
| 2016 to 2020 | 0.76 | 0.66 | 0.88 | <0.001 | 0.76 | 0.66 | 0.88 | <0.001 | 0.73 | 0.66 | 0.80 | <0.001 |
| Coronary heart disease | 1.17 | 1.06 | 1.28 | <0.001 | 1.17 | 1.06 | 1.28 | <0.001 | 1.21 | 1.14 | 1.28 | <0.001 |
| Stroke | 1.07 | 0.97 | 1.18 | 0.079 | 1.07 | 0.97 | 1.18 | 0.079 | 1.23 | 1.16 | 1.30 | <0.001 |
| Diabetes | 1.21 | 1.09 | 1.35 | <0.001 | 1.21 | 1.09 | 1.35 | <0.001 | 1.35 | 1.27 | 1.43 | <0.001 |
| Epilepsy | 0.83 | 0.63 | 1.11 | 0.097 | 0.83 | 0.63 | 1.11 | 0.097 | 0.97 | 0.83 | 1.13 | 0.612 |
| Hypothyroidism | 0.90 | 0.79 | 1.02 | 0.027 | 0.90 | 0.79 | 1.02 | 0.027 | 1.01 | 0.94 | 1.08 | 0.740 |
| Arthritis | 0.76 | 0.70 | 0.83 | <0.001 | 0.76 | 0.70 | 0.83 | <0.001 | 0.80 | 0.76 | 0.84 | <0.001 |
| Anxiety | 0.76 | 0.67 | 0.87 | <0.001 | 0.76 | 0.67 | 0.87 | <0.001 | 0.80 | 0.74 | 0.86 | <0.001 |
| Migraine | 0.55 | 0.42 | 0.71 | <0.001 | 0.55 | 0.42 | 0.71 | <0.001 | 0.68 | 0.61 | 0.77 | <0.001 |
| Cancer | 1.95 | 1.79 | 2.13 | <0.001 | 1.95 | 1.79 | 2.13 | <0.001 | 2.08 | 1.97 | 2.19 | <0.001 |
| Asthma | 1.07 | 0.98 | 1.17 | 0.045 | 1.07 | 0.98 | 1.17 | 0.045 | 1.21 | 1.15 | 1.27 | <0.001 |
| Renal failure | 2.13 | 1.75 | 2.59 | <0.001 | 2.13 | 1.75 | 2.59 | <0.001 | 2.37 | 2.04 | 2.74 | <0.001 |
| Liver failure | 1.77 | 1.38 | 2.28 | <0.001 | 1.77 | 1.38 | 2.28 | <0.001 | 1.82 | 1.56 | 2.11 | <0.001 |
| Osteoporosis | 1.03 | 0.89 | 1.20 | 0.567 | 1.03 | 0.89 | 1.20 | 0.567 | 1.09 | 1.00 | 1.18 | 0.010 |
| Suicidality | 1.33 | 0.95 | 1.87 | 0.029 | 1.33 | 0.95 | 1.87 | 0.029 | 1.35 | 1.12 | 1.63 | <0.001 |
| Antihypertensive | 0.78 | 0.72 | 0.85 | <0.001 | 0.78 | 0.72 | 0.85 | <0.001 | 0.86 | 0.82 | 0.90 | <0.001 |
| Aspirin | 1.03 | 0.93 | 1.13 | 0.500 | 1.03 | 0.93 | 1.13 | 0.500 | 1.10 | 1.04 | 1.16 | <0.001 |
| Anticoagulants | 1.40 | 1.22 | 1.60 | <0.001 | 1.40 | 1.22 | 1.60 | <0.001 | 1.53 | 1.42 | 1.66 | <0.001 |
| NSAIDs | 1.22 | 1.04 | 1.44 | 0.001 | 1.22 | 1.04 | 1.44 | 0.001 | 1.17 | 1.06 | 1.28 | <0.001 |
| Anticonvulsants | 1.87 | 1.55 | 2.25 | <0.001 | 1.87 | 1.55 | 2.25 | <0.001 | 1.86 | 1.66 | 2.07 | <0.001 |
| Hypnotics | 1.33 | 1.20 | 1.48 | <0.001 | 1.33 | 1.20 | 1.48 | <0.001 | 1.37 | 1.29 | 1.46 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bisphosphonates | 1.20 | 0.94 | 1.52 | 0.056 | 1.20 | 0.94 | 1.52 | 0.056 | 1.26 | 1.07 | 1.48 | <0.001 |
| Contraceptives | 0.50 | 0.21 | 1.19 | 0.039 | 0.50 | 0.21 | 1.19 | 0.039 | 0.49 | 0.31 | 0.76 | <0.001 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 |

## A4.7 Complete case analyses (CCAs) and full set analyses (FSAs) for all outcomes

***Table A4.7a*** *CCA: unadjusted and adjusted odds ratios/mean differences (statin users vs statin non-users) for efficacy (response, remission, change in depressive score), as measured on the PHQ-9 at 2 months, 6 months, and 12 months*

| | | | **COMPLETE CASE ANALYSIS** N= see below | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Unadjusted analysis* | | | | *Adjusted analysis* | | | |
| | *Outcome* | *Time point* | *N* | *OR* | *99% CI* | *p* | *N* | *OR* | *99% CI* | *p* |
| **Efficacy** | **Response** | 2mo | 54,435 | 1.08 | 0.99, 1.18 | 0.018 | 26,245 | 1.09 | 0.94, 1.28 | 0.133 |
| | | 6mo | 13,225 | 1.03 | 0.85, 1.24 | 0.690 | 6,318 | 1.05 | 0.76, 1.46 | 0.684 |
| | | 12mo | 8,004 | 1.11 | 0.86, 1.44 | 0.291 | 3,743 | 1.17 | 0.74, 1.87 | 0.376 |
| | **Remission** | 2mo | 87,996 | 1.39 | 1.26, 1.53 | <0.001 | 26,245 | 1.19 | 0.99, 1.43 | 0.013 |
| | | 6mo | 25,695 | 1.63 | 1.37, 1.94 | <0.001 | 6,318 | 0.89 | 0.59, 1.36 | 0.505 |
| | | 12mo | 16,880 | 2.03 | 1.61, 2.56 | <0.001 | 3,743 | 1.20 | 0.72, 2.01 | 0.352 |
| | | | *N* | *MD* | *99% CI* | *p* | *N* | *MD* | *99.%CI* | |
| | **Change** | 2mo | 54,435 | 0.16 | -0.11, 0.43 | 0.120 | 26,245 | -0.15 | -0.55, 0.26 | 0.349 |
| | **in depressive** | 6mo | 13,225 | 0.34 | -0.27, 0.95 | 0.150 | 6,318 | -0.01 | -0.91, 0.94 | 0.976 |
| | **score** | 12mo | 8,004 | 0.58 | -0.30, 1.46 | 0.090 | 3,743 | -0.78 | -2.13, 0.56 | 0.133 |

***Legend***. For response and remission, an OR>1 favours statin users. For change in depression score, a MD<0 favours statin users

***Table A4.7b*** *CCA: unadjusted and adjusted odds ratios (statin users vs statin non-users) for adverse events (any adverse event, any psychiatric symptom, anxiety, sleep disturbance, memory impairment, self-harm, suicidality, completed suicide, and all-cause mortality) at 2 months, 6 months, and 12 months*

| | | **COMPLETE CASE ANALYSIS** | | | | | |
|---|---|---|---|---|---|---|---|
| | | *Unadjusted analysis N= 1,050,105* | | | *Adjusted analysis N= 88,227* | | |
| *Outcome* | *Time* | *OR* | *99% CI* | *p* | *OR* | *99% CI* | *p* |

| | | | *point* | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Adverse events** | **Any adverse event** | 2mo | 1.11 | 1.05, 1.18 | <0.001 | 0.92 | 0.84, 1.02 | 0.032 |
| | | 6mo | 1.30 | 1.22, 1.38 | <0.001 | 0.97 | 0.88, 1.06 | 0.333 |
| | | 12mo | 1.55 | 1.44, 1.66 | <0.001 | 0.99 | 0.91, 1.09 | 0.873 |
| | **Any psychiatric symptom** | 2mo | 0.84 | 0.78, 0.89 | <0.001 | 0.98 | 0.95, 1.02 | 0.172 |
| | | 6mo | 0.85 | 0.80, 0.90 | <0.001 | 0.98 | 0.95, 1.01 | 0.100 |
| | | 12mo | 0.88 | 0.83, 0.93 | <0.001 | 0.98 | 0.95, 1.01 | 0.124 |
| | **Anxiety** | 2mo | 0.57 | 0.53, 0.61 | <0.001 | 1.04 | 0.99, 1.09 | 0.059 |
| | | 6mo | 0.55 | 0.52, 0.59 | <0.001 | 1.03 | 0.98, 1.08 | 0.117 |
| | | 12mo | 0.54 | 0.51, 0.58 | <0.001 | 1.02 | 0.98, 1.07 | 0.227 |
| | **Sleep disturbance** | 2mo | 1.12 | 0.98, 1.27 | 0.027 | 1.02 | 0.88, 1.18 | 0.761 |
| | | 6mo | 1.18 | 1.06, 1.32 | <0.001 | 0.95 | 0.85, 1.06 | 0.192 |
| | | 12mo | 1.27 | 1.15, 1.40 | <0.001 | 0.98 | 0.89, 1.07 | 0.496 |
| | **Memory impairment** | 2mo | 4.76 | 4.16, 5.45 | <0.001 | 1.15 | 0.99, 1.34 | 0.013 |
| | | 6mo | 4.52 | 4.06, 5.03 | <0.001 | 1.09 | 0.98, 1.21 | 0.037 |
| | | 12mo | 4.63 | 4.22, 5.09 | <0.001 | 1.13 | 1.04, 1.23 | <0.001 |
| | **Self-harm** | 2mo | 0.29 | 0.21, 0.41 | <0.001 | 0.24 | 0.04, 1.24 | 0.025 |
| | | 6mo | 0.27 | 0.21, 0.35 | <0.001 | 0.25 | 0.06, 1.01 | 0.011 |
| | | 12mo | 0.27 | 0.22, 0.34 | <0.001 | 0.25 | 0.08, 0.73 | 0.001 |
| | **Suicidality** | 2mo | 0.64 | 0.53, 0.76 | <0.001 | 1.10 | 0.75, 1.62 | 0.504 |
| | | 6mo | 0.63 | 0.53, 0.74 | <0.001 | 0.98 | 0.68, 1.41 | 0.891 |
| | | 12mo | 0.64 | 0.53, 0.76 | <0.001 | 0.95 | 0.69, 1.32 | 0.708 |
| | **Completed suicide** | 2mo | 0.32 | 0.12, 0.87 | 0.003 | 0.83 | 0.01, 68.13 | 0.911 |
| | | 6mo | 0.27 | 0.12, 0.62 | <0.001 | 0.37 | 0.01, 13.43 | 0.479 |
| | | 12mo | 0.33 | 0.18, 0.63 | <0.001 | 0.33 | 0.01, 9.89 | 0.399 |
| | **All-cause mortality** | 2mo | 3.03 | 2.74, 3.35 | <0.001 | 0.70 | 0.41, 1.19 | 0.083 |
| | | 6mo | 3.03 | 2.74, 3.35 | <0.001 | 0.70 | 0.41, 1.19 | 0.083 |
| | | 12mo | 3.84 | 3.57, 4.13 | <0.001 | 0.78 | 0.60, 1.02 | 0.016 |

***Legend***. For adverse events, an OR<1 favours statin users

***Table A4.7c*** *FSA: unadjusted and adjusted odds ratios/mean differences (statin non-users vs statin users) for efficacy (as measured on the PHQ-9: response, remission, change in depressive score), and adverse events (any adverse event, any psychiatric symptom, anxiety, sleep disturbance, memory impairment, self-harm, suicidality, completed suicide, and all-cause mortality) at 2 months, 6 months, and 12 months*

| | | | **FULL SET ANALYSIS** N= 1,050,105 | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | *Unadjusted analysis* | | | *Adjusted analysis* | | |
| | *Outcome* | *Time point* | *OR* | *99% CI* | *p* | *OR* | *99% CI* | *p* |
| **Efficacy** | **Response** | 2mo | 0.99 | 0.83, 1.19 | 0.870 | 1.04 | 0.94, 1.15 | 0.218 |
| | | 6mo | 1.20 | 1.00, 1.44 | 0.011 | 1.04 | 0.90, 1.19 | 0.436 |
| | | 12mo | 1.43 | 1.23, 1.66 | <0.001 | 1.12 | 0.89, 1.40 | 0.144 |
| | **Remission** | 2mo | 1.09 | 0.86, 1.37 | 0.275 | 1.03 | 0.94, 1.13 | 0.335 |
| | | 6mo | 1.48 | 1.21, 1.81 | <0.001 | 1.03 | 0.89, 1.20 | 0.521 |
| | | 12mo | 1.81 | 1.53, 2.15 | <0.001 | 1.11 | 0.90, 1.38 | 0.139 |
| | | | *MD* | | | *MD* | | |
| | **Change** | 2mo | 0.67 | 0.01, 1.33 | 0.010 | -0.09 | -0.35, 0.16 | 0.272 |
| | **in depression** | 6mo | -0.24 | -1.20, 0.72 | 0.442 | -0.12 | -0.72, 0.49 | 0.509 |
| | **score** | 12mo | -0.95 | -1.66, -0.25 | 0.002 | -0.41 | -1.30, 0.49 | 0.140 |
| | *Outcome* | *Time point* | *OR* | *99% CI* | *p* | *OR* | *99% CI* | *p* |
| **Adverse events** | **Any adverse event** | 2mo | 1.11 | 1.05, 1.18 | <0.001 | 0.93 | 0.91, 0.96 | <0.001 |
| | | 6mo | 1.30 | 1.22, 1.38 | <0.001 | 0.97 | 0.94, 0.99 | 0.008 |
| | | 12mo | 1.55 | 1.44, 1.66 | <0.001 | 0.99 | 0.96, 1.03 | 0.637 |
| | **Any psychiatric** | 2mo | 0.84 | 0.78, 0.89 | <0.001 | 0.97 | 0.86, 1.09 | 0.494 |
| | **symptom** | 6mo | 0.85 | 0.80, 0.90 | <0.001 | 0.94 | 0.84, 1.04 | 0.117 |
| | | 12mo | 0.88 | 0.83, 0.93 | <0.001 | 0.92 | 0.83, 1.02 | 0.045 |
| | **Anxiety** | 2mo | 0.57 | 0.53, 0.61 | <0.001 | 1.07 | 0.92, 1.23 | 0.243 |
| | | 6mo | 0.55 | 0.52, 0.59 | <0.001 | 1.07 | 0.93, 1.22 | 0.208 |
| | | 12mo | 0.54 | 0.51, 0.58 | <0.001 | 1.05 | 0.92, 1.20 | 0.339 |
| | **Sleep disturbance** | 2mo | 1.12 | 0.98, 1.27 | 0.027 | 1.16 | 0.76, 1.77 | 0.361 |
| | | 6mo | 1.18 | 1.06, 1.32 | <0.001 | 1.05 | 0.73, 1.50 | 0.753 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 12mo | 1.27 | 1.15, 1.40 | <0.001 | 1.13 | 0.85, 1.50 | 0.254 |
| | **Memory** | 2mo | 4.76 | 4.16, 5.45 | <0.001 | 1.32 | 0.79, 2.20 | 0.159 |
| | **impairment** | 6mo | 4.52 | 4.06, 5.03 | <0.001 | 0.89 | 0.61, 1.31 | 0.448 |
| | | 12mo | 4.63 | 4.22, 5.09 | <0.001 | 0.98 | 0.73, 1.31 | 0.841 |
| | **Self-harm** | 2mo | 0.29 | 0.21, 0.41 | <0.001 | 0.76 | 0.50, 1.15 | 0.086 |
| | | 6mo | 0.27 | 0.21, 0.35 | <0.001 | 0.78 | 0.56, 1.07 | 0.044 |
| | | 12mo | 0.27 | 0.22, 0.34 | <0.001 | 0.82 | 0.62, 1.08 | 0.063 |
| | **Suicidality** | 2mo | 0.64 | 0.53, 0.76 | <0.001 | 1.02 | 0.84, 1.23 | 0.827 |
| | | 6mo | 0.63 | 0.53, 0.74 | <0.001 | 1.04 | 0.89, 1.21 | 0.546 |
| | | 12mo | 0.63 | 0.53, 0.76 | <0.001 | 1.00 | 0.88, 1.14 | 0.940 |
| | **Completed suicide** | 2mo | 0.32 | 0.12, 0.87 | 0.003 | 0.72 | 0.18, 2.87 | 0.542 |
| | | 6mo | 0.27 | 0.12, 0.62 | <0.001 | 0.54 | 0.18, 1.58 | 0.138 |
| | | 12mo | 0.33 | 0.18, 0.63 | <0.001 | 0.82 | 0.35, 1.89 | 0.539 |
| | **All-cause mortality** | 2mo | 3.03 | 2.74, 3.35 | <0.001 | 0.66 | 0.60, 0.72 | <0.001 |
| | | 6mo | 3.03 | 2.74, 3.35 | <0.001 | 0.66 | 0.60, 0.72 | <0.001 |
| | | 12mo | 3.84 | 3.57, 4.13 | <0.001 | 0.67 | 0.65, 0.73 | <0.001 |

***Legend***. For response and remission, an OR>1 favours statin users. For change in depression score, a MD<0 favours statin users. For adverse events, an OR<1 favours statin users

# Appendix to Chapter 5

## A5.1 Statins and antidepressants included

Statins were included based on those currently available in the UK according to the British National Formulary (BNF) (https://bnf.nice.org.uk):
- simvastatin
- atorvastatin
- pravastatin
- fluvastatin
- rosuvastatin

Antidepressants were categorised according to four classes as in the BNF:
- selective serotonin reuptake inhibitors (SSRIs): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline

- tricyclics (TCAs): amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dosulepine, doxepin, imipramine, iprindole, lofepramine, maprotiline, mianserin, nortriptyline, protriptyline, trimipramine, viloxazine
- monoamine oxidase inhibitors (MAOIs): isocarboaxazid, moclobemide, phenelzine, tranylcypromine
- other antidepressants: agomelatine, duloxetine, mirtazapine, nefazodone, reboxetine, tryptophan, trazodone, venlafaxine, vortioxetine

## A5.2 Missing data

***Table A5.2*** *Missing data (percentage) imputed for the full set analysis*

| Characteristic | Missing (%) | Complete |
|---|---|---|
| PHQ-9 | | |
| at baseline | 528,830 (78.56) | 673,177 |
| at 2 months | 600,720 (89.24) | 673,177 |
| at 6 months | 654,694 (97.25) | 673,177 |
| at 12 months | 661,413 (98.25) | 673,177 |
| Body Mass Index | 149,057 (22.14) | 673,177 |
| Smoking | 52,880 (7.86) | 673,177 |
| Alcohol | 333,060 (49.48) | 673,177 |
| Ethnic group | 179,854 (26.72) | 673,177 |
| Townsend deprivation score | 2,289 (0.34) | 673,177 |

## A5.3 Number of events for all outcomes

***Table A5.3*** *Number of events (percentage) for all outcomes at 2 months, 6 months, and 12 months*

| | Antidepressant-only | | Any statin + antidepressant | |
|---|---|---|---|---|
| Outcome | *Nº events* | *Nº patients* | *Nº events* | *Nº patients* |
| **Acceptability** | | | | |

| | | | | |
|---|---|---|---|---|
| 2mo | 242,951 (38.79) | 626,335 | 16,784 (35.83) | 46,842 |
| 6mo | 449,473 (71.76) | 626,335 | 28,988 (61.88) | 46,842 |
| 12mo | 554,512 (88.53) | 626,335 | 36,141 (77.16) | 46,842 |
| **Tolerability** | | | | |
| 2mo | 34,162 (5.45) | 626,335 | 3,598 (7.68) | 46,842 |
| 6mo | 54,534 (8.71) | 626,335 | 5,610 (11.98) | 46,842 |
| 12mo | 75,242 (12.01) | 626,335 | 8,614 (18.39) | 46,842 |
| **Any adverse event** | | | | |
| 2mo | 282,246 (45.06) | 626,335 | 24,409 (52.11) | 46,842 |
| 6mo | 376,136 (60.05) | 626,335 | 32,490 (69.36) | 46,842 |
| 12mo | 441,264 (70.45) | 626,335 | 37,775 (80.64) | 46,842 |
| **Self-harm** | | | | |
| 2mo | 2,154 (0.34) | 626,335 | 53 (0.11) | 46,842 |
| 6mo | 3,878 (0.62) | 626,335 | 88 (0.19) | 46,842 |
| 12mo | 5,201 (0.83) | 626,335 | 122 (0.26) | 46,842 |
| **Suicidality** | | | | |
| 2mo | 6,372 (1.02) | 626,335 | 373 (0.80) | 46,842 |
| 6mo | 9,559 (1.53) | 626,335 | 534 (1.14) | 46,842 |
| 12mo | 12,166 (1.94) | 626,335 | 652 (1.39) | 46,842 |
| **Completed suicide** | | | | |
| 2mo | 190 (0.03) | 626,335 | 7 (0.01) | 46,842 |
| 6mo | 318 (0.05) | 626,335 | 10 (0.02) | 46,842 |
| 12mo | 443 (0.07) | 626,335 | 16 (0.03) | 46,842 |
| **All-cause mortality** | | | | |
| 2mo | 3,203 (0.51) | 626,335 | 879 (1.88) | 46,842 |
| 6mo | 3,203 (0.51) | 626,335 | 879 (1.88) | 46,842 |
| 12mo | 10,797 (1.72) | 626,335 | 3,375 (7.21) | 46,842 |
| **Response** | | | | |
| 2mo | 15,701 (35.54) | 44,175 | 1,330 (37.52) | 3,545 |
| 6mo | 3,407 (34.53) | 9,868 | 264 (37.08) | 712 |
| 12mo | 1,812 (30.84) | 5,876 | 148 (35.84) | 413 |

| | | | | |
|---|---|---|---|---|
| **Remission** | | | | |
| 2mo | 9,031 (13.46) | 67,097 | 872 (16.27) | 5,360 |
| 6mo | 2,767 (16.06) | 17,227 | 273 (21.74) | 1,256 |
| 12mo | 1,506 (13.75) | 10,954 | 157 (19.38) | 810 |

## A5.4 Regression analyses for all outcomes

***Table A5.4a*** *Regression analyses for acceptability at 2 months, 6 months, and 12 months; complete case analysis (CCA) and full set analysis (FSA)*

| | **Acceptability *(CCA, N= 63,801)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | | **6 months** | | | | **12 months** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 0.84 | 0.76 | 0.94 | <0.001 | 0.86 | 0.78 | 0.95 | <0.001 | 0.79 | 0.70 | 0.88 | <0.001 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 2.60 | 2.22 | 3.03 | <0.001 | 3.13 | 2.57 | 3.82 | <0.001 | 3.02 | 2.29 | 3.99 | <0.001 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 1.60 | 1.43 | 1.79 | <0.001 | 1.71 | 1.51 | 1.93 | <0.001 | 1.62 | 1.36 | 1.92 | <0.001 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.00 | 0.99 | 1.00 | 0.680 | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.01 | 1.02 | <0.001 |
| BMI | 0.99 | 0.98 | 0.99 | <0.001 | 0.99 | 0.99 | 0.99 | <0.001 | 0.98 | 0.98 | 0.99 | <0.001 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.29 | 1.22 | 1.38 | <0.001 | 1.26 | 1.19 | 1.34 | <0.001 | 1.20 | 1.12 | 1.30 | <0.001 |
| Other | 1.38 | 1.18 | 1.62 | <0.001 | 1.26 | 1.06 | 1.50 | 0.001 | 1.16 | 0.92 | 1.47 | 0.090 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.07 | 1.00 | 1.14 | 0.012 | 1.09 | 1.02 | 1.16 | <0.001 | 1.04 | 0.96 | 1.13 | 0.210 |
| 3 | 1.12 | 1.04 | 1.20 | <0.001 | 1.20 | 1.12 | 1.29 | <0.001 | 1.16 | 1.06 | 1.27 | <0.001 |
| 4 | 1.18 | 1.09 | 1.27 | <0.001 | 1.29 | 1.19 | 1.39 | <0.001 | 1.23 | 1.12 | 1.36 | <0.001 |
| 5, most deprived | 1.29 | 1.18 | 1.42 | <0.001 | 1.40 | 1.26 | 1.57 | <0.001 | 1.34 | 1.17 | 1.52 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.06 | 0.76 | 1.49 | 0.629 | 0.91 | 0.62 | 1.35 | 0.556 | 0.95 | 0.63 | 1.42 | 0.732 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| London | 0.97 | 0.71 | 1.33 | 0.816 | 0.92 | 0.64 | 1.32 | 0.531 | 0.92 | 0.65 | 1.32 | 0.571 |
| North East | 1.08 | 0.75 | 1.55 | 0.602 | 0.98 | 0.66 | 1.44 | 0.873 | 0.90 | 0.59 | 1.36 | 0.505 |
| North West | 1.11 | 0.82 | 1.50 | 0.385 | 0.97 | 0.68 | 1.38 | 0.821 | 0.88 | 0.63 | 1.24 | 0.343 |
| South Central | 1.05 | 0.78 | 1.42 | 0.647 | 0.96 | 0.67 | 1.36 | 0.756 | 0.92 | 0.65 | 1.30 | 0.540 |
| South East | 1.04 | 0.77 | 1.41 | 0.718 | 0.99 | 0.69 | 1.41 | 0.939 | 0.94 | 0.65 | 1.36 | 0.679 |
| South West | 0.96 | 0.71 | 1.31 | 0.763 | 0.92 | 0.65 | 1.31 | 0.560 | 0.93 | 0.65 | 1.31 | 0.575 |
| West Midlands | 1.14 | 0.84 | 1.55 | 0.257 | 1.04 | 0.73 | 1.47 | 0.793 | 0.96 | 0.68 | 1.36 | 0.777 |
| Yorkshire & Humber | 0.95 | 0.67 | 1.33 | 0.684 | 0.85 | 0.59 | 1.22 | 0.253 | 0.82 | 0.56 | 1.20 | 0.174 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.95 | 0.90 | 1.00 | 0.016 | 0.93 | 0.88 | 0.99 | 0.001 | 0.91 | 0.85 | 0.97 | <0.001 |
| Light-smoker | 1.20 | 1.13 | 1.27 | <0.001 | 1.41 | 1.32 | 1.50 | <0.001 | 1.34 | 1.24 | 1.46 | <0.001 |
| Moderate-smoker | 1.17 | 0.99 | 1.39 | 0.014 | 1.46 | 1.20 | 1.78 | <0.001 | 1.31 | 1.01 | 1.71 | 0.008 |
| Heavy-smoker | 1.17 | 0.89 | 1.54 | 0.148 | 1.43 | 1.06 | 1.93 | 0.002 | 1.34 | 0.93 | 1.94 | 0.042 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.96 | 0.91 | 1.01 | 0.020 | 0.95 | 0.90 | 1.00 | 0.007 | 0.96 | 0.90 | 1.03 | 0.156 |
| Medium | 0.97 | 0.89 | 1.05 | 0.302 | 1.00 | 0.91 | 1.09 | 0.965 | 0.97 | 0.87 | 1.09 | 0.522 |
| Heavy | 1.14 | 0.95 | 1.38 | 0.064 | 1.12 | 0.91 | 1.37 | 0.168 | 1.04 | 0.81 | 1.34 | 0.671 |
| Very heavy | 1.02 | 0.86 | 1.21 | 0.770 | 1.29 | 1.07 | 1.56 | <0.001 | 1.30 | 1.00 | 1.69 | 0.011 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.62 | 1.38 | 1.89 | <0.001 | 2.33 | 1.92 | 2.83 | <0.001 | 2.97 | 2.18 | 4.03 | <0.001 |
| Asian | 1.79 | 1.56 | 2.06 | <0.001 | 2.12 | 1.80 | 2.49 | <0.001 | 1.92 | 1.53 | 2.42 | <0.001 |
| Other | 1.57 | 1.37 | 1.82 | <0.001 | 1.76 | 1.51 | 2.05 | <0.001 | 1.81 | 1.41 | 2.31 | <0.001 |
| | | | | | | | | | | | | |
| Age | 1.00 | 1.00 | 1.00 | 0.985 | 0.99 | 0.99 | 0.99 | <0.001 | 0.98 | 0.98 | 0.99 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.00 | 0.95 | 1.05 | 0.832 | 1.17 | 1.12 | 1.23 | <0.001 | 1.16 | 1.09 | 1.24 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.74 | 0.53 | 1.03 | 0.018 | 0.80 | 0.54 | 1.19 | 0.151 | 0.71 | 0.41 | 1.24 | 0.115 |
| 2011 to 2015 | 0.68 | 0.49 | 0.95 | 0.003 | 0.71 | 0.48 | 1.06 | 0.029 | 0.57 | 0.33 | 0.99 | 0.009 |
| 2016 to 2020 | 0.71 | 0.51 | 0.99 | 0.009 | 0.76 | 0.51 | 1.14 | 0.079 | 0.64 | 0.37 | 1.13 | 0.042 |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.21 | 1.04 | 1.39 | 0.001 | 1.27 | 1.10 | 1.48 | <0.001 | 1.34 | 1.12 | 1.60 | <0.001 |
| Stroke | 1.00 | 0.84 | 1.19 | 0.973 | 1.22 | 1.01 | 1.46 | 0.006 | 1.05 | 0.86 | 1.28 | 0.533 |
| Diabetes | 1.05 | 0.94 | 1.18 | 0.235 | 1.00 | 0.90 | 1.11 | 0.944 | 0.98 | 0.87 | 1.10 | 0.645 |
| Epilepsy | 0.95 | 0.77 | 1.18 | 0.551 | 1.02 | 0.83 | 1.27 | 0.783 | 0.88 | 0.67 | 1.15 | 0.207 |
| Hypothyroidism | 0.96 | 0.84 | 1.09 | 0.403 | 0.89 | 0.78 | 1.00 | 0.013 | 0.93 | 0.80 | 1.08 | 0.185 |
| Arthritis | 1.02 | 0.93 | 1.12 | 0.595 | 1.12 | 1.02 | 1.24 | 0.002 | 1.11 | 0.99 | 1.24 | 0.020 |
| Anxiety | 1.01 | 0.94 | 1.07 | 0.834 | 0.90 | 0.85 | 0.96 | <0.001 | 0.86 | 0.79 | 0.94 | <0.001 |
| Migraine | 1.03 | 0.94 | 1.12 | 0.420 | 0.98 | 0.90 | 1.07 | 0.614 | 0.93 | 0.83 | 1.04 | 0.076 |
| Cancer | 1.09 | 1.00 | 1.19 | 0.008 | 1.05 | 0.97 | 1.14 | 0.117 | 1.10 | 0.99 | 1.22 | 0.023 |
| Asthma | 1.00 | 0.95 | 1.06 | 0.853 | 1.01 | 0.95 | 1.07 | 0.747 | 0.95 | 0.88 | 1.03 | 0.091 |
| Renal failure | 1.01 | 0.66 | 1.53 | 0.968 | 1.29 | 0.83 | 2.01 | 0.141 | 1.31 | 0.76 | 2.25 | 0.200 |
| Liver failure | 0.98 | 0.77 | 1.25 | 0.834 | 0.89 | 0.71 | 1.13 | 0.225 | 0.92 | 0.69 | 1.22 | 0.436 |
| Osteoporosis | 1.22 | 0.96 | 1.55 | 0.034 | 1.30 | 1.03 | 1.66 | 0.004 | 1.21 | 0.90 | 1.62 | 0.102 |
| Suicidality | 1.11 | 0.97 | 1.27 | 0.052 | 1.19 | 1.02 | 1.37 | 0.003 | 1.13 | 0.93 | 1.38 | 0.097 |
| Antihypertensive | 0.99 | 0.91 | 1.09 | 0.801 | 0.96 | 0.88 | 1.04 | 0.194 | 0.87 | 0.79 | 0.97 | 0.001 |
| Aspirin | 1.04 | 0.90 | 1.19 | 0.492 | 1.08 | 0.94 | 1.24 | 0.144 | 1.07 | 0.91 | 1.25 | 0.298 |
| Anticoagulants | 1.20 | 0.94 | 1.52 | 0.051 | 1.25 | 0.98 | 1.59 | 0.019 | 1.18 | 0.90 | 1.54 | 0.123 |
| NSAIDs | 1.06 | 0.92 | 1.21 | 0.308 | 0.96 | 0.84 | 1.10 | 0.456 | 0.93 | 0.78 | 1.09 | 0.232 |
| Anticonvulsants | 1.02 | 0.81 | 1.28 | 0.820 | 0.97 | 0.78 | 1.22 | 0.756 | 0.79 | 0.60 | 1.03 | 0.020 |
| Hypnotics | 1.11 | 1.02 | 1.21 | 0.001 | 1.11 | 1.03 | 1.21 | 0.001 | 1.04 | 0.94 | 1.16 | 0.329 |
| Bisphosphonates | 0.90 | 0.57 | 1.43 | 0.565 | 0.77 | 0.50 | 1.19 | 0.128 | 0.95 | 0.56 | 1.61 | 0.801 |
| Contraceptives | 0.94 | 0.86 | 1.03 | 0.093 | 0.88 | 0.81 | 0.96 | <0.001 | 0.91 | 0.80 | 1.03 | 0.047 |
| *Constant* | 0.72 | 0.45 | 1.17 | 0.082 | 2.79 | 1.59 | 4.89 | <0.001 | 17.19 | 8.60 | 34.32 | <0.001 |

| | Acceptability *(FSA, N = 673,177)* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | | **6 months** | | | | **12 months** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 0.88 | 0.85 | 0.91 | <0.001 | 0.81 | 0.79 | 0.84 | <0.001 | 0.78 | 0.75 | 0.81 | <0.001 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 2.03 | 1.95 | 2.12 | <0.001 | 2.39 | 2.28 | 2.51 | <0.001 | 2.04 | 1.92 | 2.18 | <0.001 |
| MAOIs | 1.23 | 0.69 | 2.17 | 0.358 | 1.97 | 0.94 | 4.11 | 0.018 | 1.01 | 0.42 | 2.42 | 0.967 |
| Other antidepressants | 1.42 | 1.37 | 1.49 | <0.001 | 1.58 | 1.52 | 1.64 | <0.001 | 1.47 | 1.41 | 1.54 | <0.001 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.00 | 1.00 | 1.00 | 0.538 | 1.00 | 1.00 | 1.00 | <0.001 | 1.00 | 1.00 | 1.01 | <0.001 |
| BMI | 0.99 | 0.99 | 0.99 | <0.001 | 0.99 | 0.99 | 0.99 | <0.001 | 0.99 | 0.99 | 0.99 | <0.001 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.31 | 1.28 | 1.35 | <0.001 | 1.26 | 1.23 | 1.29 | <0.001 | 1.23 | 1.19 | 1.26 | <0.001 |
| Other | 0.97 | 0.92 | 1.02 | 0.162 | 0.99 | 0.95 | 1.04 | 0.757 | 0.97 | 0.91 | 1.03 | 0.207 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.06 | 1.04 | 1.08 | <0.001 | 1.11 | 1.08 | 1.13 | <0.001 | 1.06 | 1.03 | 1.10 | <0.001 |
| 3 | 1.13 | 1.10 | 1.16 | <0.001 | 1.23 | 1.19 | 1.26 | <0.001 | 1.16 | 1.12 | 1.20 | <0.001 |
| 4 | 1.21 | 1.17 | 1.25 | <0.001 | 1.35 | 1.31 | 1.40 | <0.001 | 1.29 | 1.24 | 1.35 | <0.001 |
| 5, most deprived | 1.25 | 1.20 | 1.30 | <0.001 | 1.45 | 1.38 | 1.51 | <0.001 | 1.38 | 1.31 | 1.46 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.00 | 0.83 | 1.22 | 0.949 | 0.97 | 0.80 | 1.17 | 0.642 | 0.91 | 0.72 | 1.15 | 0.284 |
| London | 1.04 | 0.86 | 1.26 | 0.569 | 1.02 | 0.85 | 1.22 | 0.787 | 0.97 | 0.78 | 1.19 | 0.670 |
| North East | 0.98 | 0.81 | 1.19 | 0.793 | 0.94 | 0.78 | 1.14 | 0.413 | 0.86 | 0.69 | 1.07 | 0.078 |
| North West | 1.08 | 0.90 | 1.30 | 0.273 | 1.02 | 0.85 | 1.21 | 0.825 | 0.87 | 0.71 | 1.07 | 0.080 |
| South Central | 1.02 | 0.85 | 1.23 | 0.765 | 1.01 | 0.85 | 1.20 | 0.893 | 0.97 | 0.79 | 1.19 | 0.675 |
| South East | 1.06 | 0.88 | 1.27 | 0.449 | 1.03 | 0.86 | 1.22 | 0.718 | 0.95 | 0.77 | 1.17 | 0.512 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South West | 1.01 | 0.84 | 1.22 | 0.838 | 1.02 | 0.85 | 1.21 | 0.818 | 0.96 | 0.78 | 1.18 | 0.615 |
| West Midlands | 1.10 | 0.92 | 1.33 | 0.179 | 1.06 | 0.89 | 1.27 | 0.392 | 0.94 | 0.77 | 1.15 | 0.437 |
| Yorkshire & Humber | 0.96 | 0.78 | 1.18 | 0.575 | 0.92 | 0.76 | 1.11 | 0.258 | 0.83 | 0.67 | 1.03 | 0.028 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.98 | 0.96 | 1.01 | 0.048 | 0.95 | 0.93 | 0.97 | <0.001 | 0.93 | 0.90 | 0.95 | <0.001 |
| Light-smoker | 1.18 | 1.16 | 1.21 | <0.001 | 1.33 | 1.30 | 1.36 | <0.001 | 1.27 | 1.24 | 1.31 | <0.001 |
| Moderate-smoker | 1.23 | 1.17 | 1.30 | <0.001 | 1.43 | 1.35 | 1.52 | <0.001 | 1.35 | 1.24 | 1.48 | <0.001 |
| Heavy-smoker | 1.21 | 1.12 | 1.30 | <0.001 | 1.44 | 1.32 | 1.58 | <0.001 | 1.36 | 1.19 | 1.55 | <0.001 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.98 | 0.96 | 1.00 | 0.002 | 0.96 | 0.94 | 0.98 | <0.001 | 0.96 | 0.94 | 0.99 | <0.001 |
| Medium | 1.00 | 0.97 | 1.03 | 0.755 | 0.99 | 0.95 | 1.03 | 0.496 | 0.98 | 0.93 | 1.03 | 0.240 |
| Heavy | 1.05 | 0.97 | 1.12 | 0.103 | 1.05 | 0.97 | 1.14 | 0.101 | 0.99 | 0.88 | 1.11 | 0.869 |
| Very heavy | 1.06 | 1.00 | 1.14 | 0.013 | 1.09 | 1.01 | 1.18 | 0.005 | 1.09 | 0.99 | 1.21 | 0.026 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.33 | 1.27 | 1.40 | <0.001 | 1.57 | 1.46 | 1.69 | <0.001 | 1.69 | 1.54 | 1.86 | <0.001 |
| Asian | 1.74 | 1.66 | 1.81 | <0.001 | 2.12 | 2.01 | 2.23 | <0.001 | 2.14 | 1.99 | 2.30 | <0.001 |
| Other | 1.43 | 1.37 | 1.50 | <0.001 | 1.66 | 1.58 | 1.76 | <0.001 | 1.88 | 1.72 | 2.05 | <0.001 |
| | | | | | | | | | | | | |
| Age | 1.00 | 1.00 | 1.00 | <0.001 | 0.99 | 0.99 | 0.99 | <0.001 | 0.98 | 0.98 | 0.98 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.00 | 0.98 | 1.01 | 0.892 | 1.14 | 1.12 | 1.16 | <0.001 | 1.16 | 1.13 | 1.19 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.88 | 0.86 | 0.90 | <0.001 | 0.82 | 0.80 | 0.84 | <0.001 | 0.70 | 0.68 | 0.73 | <0.001 |
| 2011 to 2015 | 0.80 | 0.78 | 0.82 | <0.001 | 0.73 | 0.71 | 0.75 | <0.001 | 0.56 | 0.54 | 0.59 | <0.001 |
| 2016 to 2020 | 0.84 | 0.82 | 0.86 | <0.001 | 0.78 | 0.75 | 0.80 | <0.001 | 0.65 | 0.62 | 0.68 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Coronary heart disease | 1.19 | 1.14 | 1.24 | <0.001 | 1.22 | 1.17 | 1.28 | <0.001 | 1.22 | 1.15 | 1.29 | <0.001 |
| Stroke | 0.97 | 0.92 | 1.02 | 0.088 | 1.02 | 0.98 | 1.07 | 0.190 | 0.96 | 0.91 | 1.02 | 0.096 |
| Diabetes | 1.00 | 0.97 | 1.04 | 0.791 | 1.00 | 0.96 | 1.04 | 0.976 | 0.96 | 0.91 | 1.00 | 0.012 |
| Epilepsy | 1.05 | 0.98 | 1.12 | 0.054 | 1.03 | 0.96 | 1.10 | 0.239 | 0.91 | 0.83 | 0.99 | 0.003 |
| Hypothyroidism | 0.96 | 0.93 | 1.00 | 0.014 | 0.89 | 0.85 | 0.92 | <0.001 | 0.86 | 0.82 | 0.90 | <0.001 |
| Arthritis | 1.07 | 1.04 | 1.11 | <0.001 | 1.13 | 1.10 | 1.17 | <0.001 | 1.15 | 1.11 | 1.20 | <0.001 |
| Anxiety | 1.00 | 0.98 | 1.02 | 0.984 | 0.89 | 0.87 | 0.91 | <0.001 | 0.83 | 0.80 | 0.85 | <0.001 |
| Migraine | 0.98 | 0.95 | 1.00 | 0.028 | 0.95 | 0.92 | 0.98 | <0.001 | 0.91 | 0.88 | 0.95 | <0.001 |
| Cancer | 1.10 | 1.07 | 1.13 | <0.001 | 1.10 | 1.07 | 1.14 | <0.001 | 1.14 | 1.10 | 1.18 | <0.001 |
| Asthma | 0.99 | 0.97 | 1.01 | 0.299 | 0.98 | 0.96 | 1.00 | 0.017 | 0.97 | 0.94 | 0.99 | 0.001 |
| Renal failure | 1.11 | 0.99 | 1.25 | 0.019 | 1.22 | 1.07 | 1.39 | <0.001 | 1.18 | 1.01 | 1.39 | 0.007 |
| Liver failure | 1.00 | 0.92 | 1.08 | 0.941 | 0.97 | 0.90 | 1.06 | 0.393 | 0.92 | 0.83 | 1.02 | 0.034 |
| Osteoporosis | 1.13 | 1.06 | 1.21 | <0.001 | 1.26 | 1.17 | 1.35 | <0.001 | 1.20 | 1.11 | 1.31 | <0.001 |
| Suicidality | 1.08 | 1.03 | 1.13 | <0.001 | 1.14 | 1.09 | 1.20 | <0.001 | 1.09 | 1.02 | 1.17 | 0.001 |
| Antihypertensive | 0.97 | 0.95 | 1.00 | 0.023 | 0.92 | 0.89 | 0.95 | <0.001 | 0.84 | 0.81 | 0.88 | <0.001 |
| Aspirin | 0.98 | 0.94 | 1.02 | 0.131 | 1.01 | 0.97 | 1.06 | 0.403 | 0.98 | 0.94 | 1.03 | 0.354 |
| Anticoagulants | 1.09 | 1.02 | 1.16 | 0.001 | 1.13 | 1.06 | 1.21 | <0.001 | 1.14 | 1.05 | 1.23 | <0.001 |
| NSAIDs | 1.02 | 0.98 | 1.06 | 0.144 | 0.98 | 0.94 | 1.02 | 0.142 | 0.89 | 0.84 | 0.93 | <0.001 |
| Anticonvulsants | 0.89 | 0.83 | 0.94 | <0.001 | 0.76 | 0.71 | 0.81 | <0.001 | 0.70 | 0.65 | 0.75 | <0.001 |
| Hypnotics | 1.08 | 1.06 | 1.11 | <0.001 | 1.12 | 1.09 | 1.15 | <0.001 | 1.08 | 1.04 | 1.13 | <0.001 |
| Bisphosphonates | 0.90 | 0.80 | 1.01 | 0.017 | 0.90 | 0.80 | 1.02 | 0.024 | 0.91 | 0.79 | 1.05 | 0.105 |
| Contraceptives | 0.88 | 0.85 | 0.90 | <0.001 | 0.82 | 0.79 | 0.85 | <0.001 | 0.86 | 0.82 | 0.90 | <0.001 |
| *Constant* | 0.61 | 0.50 | 0.75 | <0.001 | 3.28 | 2.71 | 3.97 | <0.001 | 23.42 | 18.72 | 29.29 | <0.001 |

***Table A5.4b*** *Regression analyses for tolerability at 2 months, 6 months, and 12 months; complete case analysis (CCA) and full set analysis (FSA)*

| | **Tolerability *(CCA, N= 63,801)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | | **6 months** | | | | **12 months** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 1.02 | 0.83 | 1.26 | 0.795 | 1.07 | 0.90 | 1.26 | 0.316 | 1.11 | 0.97 | 1.28 | 0.052 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 2.80 | 2.20 | 3.57 | <0.001 | 2.05 | 1.67 | 2.52 | <0.001 | 1.37 | 1.13 | 1.67 | <0.001 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 1.51 | 1.22 | 1.86 | <0.001 | 1.45 | 1.23 | 1.71 | <0.001 | 1.24 | 1.07 | 1.44 | <0.001 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.01 | 1.00 | 1.02 | 0.066 | 1.01 | 1.00 | 1.02 | 0.018 | 1.01 | 1.00 | 1.01 | 0.034 |
| BMI | 0.99 | 0.98 | 1.00 | 0.042 | 1.00 | 0.99 | 1.00 | 0.313 | 1.00 | 1.00 | 1.01 | 0.417 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.58 | 1.40 | 1.78 | <0.001 | 1.39 | 1.27 | 1.52 | <0.001 | 1.26 | 1.17 | 1.36 | <0.001 |
| Other | 1.09 | 0.74 | 1.61 | 0.560 | 0.96 | 0.70 | 1.32 | 0.749 | 0.97 | 0.74 | 1.27 | 0.763 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.02 | 0.86 | 1.20 | 0.765 | 1.06 | 0.93 | 1.20 | 0.272 | 1.06 | 0.96 | 1.18 | 0.136 |
| 3 | 1.09 | 0.93 | 1.28 | 0.160 | 1.15 | 1.01 | 1.31 | 0.004 | 1.11 | 1.00 | 1.23 | 0.012 |
| 4 | 1.07 | 0.89 | 1.28 | 0.346 | 1.16 | 1.01 | 1.34 | 0.004 | 1.13 | 1.00 | 1.27 | 0.011 |
| 5, most deprived | 1.22 | 1.00 | 1.48 | 0.008 | 1.25 | 1.07 | 1.45 | <0.001 | 1.16 | 1.02 | 1.33 | 0.004 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.03 | 0.69 | 1.56 | 0.836 | 0.80 | 0.58 | 1.11 | 0.076 | 0.79 | 0.56 | 1.10 | 0.069 |
| London | 0.92 | 0.66 | 1.29 | 0.524 | 0.80 | 0.63 | 1.02 | 0.018 | 0.80 | 0.62 | 1.03 | 0.025 |
| North East | 1.16 | 0.79 | 1.72 | 0.313 | 0.99 | 0.76 | 1.30 | 0.930 | 1.00 | 0.75 | 1.34 | 0.996 |
| North West | 1.10 | 0.78 | 1.55 | 0.485 | 0.98 | 0.77 | 1.25 | 0.828 | 0.96 | 0.74 | 1.24 | 0.655 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South Central | 1.04 | 0.71 | 1.51 | 0.795 | 0.90 | 0.69 | 1.16 | 0.278 | 0.80 | 0.61 | 1.05 | 0.032 |
| South East | 1.00 | 0.71 | 1.42 | 0.989 | 0.94 | 0.73 | 1.22 | 0.557 | 0.92 | 0.70 | 1.20 | 0.404 |
| South West | 0.98 | 0.68 | 1.42 | 0.883 | 0.87 | 0.65 | 1.15 | 0.192 | 0.88 | 0.66 | 1.17 | 0.245 |
| West Midlands | 1.02 | 0.72 | 1.45 | 0.883 | 0.92 | 0.71 | 1.21 | 0.441 | 0.87 | 0.66 | 1.16 | 0.218 |
| Yorkshire & Humber | 0.97 | 0.66 | 1.44 | 0.865 | 0.87 | 0.63 | 1.19 | 0.249 | 0.94 | 0.69 | 1.28 | 0.630 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.02 | 0.89 | 1.16 | 0.739 | 0.95 | 0.86 | 1.06 | 0.233 | 1.00 | 0.92 | 1.09 | 0.889 |
| Light-smoker | 1.07 | 0.94 | 1.21 | 0.195 | 1.05 | 0.95 | 1.16 | 0.199 | 0.98 | 0.90 | 1.07 | 0.581 |
| Moderate-smoker | 1.09 | 0.71 | 1.68 | 0.602 | 1.03 | 0.72 | 1.47 | 0.840 | 0.97 | 0.72 | 1.31 | 0.787 |
| Heavy-smoker | 1.09 | 0.59 | 2.00 | 0.722 | 0.90 | 0.54 | 1.48 | 0.570 | 0.80 | 0.52 | 1.23 | 0.173 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.00 | 0.89 | 1.13 | 0.978 | 1.04 | 0.95 | 1.14 | 0.244 | 1.02 | 0.95 | 1.10 | 0.464 |
| Medium | 0.82 | 0.67 | 1.01 | 0.012 | 0.91 | 0.78 | 1.06 | 0.106 | 0.93 | 0.82 | 1.05 | 0.127 |
| Heavy | 1.18 | 0.80 | 1.74 | 0.278 | 0.90 | 0.64 | 1.27 | 0.425 | 0.79 | 0.58 | 1.08 | 0.051 |
| Very heavy | 0.85 | 0.56 | 1.29 | 0.321 | 0.94 | 0.68 | 1.28 | 0.584 | 0.87 | 0.66 | 1.15 | 0.208 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.26 | 0.91 | 1.76 | 0.070 | 1.30 | 0.99 | 1.71 | 0.012 | 1.02 | 0.80 | 1.31 | 0.797 |
| Asian | 1.31 | 0.98 | 1.75 | 0.017 | 1.27 | 1.00 | 1.60 | 0.009 | 1.06 | 0.86 | 1.30 | 0.511 |
| Other | 1.28 | 0.95 | 1.72 | 0.036 | 1.13 | 0.88 | 1.44 | 0.205 | 1.00 | 0.82 | 1.23 | 0.986 |
| | | | | | | | | | | | | |
| Age | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.01 | 1.01 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.94 | 0.84 | 1.05 | 0.165 | 0.94 | 0.86 | 1.03 | 0.069 | 0.89 | 0.83 | 0.96 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.89 | 0.18 | 4.36 | 0.850 | 1.18 | 0.33 | 4.25 | 0.737 | 1.01 | 0.40 | 2.53 | 0.974 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2011 to 2015 | 0.89 | 0.18 | 4.38 | 0.847 | 1.17 | 0.33 | 4.22 | 0.746 | 1.02 | 0.41 | 2.56 | 0.953 |
| 2016 to 2020 | 1.24 | 0.25 | 6.10 | 0.729 | 1.49 | 0.41 | 5.34 | 0.424 | 1.15 | 0.46 | 2.90 | 0.691 |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.33 | 0.99 | 1.80 | 0.014 | 1.20 | 0.95 | 1.52 | 0.048 | 1.11 | 0.92 | 1.35 | 0.143 |
| Stroke | 1.10 | 0.77 | 1.57 | 0.512 | 1.21 | 0.93 | 1.57 | 0.062 | 1.10 | 0.89 | 1.37 | 0.226 |
| Diabetes | 1.22 | 0.96 | 1.54 | 0.032 | 1.15 | 0.95 | 1.38 | 0.059 | 1.16 | 1.00 | 1.34 | 0.010 |
| Epilepsy | 0.89 | 0.54 | 1.46 | 0.540 | 0.98 | 0.67 | 1.44 | 0.910 | 1.04 | 0.77 | 1.39 | 0.761 |
| Hypothyroidism | 1.08 | 0.82 | 1.42 | 0.473 | 1.04 | 0.84 | 1.30 | 0.609 | 1.07 | 0.90 | 1.27 | 0.294 |
| Arthritis | 0.96 | 0.79 | 1.18 | 0.650 | 1.03 | 0.89 | 1.20 | 0.597 | 1.09 | 0.96 | 1.23 | 0.076 |
| Anxiety | 1.34 | 1.17 | 1.55 | <0.001 | 1.31 | 1.19 | 1.46 | <0.001 | 1.39 | 1.27 | 1.51 | <0.001 |
| Migraine | 1.00 | 0.82 | 1.23 | 0.950 | 1.06 | 0.91 | 1.23 | 0.347 | 1.10 | 0.98 | 1.25 | 0.036 |
| Cancer | 1.20 | 1.00 | 1.45 | 0.010 | 1.20 | 1.05 | 1.38 | 0.001 | 1.17 | 1.04 | 1.31 | <0.001 |
| Asthma | 1.18 | 1.03 | 1.35 | 0.001 | 1.22 | 1.10 | 1.35 | <0.001 | 1.26 | 1.16 | 1.37 | <0.001 |
| Renal failure | 0.88 | 0.36 | 2.15 | 0.715 | 1.12 | 0.59 | 2.10 | 0.648 | 1.10 | 0.64 | 1.87 | 0.659 |
| Liver failure | 1.03 | 0.58 | 1.83 | 0.905 | 1.19 | 0.80 | 1.76 | 0.252 | 1.32 | 0.97 | 1.79 | 0.021 |
| Osteoporosis | 0.81 | 0.47 | 1.38 | 0.309 | 0.91 | 0.61 | 1.36 | 0.562 | 0.99 | 0.72 | 1.35 | 0.909 |
| Suicidality | 1.07 | 0.78 | 1.46 | 0.595 | 1.16 | 0.93 | 1.45 | 0.079 | 1.13 | 0.94 | 1.37 | 0.082 |
| Antihypertensive | 0.89 | 0.73 | 1.07 | 0.105 | 1.01 | 0.87 | 1.17 | 0.913 | 0.99 | 0.88 | 1.13 | 0.916 |
| Aspirin | 0.93 | 0.68 | 1.28 | 0.578 | 0.97 | 0.78 | 1.21 | 0.729 | 0.98 | 0.82 | 1.18 | 0.822 |
| Anticoagulants | 1.24 | 0.78 | 1.95 | 0.233 | 1.27 | 0.88 | 1.84 | 0.094 | 1.27 | 0.94 | 1.72 | 0.040 |
| NSAIDs | 1.05 | 0.80 | 1.38 | 0.635 | 1.10 | 0.87 | 1.38 | 0.304 | 1.11 | 0.92 | 1.34 | 0.153 |
| Anticonvulsants | 1.33 | 0.86 | 2.07 | 0.095 | 1.25 | 0.86 | 1.81 | 0.119 | 1.29 | 0.95 | 1.75 | 0.035 |
| Hypnotics | 1.19 | 1.00 | 1.43 | 0.011 | 1.10 | 0.96 | 1.26 | 0.075 | 1.09 | 0.97 | 1.22 | 0.070 |
| Bisphosphonates | 1.30 | 0.54 | 3.12 | 0.443 | 1.18 | 0.59 | 2.34 | 0.536 | 1.26 | 0.71 | 2.22 | 0.302 |
| Contraceptives | 0.98 | 0.78 | 1.24 | 0.838 | 1.00 | 0.85 | 1.19 | 0.974 | 1.08 | 0.95 | 1.23 | 0.144 |
| *Constant* | 0.02 | 0.00 | 0.12 | <0.001 | 0.03 | 0.01 | 0.13 | <0.001 | 0.06 | 0.02 | 0.16 | <0.001 |

| | **Tolerability *(FSA, N = 673,177)*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | **6 months** | | | **12 months** | | |
| | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Statins*** | 0.92 | 0.87 | 0.98 | 0.001 | 0.94 | 0.89 | 0.99 | 0.001 | 1.02 | 0.97 | 1.06 | 0.351 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 2.34 | 2.205 | 2.47 | 0.00 | 1.85 | 1.77 | 1.95 | <0.001 | 1.44 | 1.37 | 1.51 | <0.001 |
| MAOIs | 0.50 | 0.084 | 2.96 | 0.31 | 2.14 | 0.98 | 4.65 | 0.012 | 1.48 | 0.70 | 3.16 | 0.179 |
| Other antidepressants | 1.38 | 1.309 | 1.46 | 0.00 | 1.29 | 1.23 | 1.35 | <0.001 | 1.15 | 1.11 | 1.20 | <0.001 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.00 | 0.998 | 1.01 | 0.13 | 1.00 | 1.00 | 1.01 | 0.031 | 1.00 | 1.00 | 1.00 | 0.083 |
| BMI | 0.99 | 0.990 | 1.00 | 0.00 | 1.00 | 0.99 | 1.00 | <0.001 | 1.00 | 1.00 | 1.00 | 0.466 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.43 | 1.375 | 1.48 | 0.00 | 1.33 | 1.29 | 1.37 | <0.001 | 1.25 | 1.22 | 1.28 | <0.001 |
| Other | 0.73 | 0.654 | 0.81 | 0.00 | 0.75 | 0.69 | 0.82 | <0.001 | 0.79 | 0.73 | 0.86 | <0.001 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.03 | 0.989 | 1.08 | 0.05 | 1.04 | 1.01 | 1.08 | 0.003 | 1.03 | 1.00 | 1.06 | 0.017 |
| 3 | 1.11 | 1.059 | 1.16 | 0.00 | 1.11 | 1.07 | 1.16 | <0.001 | 1.06 | 1.02 | 1.10 | <0.001 |
| 4 | 1.13 | 1.067 | 1.19 | 0.00 | 1.13 | 1.07 | 1.18 | <0.001 | 1.05 | 1.01 | 1.10 | 0.002 |
| 5, most deprived | 1.21 | 1.135 | 1.29 | 0.00 | 1.19 | 1.12 | 1.25 | <0.001 | 1.10 | 1.04 | 1.15 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.88 | 0.737 | 1.06 | 0.08 | 0.91 | 0.78 | 1.07 | 0.128 | 0.93 | 0.78 | 1.12 | 0.341 |
| London | 0.91 | 0.792 | 1.04 | 0.07 | 0.88 | 0.80 | 0.97 | 0.001 | 0.86 | 0.77 | 0.95 | <0.001 |
| North East | 0.98 | 0.810 | 1.18 | 0.74 | 0.99 | 0.86 | 1.15 | 0.901 | 1.01 | 0.86 | 1.19 | 0.859 |
| North West | 1.03 | 0.901 | 1.18 | 0.55 | 1.02 | 0.93 | 1.13 | 0.594 | 1.00 | 0.90 | 1.11 | 0.965 |
| South Central | 0.92 | 0.785 | 1.07 | 0.15 | 0.91 | 0.80 | 1.02 | 0.033 | 0.87 | 0.77 | 0.99 | 0.006 |
| South East | 0.99 | 0.853 | 1.14 | 0.79 | 0.96 | 0.85 | 1.07 | 0.308 | 0.93 | 0.82 | 1.06 | 0.142 |
| South West | 1.02 | 0.881 | 1.18 | 0.71 | 1.04 | 0.93 | 1.16 | 0.390 | 1.02 | 0.90 | 1.15 | 0.730 |
| West Midlands | 0.96 | 0.834 | 1.11 | 0.50 | 0.95 | 0.85 | 1.05 | 0.178 | 0.93 | 0.82 | 1.04 | 0.090 |
| Yorkshire & Humber | 0.94 | 0.785 | 1.13 | 0.40 | 0.94 | 0.82 | 1.09 | 0.275 | 0.99 | 0.85 | 1.15 | 0.879 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.00 | 0.963 | 1.04 | 0.89 | 1.00 | 0.96 | 1.03 | 0.770 | 1.03 | 1.00 | 1.06 | 0.011 |
| Light-smoker | 1.06 | 1.023 | 1.10 | 0.00 | 1.07 | 1.04 | 1.10 | <0.001 | 1.00 | 0.98 | 1.03 | 0.813 |
| Moderate-smoker | 0.99 | 0.876 | 1.11 | 0.75 | 0.99 | 0.90 | 1.10 | 0.837 | 0.92 | 0.84 | 1.01 | 0.021 |
| Heavy-smoker | 1.09 | 0.934 | 1.28 | 0.15 | 1.08 | 0.95 | 1.22 | 0.127 | 0.98 | 0.87 | 1.10 | 0.639 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.99 | 0.955 | 1.02 | 0.39 | 0.99 | 0.96 | 1.02 | 0.254 | 0.99 | 0.97 | 1.01 | 0.255 |
| Medium | 0.99 | 0.937 | 1.06 | 0.82 | 1.00 | 0.95 | 1.05 | 0.867 | 1.00 | 0.95 | 1.04 | 0.897 |
| Heavy | 1.02 | 0.880 | 1.19 | 0.68 | 0.98 | 0.86 | 1.11 | 0.621 | 0.95 | 0.85 | 1.08 | 0.298 |
| Very heavy | 0.94 | 0.815 | 1.09 | 0.28 | 0.97 | 0.85 | 1.10 | 0.472 | 0.94 | 0.84 | 1.05 | 0.150 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.15 | 1.064 | 1.24 | 0.00 | 1.12 | 1.06 | 1.18 | <0.001 | 1.00 | 0.95 | 1.05 | 0.932 |
| Asian | 1.45 | 1.362 | 1.55 | 0.00 | 1.35 | 1.28 | 1.43 | <0.001 | 1.18 | 1.12 | 1.24 | <0.001 |
| Other | 1.30 | 1.196 | 1.41 | 0.00 | 1.22 | 1.14 | 1.31 | <0.001 | 1.09 | 1.02 | 1.15 | <0.001 |
| | | | | | | | | | | | | |
| Age | 1.01 | 1.008 | 1.01 | 0.00 | 1.01 | 1.01 | 1.01 | <0.001 | 1.01 | 1.01 | 1.01 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.93 | 0.900 | 0.96 | 0.00 | 0.91 | 0.89 | 0.93 | <0.001 | 0.86 | 0.84 | 0.88 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.01 | 0.957 | 1.06 | 0.78 | 0.99 | 0.95 | 1.03 | 0.413 | 1.04 | 0.99 | 1.08 | 0.026 |
| 2011 to 2015 | 1.04 | 0.985 | 1.10 | 0.06 | 1.01 | 0.96 | 1.06 | 0.661 | 1.07 | 1.02 | 1.12 | <0.001 |
| 2016 to 2020 | 1.21 | 1.143 | 1.27 | 0.00 | 1.14 | 1.09 | 1.20 | <0.001 | 1.12 | 1.07 | 1.18 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.16 | 1.071 | 1.25 | 0.00 | 1.15 | 1.08 | 1.23 | <0.001 | 1.11 | 1.05 | 1.17 | <0.001 |
| Stroke | 1.03 | 0.958 | 1.11 | 0.27 | 1.13 | 1.06 | 1.19 | <0.001 | 1.14 | 1.08 | 1.20 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diabetes | 1.08 | 1.010 | 1.15 | 0.00 | 1.13 | 1.06 | 1.19 | <0.001 | 1.14 | 1.09 | 1.20 | <0.001 |
| Epilepsy | 1.01 | 0.887 | 1.14 | 0.91 | 1.03 | 0.93 | 1.13 | 0.474 | 1.07 | 0.98 | 1.16 | 0.042 |
| Hypothyroidism | 1.02 | 0.949 | 1.09 | 0.50 | 1.02 | 0.96 | 1.08 | 0.412 | 1.06 | 1.01 | 1.12 | 0.001 |
| Arthritis | 1.08 | 1.021 | 1.14 | 0.00 | 1.10 | 1.05 | 1.14 | <0.001 | 1.08 | 1.04 | 1.12 | <0.001 |
| Anxiety | 1.24 | 1.187 | 1.30 | 0.00 | 1.21 | 1.17 | 1.26 | <0.001 | 1.27 | 1.23 | 1.31 | <0.001 |
| Migraine | 1.08 | 1.018 | 1.14 | 0.00 | 1.09 | 1.04 | 1.14 | <0.001 | 1.14 | 1.10 | 1.18 | <0.001 |
| Cancer | 1.21 | 1.156 | 1.27 | 0.00 | 1.23 | 1.19 | 1.28 | <0.001 | 1.18 | 1.14 | 1.22 | <0.001 |
| Asthma | 1.14 | 1.098 | 1.18 | 0.00 | 1.19 | 1.15 | 1.22 | <0.001 | 1.25 | 1.22 | 1.28 | <0.001 |
| Renal failure | 1.24 | 1.023 | 1.51 | 0.00 | 1.29 | 1.09 | 1.52 | <0.001 | 1.23 | 1.07 | 1.42 | <0.001 |
| Liver failure | 1.14 | 0.991 | 1.32 | 0.02 | 1.20 | 1.07 | 1.34 | <0.001 | 1.21 | 1.10 | 1.33 | <0.001 |
| Osteoporosis | 1.08 | 0.965 | 1.20 | 0.08 | 1.13 | 1.04 | 1.24 | <0.001 | 1.10 | 1.02 | 1.19 | 0.001 |
| Suicidality | 1.19 | 1.099 | 1.30 | 0.00 | 1.21 | 1.13 | 1.29 | <0.001 | 1.16 | 1.10 | 1.24 | <0.001 |
| Antihypertensive | 1.01 | 0.954 | 1.07 | 0.68 | 0.99 | 0.95 | 1.04 | 0.594 | 1.01 | 0.97 | 1.05 | 0.514 |
| Aspirin | 1.05 | 0.975 | 1.13 | 0.09 | 1.09 | 1.03 | 1.16 | <0.001 | 1.08 | 1.03 | 1.14 | <0.001 |
| Anticoagulants | 1.26 | 1.142 | 1.39 | 0.00 | 1.37 | 1.26 | 1.49 | <0.001 | 1.36 | 1.26 | 1.46 | <0.001 |
| NSAIDs | 1.17 | 1.090 | 1.25 | 0.00 | 1.16 | 1.10 | 1.22 | <0.001 | 1.17 | 1.11 | 1.23 | <0.001 |
| Anticonvulsants | 1.16 | 1.040 | 1.28 | 0.00 | 1.19 | 1.09 | 1.29 | <0.001 | 1.32 | 1.22 | 1.41 | <0.001 |
| Hypnotics | 1.19 | 1.135 | 1.25 | 0.00 | 1.17 | 1.12 | 1.21 | <0.001 | 1.13 | 1.09 | 1.17 | <0.001 |
| Bisphosphonates | 1.05 | 0.879 | 1.26 | 0.48 | 1.10 | 0.94 | 1.28 | 0.123 | 1.16 | 1.02 | 1.32 | 0.002 |
| Contraceptives | 0.95 | 0.885 | 1.01 | 0.03 | 0.99 | 0.94 | 1.04 | 0.539 | 1.07 | 1.03 | 1.12 | <0.001 |
| *Constant* | 0.03 | 0.023 | 0.03 | 0.00 | 0.05 | 0.05 | 0.06 | <0.001 | 0.07 | 0.06 | 0.08 | <0.001 |

***Table A5.4c*** *Regression analyses for safety (any adverse event) at 2 months, 6 months, and 12 months; complete case analysis (CCA) and full set analysis (FSA)*

| | **Safety, any adverse event *(CCA, N= 63,801)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | | **6 months** | | | | **12 months** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 0.94 | 0.85 | 1.05 | 0.140 | 0.98 | 0.88 | 1.09 | 0.605 | 1.00 | 0.89 | 1.12 | 0.961 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 1.02 | 0.87 | 1.20 | 0.767 | 1.05 | 0.90 | 1.22 | 0.444 | 1.07 | 0.90 | 1.27 | 0.314 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 1.06 | 0.95 | 1.19 | 0.170 | 1.07 | 0.96 | 1.20 | 0.119 | 1.07 | 0.96 | 1.19 | 0.112 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.00 | 1.00 | 1.01 | 0.419 | 1.00 | 0.99 | 1.00 | 0.182 | 1.00 | 0.99 | 1.00 | 0.433 |
| BMI | 1.00 | 0.99 | 1.00 | 0.021 | 1.00 | 1.00 | 1.00 | 0.757 | 1.00 | 1.00 | 1.01 | 0.057 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.93 | 1.78 | 2.09 | <0.001 | 1.83 | 1.69 | 1.97 | <0.001 | 1.75 | 1.60 | 1.90 | <0.001 |
| Other | 0.57 | 0.46 | 0.70 | <0.001 | 0.65 | 0.54 | 0.79 | <0.001 | 0.70 | 0.58 | 0.84 | <0.001 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.98 | 0.91 | 1.05 | 0.484 | 1.00 | 0.93 | 1.07 | 0.941 | 1.01 | 0.94 | 1.08 | 0.825 |
| 3 | 1.05 | 0.96 | 1.14 | 0.161 | 1.05 | 0.97 | 1.14 | 0.121 | 1.05 | 0.96 | 1.15 | 0.186 |
| 4 | 1.04 | 0.94 | 1.16 | 0.299 | 1.10 | 0.99 | 1.22 | 0.019 | 1.09 | 0.98 | 1.21 | 0.032 |
| 5, most deprived | 1.11 | 0.99 | 1.24 | 0.023 | 1.15 | 1.03 | 1.29 | 0.001 | 1.15 | 1.02 | 1.29 | 0.002 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.68 | 0.41 | 1.11 | 0.042 | 0.70 | 0.43 | 1.15 | 0.066 | 0.72 | 0.43 | 1.21 | 0.106 |
| London | 0.75 | 0.51 | 1.09 | 0.049 | 0.79 | 0.55 | 1.13 | 0.088 | 0.80 | 0.57 | 1.14 | 0.107 |
| North East | 0.80 | 0.51 | 1.24 | 0.185 | 0.84 | 0.54 | 1.31 | 0.318 | 0.93 | 0.60 | 1.43 | 0.664 |
| North West | 0.83 | 0.56 | 1.23 | 0.223 | 0.87 | 0.60 | 1.27 | 0.357 | 0.93 | 0.64 | 1.34 | 0.604 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South Central | 0.66 | 0.44 | 0.99 | 0.009 | 0.70 | 0.47 | 1.03 | 0.018 | 0.73 | 0.50 | 1.08 | 0.037 |
| South East | 0.82 | 0.54 | 1.24 | 0.216 | 0.89 | 0.59 | 1.33 | 0.459 | 0.91 | 0.61 | 1.34 | 0.511 |
| South West | 0.77 | 0.51 | 1.17 | 0.105 | 0.81 | 0.54 | 1.22 | 0.190 | 0.86 | 0.57 | 1.29 | 0.323 |
| West Midlands | 0.72 | 0.47 | 1.11 | 0.051 | 0.78 | 0.52 | 1.17 | 0.109 | 0.82 | 0.56 | 1.22 | 0.200 |
| Yorkshire & Humber | 0.90 | 0.56 | 1.44 | 0.558 | 0.90 | 0.57 | 1.42 | 0.540 | 0.92 | 0.58 | 1.44 | 0.625 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.04 | 0.98 | 1.11 | 0.065 | 1.04 | 0.98 | 1.11 | 0.056 | 1.04 | 0.97 | 1.11 | 0.143 |
| Light-smoker | 0.94 | 0.89 | 1.00 | 0.006 | 0.97 | 0.92 | 1.03 | 0.163 | 0.98 | 0.92 | 1.04 | 0.385 |
| Moderate-smoker | 0.94 | 0.77 | 1.16 | 0.458 | 0.96 | 0.80 | 1.16 | 0.561 | 0.96 | 0.79 | 1.17 | 0.596 |
| Heavy-smoker | 0.99 | 0.76 | 1.28 | 0.898 | 0.89 | 0.69 | 1.15 | 0.240 | 0.82 | 0.62 | 1.08 | 0.068 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.02 | 0.97 | 1.08 | 0.359 | 1.02 | 0.97 | 1.08 | 0.296 | 1.01 | 0.96 | 1.07 | 0.612 |
| Medium | 1.00 | 0.93 | 1.09 | 0.874 | 1.06 | 0.98 | 1.15 | 0.064 | 1.04 | 0.95 | 1.13 | 0.271 |
| Heavy | 1.05 | 0.87 | 1.26 | 0.529 | 0.96 | 0.80 | 1.16 | 0.618 | 0.92 | 0.76 | 1.12 | 0.285 |
| Very heavy | 0.97 | 0.82 | 1.15 | 0.620 | 1.01 | 0.85 | 1.20 | 0.859 | 0.94 | 0.78 | 1.13 | 0.374 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.86 | 0.72 | 1.03 | 0.028 | 1.09 | 0.92 | 1.30 | 0.191 | 1.17 | 0.97 | 1.41 | 0.034 |
| Asian | 0.87 | 0.75 | 1.00 | 0.012 | 0.97 | 0.84 | 1.13 | 0.607 | 1.02 | 0.86 | 1.20 | 0.777 |
| Other | 1.00 | 0.87 | 1.15 | 1.000 | 1.09 | 0.94 | 1.26 | 0.124 | 1.06 | 0.92 | 1.24 | 0.286 |
| | | | | | | | | | | | | |
| Age | 1.00 | 1.00 | 1.01 | 0.001 | 1.00 | 1.00 | 1.00 | 0.008 | 1.01 | 1.00 | 1.01 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.95 | 0.91 | 1.00 | 0.013 | 0.86 | 0.82 | 0.90 | <0.001 | 0.79 | 0.75 | 0.83 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.90 | 0.62 | 5.78 | 0.138 | 2.20 | 1.08 | 4.48 | 0.004 | 2.36 | 1.43 | 3.88 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2011 to 2015 | 2.35 | 0.77 | 7.17 | 0.048 | 2.51 | 1.24 | 5.10 | 0.001 | 2.61 | 1.59 | 4.29 | <0.001 |
| 2016 to 2020 | 3.21 | 1.05 | 9.82 | 0.007 | 3.10 | 1.52 | 6.33 | <0.001 | 2.86 | 1.74 | 4.72 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.07 | 0.92 | 1.23 | 0.247 | 1.22 | 1.05 | 1.42 | 0.001 | 1.40 | 1.17 | 1.68 | <0.001 |
| Stroke | 1.14 | 0.97 | 1.34 | 0.039 | 1.23 | 1.04 | 1.45 | 0.002 | 1.25 | 1.01 | 1.53 | 0.007 |
| Diabetes | 1.02 | 0.92 | 1.13 | 0.634 | 1.18 | 1.06 | 1.31 | <0.001 | 1.33 | 1.18 | 1.51 | <0.001 |
| Epilepsy | 1.18 | 0.96 | 1.44 | 0.042 | 1.23 | 0.98 | 1.53 | 0.018 | 1.23 | 0.96 | 1.58 | 0.034 |
| Hypothyroidism | 1.00 | 0.88 | 1.12 | 0.928 | 1.00 | 0.88 | 1.14 | 0.947 | 0.99 | 0.86 | 1.14 | 0.855 |
| Arthritis | 1.10 | 0.99 | 1.21 | 0.015 | 1.17 | 1.06 | 1.29 | <0.001 | 1.26 | 1.12 | 1.41 | <0.001 |
| Anxiety | 1.80 | 1.67 | 1.93 | <0.001 | 1.79 | 1.67 | 1.92 | <0.001 | 1.78 | 1.64 | 1.92 | <0.001 |
| Migraine | 1.14 | 1.05 | 1.24 | <0.001 | 1.27 | 1.16 | 1.39 | <0.001 | 1.34 | 1.22 | 1.48 | <0.001 |
| Cancer | 1.08 | 1.00 | 1.18 | 0.012 | 1.17 | 1.07 | 1.28 | <0.001 | 1.20 | 1.09 | 1.32 | <0.001 |
| Asthma | 1.18 | 1.12 | 1.25 | <0.001 | 1.38 | 1.29 | 1.47 | <0.001 | 1.52 | 1.42 | 1.63 | <0.001 |
| Renal failure | 1.31 | 0.89 | 1.95 | 0.074 | 1.69 | 1.05 | 2.74 | 0.005 | 1.93 | 1.09 | 3.42 | 0.003 |
| Liver failure | 1.15 | 0.91 | 1.45 | 0.118 | 1.40 | 1.10 | 1.79 | <0.001 | 1.41 | 1.07 | 1.86 | 0.001 |
| Osteoporosis | 1.07 | 0.82 | 1.39 | 0.515 | 1.13 | 0.86 | 1.47 | 0.250 | 1.15 | 0.85 | 1.55 | 0.245 |
| Suicidality | 1.19 | 1.04 | 1.35 | 0.001 | 1.23 | 1.08 | 1.42 | <0.001 | 1.24 | 1.07 | 1.43 | <0.001 |
| Antihypertensive | 1.05 | 0.96 | 1.15 | 0.147 | 1.09 | 1.00 | 1.19 | 0.008 | 1.09 | 0.98 | 1.21 | 0.039 |
| Aspirin | 1.07 | 0.94 | 1.22 | 0.157 | 1.08 | 0.94 | 1.23 | 0.159 | 1.13 | 0.97 | 1.32 | 0.039 |
| Anticoagulants | 1.24 | 0.98 | 1.57 | 0.019 | 1.33 | 1.05 | 1.69 | 0.002 | 1.71 | 1.27 | 2.31 | <0.001 |
| NSAIDs | 1.04 | 0.92 | 1.18 | 0.418 | 1.11 | 0.97 | 1.26 | 0.047 | 1.24 | 1.07 | 1.43 | <0.001 |
| Anticonvulsants | 1.18 | 0.94 | 1.48 | 0.064 | 1.38 | 1.08 | 1.75 | 0.001 | 1.47 | 1.11 | 1.97 | 0.001 |
| Hypnotics | 1.22 | 1.12 | 1.34 | <0.001 | 1.16 | 1.06 | 1.26 | <0.001 | 1.14 | 1.03 | 1.25 | 0.001 |
| Bisphosphonates | 1.19 | 0.77 | 1.84 | 0.314 | 1.27 | 0.80 | 2.00 | 0.180 | 1.09 | 0.64 | 1.86 | 0.683 |
| Contraceptives | 1.00 | 0.92 | 1.10 | 0.893 | 1.07 | 0.97 | 1.17 | 0.063 | 1.08 | 0.97 | 1.20 | 0.054 |
| *Constant* | 0.29 | 0.09 | 0.95 | 0.007 | 0.47 | 0.21 | 1.05 | 0.015 | 0.60 | 0.32 | 1.13 | 0.040 |

| | **Safety, any adverse event *(FSA, N = 673,177)*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | **6 months** | | | **12 months** | | |
| | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Statins*** | 0.96 | 0.92 | 0.99 | 0.001 | 0.98 | 0.95 | 1.02 | 0.174 | 0.99 | 0.95 | 1.03 | 0.468 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 1.18 | 1.13 | 1.24 | <0.001 | 1.16 | 1.11 | 1.21 | <0.001 | 1.16 | 1.11 | 1.22 | <0.001 |
| MAOIs | 0.91 | 0.52 | 1.60 | 0.655 | 0.92 | 0.53 | 1.60 | 0.691 | 0.85 | 0.48 | 1.52 | 0.474 |
| Other antidepressants | 1.04 | 1.01 | 1.08 | 0.001 | 1.05 | 1.01 | 1.09 | <0.001 | 1.04 | 1.00 | 1.07 | 0.015 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.00 | 1.00 | 1.00 | 0.213 | 1.00 | 1.00 | 1.00 | 0.855 | 1.00 | 1.00 | 1.00 | 0.786 |
| BMI | 1.00 | 1.00 | 1.00 | 0.278 | 1.00 | 1.00 | 1.00 | 0.018 | 1.00 | 1.00 | 1.00 | <0.001 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.70 | 1.63 | 1.77 | <0.001 | 1.66 | 1.59 | 1.73 | <0.001 | 1.63 | 1.57 | 1.70 | <0.001 |
| Other | 0.52 | 0.47 | 0.56 | <0.001 | 0.61 | 0.57 | 0.65 | <0.001 | 0.65 | 0.60 | 0.70 | <0.001 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.00 | 0.97 | 1.04 | 0.902 | 1.02 | 0.99 | 1.06 | 0.124 | 1.02 | 0.99 | 1.06 | 0.117 |
| 3 | 1.00 | 0.96 | 1.04 | 0.896 | 1.04 | 1.00 | 1.09 | 0.014 | 1.04 | 0.99 | 1.09 | 0.030 |
| 4 | 0.98 | 0.93 | 1.03 | 0.313 | 1.03 | 0.98 | 1.09 | 0.129 | 1.03 | 0.97 | 1.09 | 0.287 |
| 5, most deprived | 1.06 | 0.99 | 1.13 | 0.020 | 1.12 | 1.04 | 1.20 | <0.001 | 1.09 | 1.01 | 1.17 | 0.002 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.81 | 0.60 | 1.11 | 0.091 | 0.82 | 0.60 | 1.12 | 0.104 | 0.84 | 0.62 | 1.14 | 0.137 |
| London | 0.79 | 0.66 | 0.94 | 0.001 | 0.83 | 0.69 | 1.00 | 0.009 | 0.85 | 0.70 | 1.02 | 0.024 |
| North East | 0.94 | 0.71 | 1.25 | 0.588 | 0.96 | 0.72 | 1.28 | 0.696 | 0.98 | 0.73 | 1.33 | 0.879 |
| North West | 0.91 | 0.75 | 1.09 | 0.176 | 0.95 | 0.79 | 1.16 | 0.531 | 0.99 | 0.81 | 1.21 | 0.879 |
| South Central | 0.72 | 0.58 | 0.89 | <0.001 | 0.75 | 0.60 | 0.93 | 0.001 | 0.77 | 0.62 | 0.97 | 0.003 |
| South East | 0.76 | 0.60 | 0.95 | 0.002 | 0.79 | 0.63 | 1.00 | 0.011 | 0.81 | 0.64 | 1.03 | 0.024 |
| South West | 0.93 | 0.76 | 1.15 | 0.379 | 0.96 | 0.78 | 1.19 | 0.637 | 0.98 | 0.79 | 1.22 | 0.817 |
| West Midlands | 0.75 | 0.61 | 0.91 | <0.001 | 0.80 | 0.65 | 0.98 | 0.004 | 0.84 | 0.68 | 1.04 | 0.032 |
| Yorkshire & Humber | 0.92 | 0.72 | 1.18 | 0.389 | 0.92 | 0.71 | 1.19 | 0.394 | 0.93 | 0.71 | 1.21 | 0.449 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.02 | 0.99 | 1.04 | 0.083 | 1.04 | 1.02 | 1.07 | <0.001 | 1.05 | 1.02 | 1.08 | <0.001 |
| Light-smoker | 0.94 | 0.92 | 0.96 | <0.001 | 0.97 | 0.95 | 0.99 | <0.001 | 0.98 | 0.96 | 1.00 | 0.029 |
| Moderate-smoker | 0.91 | 0.86 | 0.97 | <0.001 | 0.94 | 0.89 | 1.01 | 0.020 | 0.96 | 0.90 | 1.03 | 0.133 |
| Heavy-smoker | 0.96 | 0.87 | 1.05 | 0.266 | 0.97 | 0.88 | 1.06 | 0.359 | 0.96 | 0.87 | 1.05 | 0.244 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.99 | 0.98 | 1.01 | 0.423 | 0.99 | 0.97 | 1.01 | 0.173 | 0.98 | 0.96 | 1.00 | 0.031 |
| Medium | 1.01 | 0.98 | 1.04 | 0.414 | 1.01 | 0.98 | 1.04 | 0.232 | 1.00 | 0.97 | 1.04 | 0.725 |
| Heavy | 1.00 | 0.92 | 1.08 | 0.928 | 1.01 | 0.94 | 1.08 | 0.733 | 1.01 | 0.93 | 1.09 | 0.760 |
| Very heavy | 1.00 | 0.94 | 1.07 | 0.988 | 1.00 | 0.94 | 1.07 | 0.968 | 0.99 | 0.92 | 1.06 | 0.693 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.91 | 0.87 | 0.95 | <0.001 | 0.94 | 0.90 | 0.98 | <0.001 | 0.93 | 0.89 | 0.98 | <0.001 |
| Asian | 0.95 | 0.90 | 1.01 | 0.033 | 1.08 | 1.01 | 1.15 | 0.003 | 1.14 | 1.06 | 1.22 | <0.001 |
| Other | 0.97 | 0.92 | 1.01 | 0.057 | 1.03 | 0.98 | 1.08 | 0.181 | 1.03 | 0.98 | 1.09 | 0.109 |
| | | | | | | | | | | | | |
| Age | 1.00 | 1.00 | 1.01 | <0.001 | 1.00 | 1.00 | 1.01 | <0.001 | 1.01 | 1.01 | 1.01 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.93 | 0.92 | 0.94 | <0.001 | 0.83 | 0.81 | 0.84 | <0.001 | 0.76 | 0.75 | 0.78 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.10 | 1.04 | 1.16 | <0.001 | 1.07 | 1.01 | 1.13 | 0.002 | 1.04 | 0.98 | 1.10 | 0.102 |
| 2011 to 2015 | 1.26 | 1.18 | 1.35 | <0.001 | 1.20 | 1.13 | 1.28 | <0.001 | 1.15 | 1.07 | 1.22 | <0.001 |
| 2016 to 2020 | 1.40 | 1.31 | 1.51 | <0.001 | 1.22 | 1.14 | 1.31 | <0.001 | 1.06 | 0.99 | 1.13 | 0.043 |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.09 | 1.04 | 1.14 | <0.001 | 1.17 | 1.11 | 1.23 | <0.001 | 1.29 | 1.22 | 1.37 | <0.001 |
| Stroke | 1.08 | 1.03 | 1.13 | <0.001 | 1.18 | 1.12 | 1.24 | <0.001 | 1.24 | 1.16 | 1.31 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diabetes | 1.04 | 1.00 | 1.08 | 0.004 | 1.15 | 1.11 | 1.19 | <0.001 | 1.27 | 1.22 | 1.33 | <0.001 |
| Epilepsy | 1.00 | 0.94 | 1.07 | 0.993 | 1.12 | 1.04 | 1.19 | <0.001 | 1.19 | 1.10 | 1.28 | <0.001 |
| Hypothyroidism | 1.01 | 0.98 | 1.05 | 0.349 | 1.04 | 1.00 | 1.09 | 0.009 | 1.08 | 1.03 | 1.13 | <0.001 |
| Arthritis | 1.07 | 1.03 | 1.10 | <0.001 | 1.17 | 1.13 | 1.21 | <0.001 | 1.25 | 1.20 | 1.30 | <0.001 |
| Anxiety | 1.57 | 1.51 | 1.62 | <0.001 | 1.61 | 1.56 | 1.67 | <0.001 | 1.63 | 1.57 | 1.69 | <0.001 |
| Migraine | 1.11 | 1.07 | 1.14 | <0.001 | 1.19 | 1.16 | 1.23 | <0.001 | 1.28 | 1.24 | 1.33 | <0.001 |
| Cancer | 1.10 | 1.07 | 1.13 | <0.001 | 1.17 | 1.14 | 1.21 | <0.001 | 1.26 | 1.22 | 1.31 | <0.001 |
| Asthma | 1.21 | 1.18 | 1.23 | <0.001 | 1.38 | 1.35 | 1.41 | <0.001 | 1.52 | 1.48 | 1.56 | <0.001 |
| Renal failure | 1.30 | 1.15 | 1.47 | <0.001 | 1.39 | 1.21 | 1.60 | <0.001 | 1.64 | 1.38 | 1.95 | <0.001 |
| Liver failure | 1.05 | 0.98 | 1.14 | 0.073 | 1.22 | 1.12 | 1.33 | <0.001 | 1.27 | 1.16 | 1.40 | <0.001 |
| Osteoporosis | 1.09 | 1.02 | 1.16 | 0.001 | 1.18 | 1.10 | 1.26 | <0.001 | 1.27 | 1.17 | 1.39 | <0.001 |
| Suicidality | 1.10 | 1.05 | 1.15 | <0.001 | 1.16 | 1.10 | 1.22 | <0.001 | 1.15 | 1.09 | 1.22 | <0.001 |
| Antihypertensive | 0.99 | 0.96 | 1.03 | 0.633 | 1.04 | 1.01 | 1.08 | 0.002 | 1.05 | 1.01 | 1.10 | <0.001 |
| Aspirin | 1.07 | 1.02 | 1.11 | <0.001 | 1.12 | 1.07 | 1.17 | <0.001 | 1.18 | 1.12 | 1.24 | <0.001 |
| Anticoagulants | 1.27 | 1.19 | 1.36 | <0.001 | 1.44 | 1.34 | 1.56 | <0.001 | 1.63 | 1.49 | 1.79 | <0.001 |
| NSAIDs | 1.11 | 1.07 | 1.15 | <0.001 | 1.16 | 1.12 | 1.20 | <0.001 | 1.20 | 1.15 | 1.25 | <0.001 |
| Anticonvulsants | 1.28 | 1.21 | 1.36 | <0.001 | 1.39 | 1.30 | 1.48 | <0.001 | 1.49 | 1.38 | 1.60 | <0.001 |
| Hypnotics | 1.23 | 1.20 | 1.27 | <0.001 | 1.18 | 1.15 | 1.22 | <0.001 | 1.15 | 1.12 | 1.19 | <0.001 |
| Bisphosphonates | 1.12 | 0.99 | 1.26 | 0.017 | 1.15 | 1.01 | 1.31 | 0.005 | 1.13 | 0.97 | 1.32 | 0.040 |
| Contraceptives | 1.03 | 1.00 | 1.06 | 0.029 | 1.08 | 1.04 | 1.11 | <0.001 | 1.11 | 1.07 | 1.15 | <0.001 |
| *Constant* | 0.55 | 0.46 | 0.66 | <0.001 | 0.96 | 0.79 | 1.16 | 0.548 | 1.42 | 1.16 | 1.74 | <0.001 |

***Table A5.4d*** *Regression analyses for safety (self-harm) at 2 months, 6 months, and 12 months; complete case analysis (CCA) and full set analysis (FSA)*

| | **Safety, self-harm *(CCA, N= 63,092)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | | **6 months** | | | | **12 months** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 0.14 | 0.01 | 1.46 | 0.031 | 0.22 | 0.04 | 1.16 | 0.019 | 0.20 | 0.06 | 0.72 | 0.001 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 1.14 | 0.26 | 5.12 | 0.816 | 1.19 | 0.41 | 3.46 | 0.682 | 0.96 | 0.35 | 2.59 | 0.912 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 1.18 | 0.54 | 2.55 | 0.585 | 1.23 | 0.69 | 2.17 | 0.360 | 1.18 | 0.72 | 1.93 | 0.391 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.08 | 1.03 | 1.13 | <0.001 | 1.07 | 1.03 | 1.11 | <0.001 | 1.07 | 1.03 | 1.10 | <0.001 |
| BMI | 0.97 | 0.92 | 1.02 | 0.144 | 0.99 | 0.96 | 1.02 | 0.285 | 0.97 | 0.95 | 1.00 | 0.015 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.81 | 0.50 | 1.32 | 0.260 | 0.91 | 0.65 | 1.27 | 0.475 | 0.91 | 0.69 | 1.21 | 0.408 |
| Other | 2.14 | 0.63 | 7.28 | 0.110 | 1.09 | 0.32 | 3.74 | 0.853 | 0.90 | 0.29 | 2.76 | 0.811 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.91 | 0.47 | 1.75 | 0.698 | 1.01 | 0.62 | 1.65 | 0.937 | 1.12 | 0.73 | 1.72 | 0.483 |
| 3 | 0.77 | 0.38 | 1.55 | 0.339 | 0.90 | 0.55 | 1.48 | 0.593 | 1.09 | 0.71 | 1.68 | 0.599 |
| 4 | 0.93 | 0.47 | 1.85 | 0.800 | 1.11 | 0.66 | 1.86 | 0.601 | 1.44 | 0.92 | 2.25 | 0.038 |
| 5, most deprived | 0.80 | 0.39 | 1.65 | 0.435 | 0.88 | 0.51 | 1.52 | 0.550 | 1.09 | 0.67 | 1.76 | 0.650 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.32 | 0.04 | 2.28 | 0.135 | 0.38 | 0.10 | 1.52 | 0.072 | 0.31 | 0.08 | 1.18 | 0.024 |
| London | 0.55 | 0.20 | 1.57 | 0.144 | 0.64 | 0.30 | 1.33 | 0.114 | 0.71 | 0.37 | 1.36 | 0.172 |
| North East | 0.31 | 0.07 | 1.48 | 0.054 | 0.66 | 0.25 | 1.73 | 0.268 | 0.85 | 0.39 | 1.87 | 0.607 |
| North West | 0.66 | 0.22 | 1.93 | 0.316 | 0.63 | 0.29 | 1.39 | 0.130 | 0.73 | 0.37 | 1.44 | 0.230 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South Central | 0.89 | 0.30 | 2.61 | 0.785 | 1.09 | 0.52 | 2.29 | 0.768 | 1.26 | 0.66 | 2.40 | 0.354 |
| South East | 0.82 | 0.28 | 2.38 | 0.634 | 0.81 | 0.37 | 1.76 | 0.476 | 0.87 | 0.43 | 1.79 | 0.630 |
| South West | 0.70 | 0.21 | 2.31 | 0.448 | 0.81 | 0.34 | 1.94 | 0.540 | 0.89 | 0.42 | 1.92 | 0.708 |
| West Midlands | 0.39 | 0.11 | 1.37 | 0.055 | 0.56 | 0.23 | 1.34 | 0.084 | 0.73 | 0.35 | 1.52 | 0.266 |
| Yorkshire & Humber | 0.95 | 0.31 | 2.88 | 0.902 | 0.76 | 0.34 | 1.71 | 0.388 | 0.86 | 0.42 | 1.76 | 0.584 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.02 | 0.58 | 1.81 | 0.918 | 0.98 | 0.63 | 1.54 | 0.930 | 1.05 | 0.73 | 1.52 | 0.708 |
| Light-smoker | 1.21 | 0.73 | 2.01 | 0.335 | 1.44 | 1.03 | 2.01 | 0.005 | 1.43 | 1.07 | 1.91 | 0.002 |
| Moderate-smoker | 1.69 | 0.50 | 5.67 | 0.265 | 1.48 | 0.58 | 3.80 | 0.279 | 1.84 | 0.90 | 3.79 | 0.029 |
| Heavy-smoker | 2.95 | 0.71 | 12.20 | 0.050 | 2.16 | 0.62 | 7.47 | 0.111 | 1.84 | 0.60 | 5.69 | 0.162 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.56 | 0.98 | 2.48 | 0.013 | 1.51 | 1.08 | 2.12 | 0.002 | 1.46 | 1.08 | 1.97 | 0.001 |
| Medium | 2.81 | 1.66 | 4.77 | <0.001 | 2.14 | 1.38 | 3.30 | <0.001 | 2.49 | 1.72 | 3.61 | <0.001 |
| Heavy | 1.56 | 0.33 | 7.48 | 0.463 | 1.87 | 0.67 | 5.23 | 0.119 | 1.93 | 0.82 | 4.51 | 0.047 |
| Very heavy | 2.28 | 0.77 | 6.76 | 0.050 | 2.28 | 1.06 | 4.90 | 0.006 | 1.88 | 0.94 | 3.77 | 0.020 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 2.04 | 0.71 | 5.90 | 0.083 | 1.67 | 0.77 | 3.64 | 0.090 | 1.18 | 0.53 | 2.62 | 0.592 |
| Asian | 1.22 | 0.41 | 3.58 | 0.639 | 1.00 | 0.43 | 2.29 | 0.990 | 1.17 | 0.55 | 2.48 | 0.589 |
| Other | 0.71 | 0.19 | 2.60 | 0.494 | 0.85 | 0.37 | 1.97 | 0.614 | 0.93 | 0.47 | 1.84 | 0.774 |
| | | | | | | | | | | | | |
| Age | 0.97 | 0.95 | 0.99 | 0.001 | 0.96 | 0.94 | 0.98 | <0.001 | 0.97 | 0.95 | 0.98 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.29 | 0.83 | 2.01 | 0.135 | 1.31 | 0.94 | 1.83 | 0.035 | 1.10 | 0.83 | 1.45 | 0.401 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.54 | 0.32 | 0.92 | 0.003 | 0.66 | 0.45 | 0.97 | 0.005 | 0.77 | 0.55 | 1.06 | 0.037 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2011 to 2015 | 0.65 | 0.40 | 1.07 | 0.026 | 0.67 | 0.47 | 0.98 | 0.006 | 0.74 | 0.54 | 1.02 | 0.014 |
| 2016 to 2020 | 1.00 | | | | 1.00 | | | | 1.00 | | | |
| | | | | | | | | | | | | |
| Coronary heart disease | 7.08 | 1.65 | 30.40 | 0.001 | 3.43 | 0.70 | 16.91 | 0.046 | 3.03 | 0.70 | 13.05 | 0.051 |
| Stroke | 1.56 | 0.20 | 12.20 | 0.575 | 0.95 | 0.14 | 6.23 | 0.940 | 1.44 | 0.40 | 5.27 | 0.466 |
| Diabetes | 0.46 | 0.07 | 3.04 | 0.293 | 0.62 | 0.18 | 2.15 | 0.319 | 0.77 | 0.30 | 2.01 | 0.490 |
| Epilepsy | 2.37 | 0.62 | 9.08 | 0.099 | 1.91 | 0.66 | 5.49 | 0.114 | 1.36 | 0.49 | 3.81 | 0.436 |
| Hypothyroidism | 1.50 | 0.37 | 6.02 | 0.453 | 1.43 | 0.51 | 4.07 | 0.374 | 1.11 | 0.43 | 2.90 | 0.771 |
| Arthritis | 1.49 | 0.48 | 4.58 | 0.365 | 1.37 | 0.56 | 3.35 | 0.365 | 0.94 | 0.39 | 2.24 | 0.846 |
| Anxiety | 1.05 | 0.60 | 1.81 | 0.832 | 1.01 | 0.67 | 1.52 | 0.951 | 0.99 | 0.69 | 1.41 | 0.914 |
| Migraine | 0.87 | 0.39 | 1.96 | 0.658 | 1.41 | 0.81 | 2.46 | 0.110 | 1.26 | 0.78 | 2.05 | 0.216 |
| Cancer | 0.77 | 0.28 | 2.11 | 0.508 | 1.13 | 0.57 | 2.21 | 0.650 | 1.04 | 0.59 | 1.84 | 0.854 |
| Asthma | 1.14 | 0.68 | 1.90 | 0.521 | 1.02 | 0.70 | 1.47 | 0.910 | 1.14 | 0.84 | 1.53 | 0.269 |
| Renal failure | 6.51 | 0.75 | 56.74 | 0.026 | 6.72 | 1.33 | 33.89 | 0.002 | 4.30 | 0.84 | 22.13 | 0.022 |
| Liver failure | 0.85 | 0.07 | 10.09 | 0.864 | 1.81 | 0.48 | 6.82 | 0.251 | 1.65 | 0.50 | 5.45 | 0.281 |
| Osteoporosis | 1.00 | | | | 1.00 | | | | 1.00 | | | |
| Suicidality | 6.03 | 3.51 | 10.37 | <0.001 | 5.80 | 3.88 | 8.65 | <0.001 | 5.93 | 4.25 | 8.28 | <0.001 |
| Antihypertensive | 1.06 | 0.37 | 2.98 | 0.891 | 0.90 | 0.34 | 2.34 | 0.767 | 1.15 | 0.53 | 2.48 | 0.638 |
| Aspirin | 0.33 | 0.02 | 6.57 | 0.341 | 1.55 | 0.26 | 9.15 | 0.522 | 1.37 | 0.34 | 5.53 | 0.561 |
| Anticoagulants | 2.60 | 0.41 | 16.38 | 0.180 | 2.18 | 0.38 | 12.62 | 0.255 | 1.44 | 0.24 | 8.50 | 0.594 |
| NSAIDs | 1.55 | 0.52 | 4.66 | 0.302 | 1.35 | 0.58 | 3.13 | 0.359 | 1.08 | 0.49 | 2.38 | 0.814 |
| Anticonvulsants | 0.39 | 0.03 | 5.28 | 0.356 | 0.70 | 0.14 | 3.59 | 0.572 | 0.61 | 0.13 | 2.96 | 0.421 |
| Hypnotics | 2.64 | 1.52 | 4.59 | <0.001 | 1.99 | 1.28 | 3.07 | <0.001 | 1.96 | 1.37 | 2.81 | <0.001 |
| Bisphosphonates | 1.00 | | | | 1.00 | | | | 1.00 | | | |
| Contraceptives | 1.45 | 0.68 | 3.10 | 0.202 | 1.11 | 0.62 | 1.98 | 0.647 | 1.07 | 0.66 | 1.74 | 0.707 |
| *Constant* | 0.00 | 0.00 | 0.03 | <0.001 | 0.01 | 0.00 | 0.03 | <0.001 | 0.01 | 0.00 | 0.03 | <0.001 |

| | **Safety, self-harm *(FSA, N = 673,177)*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | **6 months** | | | **12 months** | | |
| | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Statins*** | 0.70 | 0.44 | 1.12 | 0.049 | 0.73 | 0.51 | 1.05 | 0.026 | 0.81 | 0.60 | 1.09 | 0.068 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 1.20 | 0.94 | 1.53 | 0.055 | 1.13 | 0.93 | 1.36 | 0.104 | 1.08 | 0.92 | 1.28 | 0.220 |
| MAOIs | 1.00 | | | | 2.43 | 0.17 | 35.18 | 0.392 | 1.82 | 0.13 | 26.09 | 0.564 |
| Other antidepressants | 1.46 | 1.21 | 1.77 | <0.001 | 1.49 | 1.29 | 1.73 | <0.001 | 1.48 | 1.31 | 1.68 | <0.001 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.01 | 1.00 | 1.03 | 0.048 | 1.01 | 1.00 | 1.03 | 0.003 | 1.01 | 1.00 | 1.03 | 0.002 |
| BMI | 0.99 | 0.98 | 1.00 | 0.017 | 0.99 | 0.98 | 1.00 | 0.024 | 0.99 | 0.99 | 1.00 | 0.021 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.94 | 0.80 | 1.10 | 0.298 | 0.91 | 0.81 | 1.02 | 0.031 | 0.92 | 0.83 | 1.01 | 0.023 |
| Other | 0.75 | 0.52 | 1.09 | 0.050 | 0.74 | 0.56 | 0.97 | 0.004 | 0.79 | 0.63 | 0.99 | 0.008 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.03 | 0.84 | 1.27 | 0.673 | 1.04 | 0.89 | 1.21 | 0.515 | 1.06 | 0.93 | 1.22 | 0.238 |
| 3 | 1.08 | 0.89 | 1.32 | 0.314 | 1.16 | 1.00 | 1.36 | 0.012 | 1.21 | 1.06 | 1.39 | <0.001 |
| 4 | 1.12 | 0.91 | 1.38 | 0.164 | 1.28 | 1.09 | 1.50 | <0.001 | 1.32 | 1.14 | 1.52 | <0.001 |
| 5, most deprived | 1.28 | 1.00 | 1.63 | 0.009 | 1.34 | 1.11 | 1.60 | <0.001 | 1.45 | 1.24 | 1.69 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.92 | 0.57 | 1.47 | 0.638 | 0.88 | 0.61 | 1.27 | 0.366 | 0.80 | 0.57 | 1.11 | 0.081 |
| London | 0.61 | 0.41 | 0.91 | 0.001 | 0.59 | 0.45 | 0.77 | <0.001 | 0.59 | 0.48 | 0.73 | <0.001 |
| North East | 0.92 | 0.59 | 1.43 | 0.615 | 0.95 | 0.70 | 1.28 | 0.637 | 1.01 | 0.77 | 1.32 | 0.945 |
| North West | 0.72 | 0.50 | 1.03 | 0.018 | 0.74 | 0.57 | 0.96 | 0.003 | 0.75 | 0.61 | 0.92 | <0.001 |
| South Central | 0.82 | 0.54 | 1.24 | 0.215 | 0.81 | 0.61 | 1.09 | 0.065 | 0.86 | 0.69 | 1.09 | 0.100 |
| South East | 1.01 | 0.67 | 1.55 | 0.929 | 0.90 | 0.65 | 1.23 | 0.374 | 0.91 | 0.70 | 1.19 | 0.364 |
| South West | 0.89 | 0.58 | 1.36 | 0.487 | 0.88 | 0.66 | 1.18 | 0.273 | 0.91 | 0.71 | 1.15 | 0.296 |
| West Midlands | 0.61 | 0.41 | 0.91 | 0.001 | 0.58 | 0.43 | 0.78 | <0.001 | 0.63 | 0.50 | 0.80 | <0.001 |
| Yorkshire & Humber | 0.78 | 0.49 | 1.22 | 0.153 | 0.80 | 0.56 | 1.13 | 0.096 | 0.84 | 0.63 | 1.14 | 0.143 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.90 | 0.75 | 1.08 | 0.147 | 0.88 | 0.76 | 1.02 | 0.027 | 0.87 | 0.76 | 0.98 | 0.003 |
| Light-smoker | 1.16 | 1.01 | 1.33 | 0.004 | 1.22 | 1.10 | 1.35 | <0.001 | 1.28 | 1.17 | 1.40 | <0.001 |
| Moderate-smoker | 1.43 | 1.03 | 1.98 | 0.004 | 1.45 | 1.13 | 1.88 | <0.001 | 1.47 | 1.18 | 1.83 | <0.001 |
| Heavy-smoker | 1.29 | 0.76 | 2.19 | 0.221 | 1.37 | 0.89 | 2.09 | 0.060 | 1.49 | 1.05 | 2.11 | 0.003 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.02 | 0.86 | 1.20 | 0.805 | 1.05 | 0.92 | 1.19 | 0.321 | 1.07 | 0.97 | 1.18 | 0.084 |
| Medium | 1.20 | 0.96 | 1.51 | 0.034 | 1.21 | 1.03 | 1.43 | 0.003 | 1.20 | 1.04 | 1.39 | 0.001 |
| Heavy | 1.50 | 0.97 | 2.32 | 0.016 | 1.47 | 1.06 | 2.04 | 0.003 | 1.58 | 1.21 | 2.07 | <0.001 |
| Very heavy | 1.36 | 0.91 | 2.04 | 0.050 | 1.49 | 1.06 | 2.07 | 0.002 | 1.53 | 1.16 | 2.00 | <0.001 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.02 | 0.73 | 1.40 | 0.901 | 1.00 | 0.79 | 1.28 | 0.958 | 0.94 | 0.74 | 1.19 | 0.473 |
| Asian | 0.99 | 0.75 | 1.29 | 0.885 | 0.88 | 0.71 | 1.09 | 0.129 | 0.94 | 0.78 | 1.13 | 0.376 |
| Other | 0.89 | 0.65 | 1.22 | 0.334 | 1.04 | 0.82 | 1.32 | 0.650 | 1.03 | 0.84 | 1.26 | 0.750 |
| | | | | | | | | | | | | |
| Age | 0.97 | 0.96 | 0.97 | <0.001 | 0.96 | 0.96 | 0.97 | <0.001 | 0.96 | 0.96 | 0.97 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.30 | 1.15 | 1.46 | <0.001 | 1.18 | 1.08 | 1.30 | <0.001 | 1.12 | 1.03 | 1.22 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.99 | 0.79 | 1.23 | 0.873 | 1.02 | 0.87 | 1.19 | 0.793 | 1.00 | 0.87 | 1.15 | 0.970 |
| 2011 to 2015 | 1.06 | 0.85 | 1.31 | 0.525 | 1.08 | 0.90 | 1.28 | 0.282 | 1.07 | 0.91 | 1.25 | 0.285 |
| 2016 to 2020 | 1.28 | 1.01 | 1.62 | 0.008 | 1.32 | 1.10 | 1.59 | <0.001 | 1.27 | 1.09 | 1.49 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.13 | 0.58 | 2.18 | 0.640 | 1.33 | 0.81 | 2.18 | 0.134 | 1.35 | 0.88 | 2.07 | 0.068 |
| Stroke | 0.89 | 0.48 | 1.65 | 0.620 | 1.03 | 0.63 | 1.66 | 0.885 | 1.01 | 0.66 | 1.55 | 0.939 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diabetes | 1.19 | 0.80 | 1.75 | 0.261 | 1.15 | 0.84 | 1.57 | 0.261 | 1.12 | 0.85 | 1.46 | 0.291 |
| Epilepsy | 1.22 | 0.79 | 1.90 | 0.245 | 1.10 | 0.77 | 1.57 | 0.485 | 1.11 | 0.81 | 1.53 | 0.380 |
| Hypothyroidism | 0.87 | 0.55 | 1.39 | 0.447 | 0.88 | 0.61 | 1.26 | 0.362 | 0.88 | 0.64 | 1.21 | 0.292 |
| Arthritis | 1.55 | 1.11 | 2.17 | 0.001 | 1.36 | 1.03 | 1.80 | 0.004 | 1.23 | 0.97 | 1.58 | 0.026 |
| Anxiety | 1.07 | 0.90 | 1.27 | 0.345 | 1.02 | 0.89 | 1.17 | 0.700 | 1.02 | 0.92 | 1.14 | 0.581 |
| Migraine | 0.78 | 0.59 | 1.01 | 0.014 | 0.88 | 0.73 | 1.07 | 0.084 | 0.90 | 0.76 | 1.06 | 0.092 |
| Cancer | 1.03 | 0.78 | 1.36 | 0.818 | 1.03 | 0.83 | 1.28 | 0.713 | 0.99 | 0.82 | 1.20 | 0.943 |
| Asthma | 1.01 | 0.87 | 1.17 | 0.836 | 1.06 | 0.95 | 1.17 | 0.192 | 1.11 | 1.02 | 1.22 | 0.002 |
| Renal failure | 0.92 | 0.25 | 3.46 | 0.875 | 0.72 | 0.22 | 2.33 | 0.467 | 0.77 | 0.29 | 2.08 | 0.506 |
| Liver failure | 0.97 | 0.49 | 1.90 | 0.897 | 1.25 | 0.79 | 1.98 | 0.219 | 1.18 | 0.78 | 1.78 | 0.315 |
| Osteoporosis | 1.13 | 0.48 | 2.67 | 0.704 | 1.10 | 0.53 | 2.28 | 0.736 | 1.05 | 0.55 | 2.01 | 0.850 |
| Suicidality | 7.10 | 5.92 | 8.51 | <0.001 | 6.32 | 5.48 | 7.29 | <0.001 | 5.87 | 5.21 | 6.62 | <0.001 |
| Antihypertensive | 1.14 | 0.83 | 1.58 | 0.281 | 1.08 | 0.82 | 1.43 | 0.464 | 1.10 | 0.86 | 1.40 | 0.311 |
| Aspirin | 0.87 | 0.48 | 1.60 | 0.562 | 1.03 | 0.65 | 1.63 | 0.877 | 0.88 | 0.58 | 1.35 | 0.450 |
| Anticoagulants | 1.02 | 0.45 | 2.32 | 0.951 | 0.79 | 0.36 | 1.73 | 0.444 | 0.93 | 0.48 | 1.79 | 0.767 |
| NSAIDs | 0.85 | 0.59 | 1.22 | 0.253 | 1.03 | 0.81 | 1.32 | 0.730 | 1.05 | 0.85 | 1.30 | 0.526 |
| Anticonvulsants | 1.43 | 0.92 | 2.23 | 0.035 | 1.41 | 0.99 | 2.01 | 0.013 | 1.34 | 0.98 | 1.83 | 0.016 |
| Hypnotics | 2.18 | 1.84 | 2.58 | <0.001 | 1.99 | 1.74 | 2.28 | <0.001 | 1.92 | 1.71 | 2.15 | <0.001 |
| Bisphosphonates | 1.69 | 0.44 | 6.51 | 0.316 | 1.42 | 0.42 | 4.81 | 0.460 | 1.09 | 0.33 | 3.62 | 0.849 |
| Contraceptives | 1.01 | 0.79 | 1.29 | 0.942 | 0.90 | 0.76 | 1.06 | 0.104 | 0.86 | 0.74 | 1.00 | 0.013 |
| *Constant* | 0.01 | 0.00 | 0.01 | <0.001 | 0.02 | 0.01 | 0.03 | <0.001 | 0.02 | 0.01 | 0.03 | <0.001 |

***Table A5.4e*** *Regression analyses for safety (suicidality) at 2 months, 6 months, and 12 months; complete case analysis (CCA) and full set analysis (FSA)*

| | **Safety, suicidality *(CCA, N= 63,801)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months)** | | | | **6 months** | | | | **12 months** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 1.07 | 0.70 | 1.64 | 0.684 | 0.94 | 0.63 | 1.40 | 0.693 | 0.97 | 0.66 | 1.43 | 0.840 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 1.40 | 0.81 | 2.42 | 0.117 | 1.46 | 0.94 | 2.28 | 0.028 | 1.32 | 0.84 | 2.10 | 0.115 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 1.04 | 0.71 | 1.54 | 0.786 | 1.04 | 0.75 | 1.42 | 0.780 | 1.08 | 0.82 | 1.43 | 0.458 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.02 | 1.00 | 1.05 | 0.025 | 1.02 | 1.00 | 1.05 | 0.018 | 1.03 | 1.00 | 1.05 | 0.007 |
| BMI | 0.99 | 0.97 | 1.00 | 0.066 | 0.99 | 0.98 | 1.01 | 0.138 | 0.99 | 0.98 | 1.01 | 0.164 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.61 | 0.88 | 2.95 | 0.044 | 1.54 | 0.88 | 2.72 | 0.047 | 1.55 | 0.91 | 2.64 | 0.034 |
| Other | 1.42 | 0.81 | 2.49 | 0.107 | 1.00 | 0.59 | 1.71 | 0.995 | 1.01 | 0.61 | 1.65 | 0.975 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.88 | 0.61 | 1.26 | 0.357 | 0.86 | 0.60 | 1.23 | 0.281 | 0.88 | 0.63 | 1.23 | 0.318 |
| 3 | 1.08 | 0.67 | 1.72 | 0.690 | 1.08 | 0.71 | 1.65 | 0.648 | 1.07 | 0.71 | 1.62 | 0.664 |
| 4 | 1.76 | 1.06 | 2.94 | 0.004 | 1.77 | 1.09 | 2.90 | 0.003 | 1.72 | 1.08 | 2.74 | 0.003 |
| 5, most deprived | 2.57 | 1.48 | 4.46 | <0.001 | 2.48 | 1.53 | 4.01 | <0.001 | 2.43 | 1.53 | 3.85 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.60 | 0.19 | 1.94 | 0.265 | 0.37 | 0.12 | 1.09 | 0.017 | 0.46 | 0.16 | 1.34 | 0.062 |
| London | 1.66 | 0.55 | 5.02 | 0.235 | 1.54 | 0.57 | 4.16 | 0.264 | 1.54 | 0.61 | 3.91 | 0.232 |
| North East | 0.20 | 0.05 | 0.74 | 0.002 | 0.31 | 0.09 | 1.04 | 0.013 | 0.35 | 0.11 | 1.08 | 0.016 |
| North West | 0.55 | 0.16 | 1.84 | 0.201 | 0.49 | 0.17 | 1.42 | 0.085 | 0.49 | 0.18 | 1.31 | 0.062 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South Central | 0.75 | 0.20 | 2.77 | 0.568 | 0.58 | 0.17 | 1.94 | 0.245 | 0.56 | 0.19 | 1.72 | 0.187 |
| South East | 2.38 | 0.68 | 8.28 | 0.073 | 2.13 | 0.67 | 6.71 | 0.091 | 2.02 | 0.68 | 6.05 | 0.097 |
| South West | 0.48 | 0.13 | 1.87 | 0.166 | 0.49 | 0.13 | 1.83 | 0.165 | 0.49 | 0.14 | 1.67 | 0.133 |
| West Midlands | 0.37 | 0.12 | 1.18 | 0.028 | 0.44 | 0.16 | 1.21 | 0.037 | 0.53 | 0.20 | 1.36 | 0.082 |
| Yorkshire & Humber | 2.18 | 0.25 | 18.86 | 0.352 | 1.80 | 0.23 | 14.07 | 0.459 | 1.67 | 0.22 | 12.45 | 0.510 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.97 | 0.77 | 1.21 | 0.690 | 1.01 | 0.84 | 1.22 | 0.872 | 0.94 | 0.79 | 1.12 | 0.390 |
| Light-smoker | 0.87 | 0.69 | 1.11 | 0.150 | 0.96 | 0.79 | 1.15 | 0.533 | 0.97 | 0.80 | 1.16 | 0.624 |
| Moderate-smoker | 0.79 | 0.37 | 1.70 | 0.434 | 0.70 | 0.37 | 1.31 | 0.144 | 0.83 | 0.50 | 1.38 | 0.341 |
| Heavy-smoker | 1.11 | 0.48 | 2.56 | 0.753 | 0.86 | 0.38 | 1.95 | 0.642 | 1.06 | 0.49 | 2.26 | 0.853 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.93 | 0.75 | 1.15 | 0.392 | 0.98 | 0.82 | 1.19 | 0.813 | 0.97 | 0.82 | 1.14 | 0.636 |
| Medium | 0.94 | 0.69 | 1.28 | 0.587 | 0.99 | 0.74 | 1.32 | 0.925 | 1.02 | 0.80 | 1.30 | 0.850 |
| Heavy | 1.29 | 0.73 | 2.26 | 0.246 | 1.20 | 0.71 | 2.03 | 0.372 | 1.30 | 0.82 | 2.08 | 0.141 |
| Very heavy | 0.91 | 0.48 | 1.72 | 0.698 | 0.95 | 0.55 | 1.61 | 0.786 | 1.10 | 0.70 | 1.70 | 0.596 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.94 | 0.59 | 1.50 | 0.725 | 1.05 | 0.71 | 1.55 | 0.745 | 1.03 | 0.73 | 1.45 | 0.850 |
| Asian | 1.08 | 0.65 | 1.80 | 0.695 | 1.10 | 0.71 | 1.69 | 0.579 | 1.11 | 0.74 | 1.65 | 0.520 |
| Other | 0.92 | 0.61 | 1.38 | 0.584 | 0.84 | 0.58 | 1.21 | 0.218 | 0.82 | 0.59 | 1.15 | 0.128 |
| | | | | | | | | | | | | |
| Age | 1.00 | 0.98 | 1.01 | 0.336 | 0.99 | 0.98 | 1.00 | 0.064 | 0.99 | 0.98 | 1.00 | 0.021 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.27 | 1.07 | 1.50 | <0.001 | 1.28 | 1.10 | 1.49 | <0.001 | 1.28 | 1.11 | 1.47 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.69 | 0.11 | 4.37 | 0.600 | 1.08 | 0.17 | 6.64 | 0.917 | 0.68 | 0.21 | 2.22 | 0.404 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2011 to 2015 | 0.66 | 0.10 | 4.19 | 0.564 | 0.90 | 0.15 | 5.45 | 0.886 | 0.59 | 0.19 | 1.84 | 0.234 |
| 2016 to 2020 | 0.71 | 0.11 | 4.46 | 0.634 | 1.03 | 0.17 | 6.11 | 0.962 | 0.63 | 0.21 | 1.90 | 0.279 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.57 | 0.27 | 1.19 | 0.050 | 0.70 | 0.38 | 1.29 | 0.132 | 0.88 | 0.50 | 1.54 | 0.554 |
| Stroke | 0.57 | 0.21 | 1.55 | 0.147 | 0.86 | 0.38 | 1.94 | 0.627 | 0.93 | 0.47 | 1.86 | 0.784 |
| Diabetes | 0.87 | 0.56 | 1.33 | 0.389 | 1.02 | 0.70 | 1.48 | 0.905 | 0.97 | 0.68 | 1.37 | 0.803 |
| Epilepsy | 0.69 | 0.23 | 2.04 | 0.379 | 0.73 | 0.32 | 1.63 | 0.307 | 0.79 | 0.40 | 1.58 | 0.385 |
| Hypothyroidism | 0.90 | 0.53 | 1.52 | 0.594 | 0.88 | 0.55 | 1.40 | 0.470 | 0.80 | 0.51 | 1.25 | 0.191 |
| Arthritis | 0.70 | 0.39 | 1.25 | 0.109 | 0.84 | 0.55 | 1.29 | 0.290 | 0.85 | 0.57 | 1.28 | 0.308 |
| Anxiety | 0.98 | 0.80 | 1.21 | 0.813 | 1.01 | 0.85 | 1.21 | 0.839 | 1.03 | 0.87 | 1.22 | 0.629 |
| Migraine | 0.94 | 0.63 | 1.39 | 0.669 | 0.97 | 0.71 | 1.32 | 0.783 | 0.94 | 0.70 | 1.26 | 0.591 |
| Cancer | 0.87 | 0.62 | 1.23 | 0.303 | 0.82 | 0.62 | 1.09 | 0.073 | 0.81 | 0.62 | 1.05 | 0.038 |
| Asthma | 1.09 | 0.85 | 1.39 | 0.389 | 1.11 | 0.91 | 1.36 | 0.188 | 1.14 | 0.95 | 1.37 | 0.066 |
| Renal failure | 2.19 | 0.67 | 7.20 | 0.090 | 1.80 | 0.60 | 5.39 | 0.167 | 2.04 | 0.82 | 5.09 | 0.044 |
| Liver failure | 1.07 | 0.51 | 2.24 | 0.823 | 1.06 | 0.55 | 2.06 | 0.813 | 1.13 | 0.64 | 2.01 | 0.569 |
| Osteoporosis | 1.09 | 0.40 | 2.96 | 0.815 | 1.06 | 0.42 | 2.68 | 0.868 | 1.03 | 0.43 | 2.44 | 0.932 |
| Suicidality | 3.92 | 2.81 | 5.46 | <0.001 | 3.65 | 2.68 | 4.96 | <0.001 | 3.52 | 2.64 | 4.69 | <0.001 |
| Antihypertensive | 1.18 | 0.81 | 1.71 | 0.256 | 1.15 | 0.83 | 1.59 | 0.281 | 1.12 | 0.82 | 1.52 | 0.354 |
| Aspirin | 1.27 | 0.69 | 2.31 | 0.313 | 1.02 | 0.61 | 1.69 | 0.937 | 1.01 | 0.65 | 1.58 | 0.949 |
| Anticoagulants | 0.87 | 0.29 | 2.60 | 0.746 | 0.81 | 0.29 | 2.28 | 0.607 | 0.85 | 0.34 | 2.12 | 0.648 |
| NSAIDs | 1.30 | 0.80 | 2.09 | 0.164 | 1.35 | 0.93 | 1.96 | 0.040 | 1.39 | 0.98 | 1.97 | 0.016 |
| Anticonvulsants | 0.61 | 0.21 | 1.78 | 0.234 | 0.91 | 0.42 | 1.96 | 0.746 | 0.82 | 0.39 | 1.69 | 0.474 |
| Hypnotics | 1.09 | 0.73 | 1.63 | 0.583 | 1.04 | 0.76 | 1.42 | 0.771 | 1.00 | 0.75 | 1.34 | 0.975 |
| Bisphosphonates | 2.76 | 0.80 | 9.55 | 0.035 | 2.47 | 0.66 | 9.24 | 0.077 | 2.10 | 0.56 | 7.92 | 0.151 |
| Contraceptives | 1.04 | 0.77 | 1.42 | 0.731 | 1.05 | 0.81 | 1.35 | 0.638 | 0.98 | 0.79 | 1.22 | 0.791 |
| *Constant* | 0.01 | 0.00 | 0.11 | <0.001 | 0.01 | 0.00 | 0.11 | <0.001 | 0.03 | 0.01 | 0.11 | <0.001 |

| | **Safety, suicidality *(FSA, N = 673,177)*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | **6 months** | | | **12 months** | | |
| | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Statins*** | 1.08 | 0.89 | 1.31 | 0.298 | 1.07 | 0.91 | 1.27 | 0.272 | 1.04 | 0.89 | 1.20 | 0.550 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 1.28 | 1.03 | 1.59 | 0.004 | 1.20 | 1.00 | 1.44 | 0.008 | 1.13 | 0.96 | 1.33 | 0.052 |
| MAOIs | 1.00 | | | | 1.10 | 0.08 | 14.65 | 0.921 | 0.84 | 0.06 | 11.08 | 0.860 |
| Other antidepressants | 1.16 | 0.99 | 1.36 | 0.017 | 1.23 | 1.07 | 1.41 | <0.001 | 1.24 | 1.10 | 1.40 | <0.001 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.01 | 1.00 | 1.02 | 0.040 | 1.01 | 1.00 | 1.02 | 0.023 | 1.01 | 1.00 | 1.02 | 0.004 |
| BMI | 0.99 | 0.99 | 1.00 | 0.060 | 1.00 | 0.99 | 1.00 | 0.117 | 1.00 | 0.99 | 1.00 | 0.536 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.23 | 0.93 | 1.64 | 0.060 | 1.15 | 0.89 | 1.48 | 0.153 | 1.12 | 0.89 | 1.40 | 0.203 |
| Other | 1.14 | 0.85 | 1.52 | 0.241 | 1.02 | 0.80 | 1.30 | 0.825 | 1.01 | 0.83 | 1.23 | 0.851 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.03 | 0.87 | 1.22 | 0.677 | 1.01 | 0.86 | 1.20 | 0.821 | 1.03 | 0.89 | 1.19 | 0.625 |
| 3 | 1.09 | 0.89 | 1.33 | 0.292 | 1.12 | 0.93 | 1.35 | 0.111 | 1.15 | 0.98 | 1.36 | 0.028 |
| 4 | 1.40 | 1.10 | 1.78 | <0.001 | 1.43 | 1.14 | 1.80 | <0.001 | 1.47 | 1.20 | 1.80 | <0.001 |
| 5, most deprived | 2.08 | 1.59 | 2.72 | <0.001 | 2.04 | 1.58 | 2.64 | <0.001 | 2.08 | 1.64 | 2.62 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.56 | 0.22 | 1.47 | 0.123 | 0.53 | 0.21 | 1.34 | 0.078 | 0.54 | 0.23 | 1.26 | 0.062 |
| London | 1.25 | 0.59 | 2.63 | 0.443 | 1.27 | 0.59 | 2.69 | 0.423 | 1.25 | 0.63 | 2.48 | 0.399 |
| North East | 0.52 | 0.21 | 1.25 | 0.054 | 0.59 | 0.24 | 1.42 | 0.123 | 0.63 | 0.27 | 1.47 | 0.158 |
| North West | 0.66 | 0.29 | 1.50 | 0.191 | 0.66 | 0.30 | 1.45 | 0.174 | 0.67 | 0.33 | 1.35 | 0.140 |
| South Central | 0.43 | 0.19 | 0.94 | 0.006 | 0.44 | 0.20 | 0.96 | 0.006 | 0.47 | 0.23 | 0.95 | 0.006 |
| South East | 1.33 | 0.51 | 3.50 | 0.447 | 1.29 | 0.50 | 3.34 | 0.486 | 1.26 | 0.53 | 2.99 | 0.500 |
| South West | 0.59 | 0.27 | 1.30 | 0.086 | 0.57 | 0.26 | 1.24 | 0.062 | 0.59 | 0.29 | 1.20 | 0.055 |
| West Midlands | 0.42 | 0.20 | 0.90 | 0.003 | 0.46 | 0.22 | 0.99 | 0.009 | 0.49 | 0.24 | 0.97 | 0.007 |
| Yorkshire & Humber | 0.76 | 0.19 | 2.99 | 0.610 | 0.73 | 0.20 | 2.68 | 0.532 | 0.73 | 0.23 | 2.37 | 0.496 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.96 | 0.85 | 1.08 | 0.355 | 0.95 | 0.86 | 1.05 | 0.200 | 0.94 | 0.86 | 1.03 | 0.071 |
| Light-smoker | 0.94 | 0.84 | 1.05 | 0.126 | 0.97 | 0.88 | 1.07 | 0.375 | 1.00 | 0.91 | 1.09 | 0.963 |
| Moderate-smoker | 0.89 | 0.64 | 1.24 | 0.365 | 0.85 | 0.64 | 1.12 | 0.133 | 0.89 | 0.71 | 1.13 | 0.229 |
| Heavy-smoker | 0.86 | 0.55 | 1.37 | 0.410 | 0.96 | 0.68 | 1.36 | 0.761 | 0.97 | 0.72 | 1.31 | 0.789 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.99 | 0.89 | 1.10 | 0.873 | 1.00 | 0.92 | 1.08 | 0.920 | 1.00 | 0.93 | 1.08 | 0.953 |
| Medium | 1.06 | 0.90 | 1.25 | 0.355 | 1.06 | 0.93 | 1.22 | 0.235 | 1.05 | 0.93 | 1.19 | 0.310 |
| Heavy | 1.19 | 0.83 | 1.70 | 0.191 | 1.11 | 0.85 | 1.46 | 0.294 | 1.14 | 0.87 | 1.48 | 0.202 |
| Very heavy | 1.20 | 0.92 | 1.56 | 0.082 | 1.17 | 0.93 | 1.47 | 0.068 | 1.23 | 1.02 | 1.48 | 0.004 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.93 | 0.77 | 1.12 | 0.336 | 0.96 | 0.82 | 1.13 | 0.532 | 0.94 | 0.81 | 1.08 | 0.236 |
| Asian | 1.36 | 1.09 | 1.70 | <0.001 | 1.34 | 1.09 | 1.65 | <0.001 | 1.32 | 1.08 | 1.62 | <0.001 |
| Other | 1.12 | 0.92 | 1.37 | 0.136 | 1.14 | 0.98 | 1.34 | 0.027 | 1.14 | 0.97 | 1.33 | 0.034 |
| | | | | | | | | | | | | |
| Age | 0.99 | 0.98 | 0.99 | <0.001 | 0.99 | 0.98 | 0.99 | <0.001 | 0.98 | 0.98 | 0.99 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.32 | 1.21 | 1.43 | <0.001 | 1.29 | 1.19 | 1.39 | <0.001 | 1.27 | 1.19 | 1.36 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 3.64 | 2.43 | 5.46 | <0.001 | 3.43 | 2.43 | 4.84 | <0.001 | 3.04 | 2.26 | 4.09 | <0.001 |
| 2011 to 2015 | 3.45 | 2.12 | 5.63 | <0.001 | 3.05 | 2.04 | 4.56 | <0.001 | 2.75 | 1.96 | 3.87 | <0.001 |
| 2016 to 2020 | 3.17 | 1.88 | 5.35 | <0.001 | 2.88 | 1.85 | 4.47 | <0.001 | 2.60 | 1.78 | 3.79 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.87 | 0.64 | 1.16 | 0.210 | 0.86 | 0.67 | 1.11 | 0.125 | 0.92 | 0.74 | 1.15 | 0.344 |
| Stroke | 0.86 | 0.63 | 1.17 | 0.198 | 0.98 | 0.78 | 1.24 | 0.833 | 0.99 | 0.80 | 1.24 | 0.925 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diabetes | 0.96 | 0.80 | 1.17 | 0.629 | 1.02 | 0.87 | 1.20 | 0.700 | 1.03 | 0.89 | 1.18 | 0.648 |
| Epilepsy | 0.91 | 0.66 | 1.24 | 0.426 | 0.89 | 0.69 | 1.15 | 0.252 | 0.91 | 0.73 | 1.14 | 0.281 |
| Hypothyroidism | 1.03 | 0.85 | 1.24 | 0.733 | 0.97 | 0.82 | 1.15 | 0.618 | 0.92 | 0.78 | 1.08 | 0.160 |
| Arthritis | 0.79 | 0.64 | 0.97 | 0.003 | 0.86 | 0.73 | 1.02 | 0.020 | 0.93 | 0.80 | 1.07 | 0.187 |
| Anxiety | 1.12 | 1.02 | 1.24 | 0.002 | 1.17 | 1.08 | 1.28 | <0.001 | 1.18 | 1.10 | 1.28 | <0.001 |
| Migraine | 1.00 | 0.86 | 1.16 | 0.995 | 0.97 | 0.86 | 1.09 | 0.489 | 0.97 | 0.87 | 1.08 | 0.465 |
| Cancer | 0.95 | 0.82 | 1.11 | 0.431 | 0.91 | 0.79 | 1.03 | 0.055 | 0.91 | 0.81 | 1.02 | 0.029 |
| Asthma | 1.01 | 0.91 | 1.12 | 0.802 | 1.03 | 0.94 | 1.12 | 0.425 | 1.05 | 0.98 | 1.13 | 0.089 |
| Renal failure | 0.74 | 0.36 | 1.54 | 0.292 | 0.86 | 0.49 | 1.52 | 0.500 | 0.97 | 0.59 | 1.61 | 0.885 |
| Liver failure | 0.80 | 0.56 | 1.16 | 0.123 | 0.84 | 0.62 | 1.14 | 0.148 | 0.86 | 0.65 | 1.14 | 0.164 |
| Osteoporosis | 1.04 | 0.71 | 1.53 | 0.787 | 0.95 | 0.67 | 1.34 | 0.683 | 0.92 | 0.67 | 1.26 | 0.472 |
| Suicidality | 3.53 | 3.01 | 4.14 | <0.001 | 3.55 | 3.07 | 4.10 | <0.001 | 3.42 | 2.98 | 3.92 | <0.001 |
| Antihypertensive | 1.12 | 0.96 | 1.32 | 0.062 | 1.11 | 0.97 | 1.27 | 0.052 | 1.06 | 0.94 | 1.20 | 0.198 |
| Aspirin | 0.94 | 0.72 | 1.22 | 0.520 | 0.89 | 0.71 | 1.11 | 0.164 | 0.91 | 0.76 | 1.09 | 0.172 |
| Anticoagulants | 0.78 | 0.49 | 1.23 | 0.155 | 0.70 | 0.47 | 1.05 | 0.025 | 0.69 | 0.48 | 0.99 | 0.008 |
| NSAIDs | 1.02 | 0.87 | 1.20 | 0.712 | 1.12 | 0.99 | 1.27 | 0.022 | 1.16 | 1.03 | 1.31 | 0.001 |
| Anticonvulsants | 1.41 | 1.11 | 1.78 | <0.001 | 1.39 | 1.13 | 1.70 | <0.001 | 1.37 | 1.14 | 1.66 | <0.001 |
| Hypnotics | 1.37 | 1.19 | 1.57 | <0.001 | 1.30 | 1.16 | 1.46 | <0.001 | 1.29 | 1.16 | 1.44 | <0.001 |
| Bisphosphonates | 1.19 | 0.59 | 2.38 | 0.531 | 1.40 | 0.79 | 2.47 | 0.131 | 1.22 | 0.71 | 2.09 | 0.348 |
| Contraceptives | 0.90 | 0.77 | 1.04 | 0.061 | 0.88 | 0.78 | 1.00 | 0.008 | 0.85 | 0.76 | 0.95 | <0.001 |
| *Constant* | 0.00 | 0.00 | 0.01 | <0.001 | 0.01 | 0.00 | 0.02 | <0.001 | 0.01 | 0.00 | 0.02 | <0.001 |

***Table A5.4f*** *Regression analyses for safety (completed suicide) at 2 months, 6 months, and 12 months; complete case analysis (CCA) and full set analysis (FSA)*

| | **Safety, completed suicide *(CCA)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months *(N= 41,940)*** | | | | **6 months *(N= 49,496)*** | | | | **12 months *(N= 53,588)*** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 0.81 | 0.01 | 81.94 | 0.908 | 0.36 | 0.01 | 13.65 | 0.473 | 0.32 | 0.01 | 10.19 | 0.394 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 1.00 | | | | | | | | 1.14 | 0.09 | 14.15 | 0.894 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 1.00 | | | | 0.49 | 0.04 | 5.95 | 0.462 | 0.81 | 0.13 | 4.99 | 0.769 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 0.96 | 0.78 | 1.18 | 0.610 | 1.03 | 0.88 | 1.20 | 0.675 | 1.03 | 0.88 | 1.21 | 0.642 |
| BMI | 0.99 | 0.89 | 1.09 | 0.745 | 1.00 | 0.93 | 1.07 | 0.973 | 1.02 | 0.95 | 1.09 | 0.513 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 2.21 | 0.52 | 9.33 | 0.156 | 1.43 | 0.51 | 4.06 | 0.372 | 1.80 | 0.76 | 4.24 | 0.077 |
| Other | 4.17 | 0.24 | 71.57 | 0.196 | 1.82 | 0.12 | 28.01 | 0.574 | 3.14 | 0.47 | 21.03 | 0.121 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.69 | 0.12 | 3.90 | 0.585 | 0.40 | 0.09 | 1.76 | 0.112 | 0.53 | 0.14 | 2.04 | 0.222 |
| 3 | 0.76 | 0.09 | 6.37 | 0.738 | 0.51 | 0.11 | 2.45 | 0.271 | 1.08 | 0.31 | 3.71 | 0.877 |
| 4 | 1.22 | 0.12 | 12.06 | 0.820 | 0.84 | 0.19 | 3.75 | 0.757 | 1.14 | 0.29 | 4.50 | 0.805 |
| 5, most deprived | 0.90 | 0.05 | 17.57 | 0.925 | 0.66 | 0.11 | 3.97 | 0.548 | 0.97 | 0.18 | 5.34 | 0.966 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.00 | | | | | | | | 1.13 | 0.04 | 36.45 | 0.928 |
| London | 0.13 | 0.00 | 4.67 | 0.141 | 1.01 | 0.08 | 13.46 | 0.992 | 1.26 | 0.11 | 14.47 | 0.810 |
| North East | 1.00 | | | | 0.74 | 0.02 | 24.43 | 0.826 | 0.68 | 0.02 | 21.58 | 0.777 |
| North West | 0.18 | 0.00 | 7.75 | 0.242 | 0.52 | 0.03 | 10.37 | 0.578 | 0.70 | 0.04 | 10.93 | 0.736 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South Central | 1.51 | 0.14 | 15.94 | 0.653 | 1.38 | 0.10 | 19.25 | 0.750 | 1.88 | 0.14 | 25.23 | 0.533 |
| South East | 0.27 | 0.01 | 9.27 | 0.336 | 0.58 | 0.03 | 11.80 | 0.641 | 0.88 | 0.06 | 13.13 | 0.906 |
| South West | 0.80 | 0.04 | 14.95 | 0.843 | 2.33 | 0.17 | 31.03 | 0.400 | 2.26 | 0.18 | 28.80 | 0.410 |
| West Midlands | 0.96 | 0.07 | 12.80 | 0.968 | 1.16 | 0.08 | 16.81 | 0.885 | 1.40 | 0.11 | 18.21 | 0.735 |
| Yorkshire & Humber | 1.25 | 0.06 | 24.69 | 0.847 | 1.76 | 0.10 | 31.10 | 0.611 | 2.27 | 0.15 | 34.12 | 0.436 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.52 | 0.06 | 4.21 | 0.424 | 1.64 | 0.50 | 5.33 | 0.284 | 0.93 | 0.32 | 2.69 | 0.853 |
| Light-smoker | 1.03 | 0.19 | 5.49 | 0.968 | 1.65 | 0.47 | 5.74 | 0.302 | 1.12 | 0.41 | 3.12 | 0.767 |
| Moderate-smoker | 1.00 | | | | | | | | 1.00 | | | |
| Heavy-smoker | 1.00 | | | | | | | | 1.00 | | | |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.85 | 0.42 | 8.25 | 0.287 | 1.92 | 0.62 | 5.99 | 0.138 | 2.07 | 0.77 | 5.54 | 0.057 |
| Medium | 2.10 | 0.21 | 20.49 | 0.402 | 3.20 | 0.81 | 12.62 | 0.029 | 2.28 | 0.60 | 8.59 | 0.110 |
| Heavy | 6.92 | 0.34 | 141.55 | 0.099 | 6.23 | 0.82 | 47.46 | 0.020 | 4.39 | 0.63 | 30.57 | 0.050 |
| Very heavy | 9.25 | 1.14 | 75.23 | 0.006 | 5.79 | 0.94 | 35.79 | 0.013 | 4.44 | 0.78 | 25.39 | 0.028 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.00 | | | | | | | | 1.00 | | | |
| Asian | 1.00 | | | | | | | | 0.84 | 0.06 | 12.12 | 0.869 |
| Other | 2.82 | 0.14 | 58.39 | 0.379 | 0.99 | 0.06 | 16.20 | 0.994 | 1.50 | 0.21 | 10.64 | 0.592 |
| | | | | | | | | | | | | |
| Age | 0.98 | 0.93 | 1.04 | 0.413 | 0.99 | 0.95 | 1.04 | 0.664 | 1.00 | 0.96 | 1.04 | 0.905 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 2.80 | 0.60 | 13.11 | 0.085 | 1.70198 | 0.66 | 4.38 | 0.148 | 1.84 | 0.81 | 4.22 | 0.057 |
| | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.33 | 0.19 | 9.05 | 0.705 | 1.87 | 0.37 | 9.43 | 0.321 | 2.65 | 0.55 | 12.84 | 0.112 |
| 2011 to 2015 | 1.33 | 0.18 | 9.88 | 0.714 | 1.50 | 0.29 | 7.66 | 0.520 | 2.23 | 0.46 | 10.74 | 0.190 |
| 2016 to 2020 | 1.00 | | | | | | | | 1.00 | | | |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.00 | | | | | | | | 1.00 | | | |
| Stroke | 1.00 | | | | | | | | 1.00 | | | |
| Diabetes | 4.42 | 0.22 | 87.31 | 0.199 | 4.07 | 0.49 | 33.97 | 0.088 | 2.93 | 0.42 | 20.65 | 0.157 |
| Epilepsy | 1.00 | | | | | | | | 1.00 | | | |
| Hypothyroidism | 1.00 | | | | | | | | 1.00 | | | |
| Arthritis | 1.78 | 0.08 | 39.36 | 0.630 | 0.71 | 0.04 | 13.25 | 0.764 | 0.52 | 0.03 | 8.74 | 0.550 |
| Anxiety | 0.94 | 0.12 | 7.16 | 0.938 | 0.91 | 0.21 | 3.90 | 0.873 | 1.16 | 0.34 | 3.87 | 0.759 |
| Migraine | 1.00 | | | | 0.53 | 0.04 | 6.82 | 0.522 | 0.40 | 0.03 | 4.93 | 0.343 |
| Cancer | 1.41 | 0.09 | 23.31 | 0.751 | 0.60 | 0.04 | 8.49 | 0.617 | 0.44 | 0.03 | 6.25 | 0.428 |
| Asthma | 0.29 | 0.02 | 4.04 | 0.226 | 0.62 | 0.16 | 2.44 | 0.375 | 0.77 | 0.25 | 2.34 | 0.541 |
| Renal failure | 1.00 | | | | | | | | 1.00 | | | |
| Liver failure | 6.41 | 0.25 | 166.47 | 0.142 | 2.42 | 0.11 | 53.42 | 0.463 | 2.16 | 0.12 | 38.26 | 0.492 |
| Osteoporosis | 1.00 | | | | | | | | 1.00 | | | |
| Suicidality | 6.67 | 1.22 | 36.50 | 0.004 | 4.62 | 1.17 | 18.25 | 0.004 | 3.44 | 0.96 | 12.35 | 0.013 |
| Antihypertensive | 0.73 | 0.03 | 19.61 | 0.807 | 0.92 | 0.09 | 9.23 | 0.930 | 0.71 | 0.08 | 6.37 | 0.690 |
| Aspirin | 1.00 | | | | | | | | 1.00 | | | |
| Anticoagulants | 1.00 | | | | | | | | 1.00 | | | |
| NSAIDs | 2.54 | 0.14 | 47.84 | 0.413 | 1.11 | 0.07 | 16.34 | 0.924 | 1.72 | 0.25 | 11.68 | 0.463 |
| Anticonvulsants | 1.00 | | | | 6.86 | 0.30 | 155.14 | 0.112 | 4.89 | 0.30 | 78.92 | 0.142 |
| Hypnotics | 3.13 | 0.59 | 16.73 | 0.079 | 1.52 | 0.37 | 6.35 | 0.447 | 2.15 | 0.70 | 6.60 | 0.079 |
| Bisphosphonates | 1.00 | | | | | | | | 1.00 | | | |
| Contraceptives | 3.92 | 0.35 | 44.04 | 0.146 | 1.39 | 0.17 | 11.22 | 0.682 | 1.06 | 0.14 | 8.11 | 0.940 |
| *Constant* | 0.00 | 0.00 | 0.67 | 0.007 | 0.00 | 4.69 | 0.03 | <0.001 | 0.00 | 0.00 | 0.01 | <0.001 |

| | Safety, completed suicide *(FSA, N = 673,177)* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | | **6 months** | | | | **12 months** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 0.98 | 0.24 | 3.98 | 0.977 | 0.81 | 0.28 | 2.36 | 0.609 | 1.09 | 0.48 | 2.47 | 0.794 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 0.70 | 0.27 | 1.76 | 0.314 | 0.90 | 0.47 | 1.73 | 0.680 | 0.96 | 0.56 | 1.62 | 0.832 |
| MAOIs | 1.00 | | | | | | | | 10.96 | 0.78 | 154.60 | 0.020 |
| Other antidepressants | 1.29 | 0.65 | 2.56 | 0.344 | 1.41 | 0.85 | 2.33 | 0.080 | 1.69 | 1.14 | 2.51 | 0.001 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.00 | 0.96 | 1.05 | 0.896 | 1.01 | 0.97 | 1.05 | 0.585 | 1.02 | 0.98 | 1.05 | 0.225 |
| BMI | 1.00 | 0.96 | 1.04 | 0.859 | 1.00 | 0.97 | 1.03 | 0.851 | 1.00 | 0.97 | 1.02 | 0.747 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.86 | 0.54 | 1.36 | 0.399 | 0.77 | 0.52 | 1.14 | 0.087 | 0.88 | 0.64 | 1.22 | 0.318 |
| Other | 0.75 | 0.24 | 2.39 | 0.529 | 0.95 | 0.44 | 2.07 | 0.871 | 1.08 | 0.58 | 2.01 | 0.762 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.05 | 0.54 | 2.07 | 0.838 | 0.86 | 0.50 | 1.46 | 0.456 | 0.96 | 0.61 | 1.51 | 0.826 |
| 3 | 1.36 | 0.73 | 2.56 | 0.204 | 1.26 | 0.77 | 2.06 | 0.222 | 1.48 | 1.00 | 2.21 | 0.011 |
| 4 | 1.49 | 0.76 | 2.92 | 0.125 | 1.25 | 0.74 | 2.10 | 0.271 | 1.38 | 0.88 | 2.19 | 0.067 |
| 5, most deprived | 1.01 | 0.48 | 2.14 | 0.973 | 1.03 | 0.58 | 1.85 | 0.888 | 1.29 | 0.77 | 2.15 | 0.202 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.01 | 0.28 | 3.62 | 0.985 | 1.23 | 0.42 | 3.63 | 0.626 | 1.67 | 0.64 | 4.34 | 0.170 |
| London | 0.79 | 0.27 | 2.27 | 0.558 | 1.01 | 0.45 | 2.30 | 0.971 | 1.21 | 0.56 | 2.60 | 0.528 |
| North East | 1.43 | 0.39 | 5.18 | 0.478 | 1.54 | 0.41 | 5.79 | 0.402 | 1.58 | 0.40 | 6.19 | 0.387 |
| North West | 1.06 | 0.36 | 3.06 | 0.894 | 1.11 | 0.48 | 2.60 | 0.746 | 1.44 | 0.66 | 3.14 | 0.230 |
| South Central | 1.21 | 0.41 | 3.54 | 0.649 | 1.17 | 0.49 | 2.77 | 0.639 | 1.59 | 0.70 | 3.60 | 0.144 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South East | 0.96 | 0.31 | 2.92 | 0.918 | 0.91 | 0.38 | 2.21 | 0.793 | 1.22 | 0.54 | 2.77 | 0.536 |
| South West | 1.27 | 0.42 | 3.86 | 0.580 | 1.35 | 0.55 | 3.31 | 0.394 | 1.77 | 0.76 | 4.07 | 0.080 |
| West Midlands | 0.70 | 0.20 | 2.40 | 0.456 | 0.79 | 0.31 | 2.01 | 0.515 | 0.90 | 0.37 | 2.20 | 0.751 |
| Yorkshire & Humber | 1.11 | 0.33 | 3.72 | 0.817 | 1.10 | 0.39 | 3.12 | 0.809 | 1.62 | 0.58 | 4.48 | 0.224 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.91 | 0.45 | 1.84 | 0.731 | 1.09 | 0.68 | 1.76 | 0.645 | 0.87 | 0.57 | 1.32 | 0.396 |
| Light-smoker | 1.31 | 0.81 | 2.12 | 0.151 | 1.15 | 0.78 | 1.69 | 0.350 | 1.07 | 0.77 | 1.48 | 0.604 |
| Moderate-smoker | 2.57 | 0.97 | 6.83 | 0.013 | 1.50 | 0.58 | 3.87 | 0.275 | 1.44 | 0.68 | 3.07 | 0.213 |
| Heavy-smoker | 0.92 | 0.15 | 5.79 | 0.909 | 0.88 | 0.20 | 3.78 | 0.817 | 0.74 | 0.20 | 2.67 | 0.543 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.20 | 0.67 | 2.17 | 0.400 | 1.21 | 0.78 | 1.87 | 0.255 | 1.18 | 0.81 | 1.72 | 0.245 |
| Medium | 1.33 | 0.64 | 2.75 | 0.309 | 1.31 | 0.79 | 2.18 | 0.171 | 1.21 | 0.77 | 1.90 | 0.273 |
| Heavy | 1.54 | 0.35 | 6.82 | 0.447 | 1.76 | 0.60 | 5.19 | 0.174 | 1.63 | 0.61 | 4.35 | 0.194 |
| Very heavy | 2.18 | 0.73 | 6.56 | 0.066 | 2.20 | 0.97 | 5.00 | 0.014 | 2.06 | 0.97 | 4.36 | 0.013 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.14 | 0.41 | 3.21 | 0.737 | 1.00 | 0.38 | 2.68 | 0.989 | 0.89 | 0.40 | 1.95 | 0.688 |
| Asian | 0.61 | 0.17 | 2.21 | 0.322 | 0.72 | 0.30 | 1.71 | 0.329 | 0.97 | 0.47 | 1.98 | 0.900 |
| Other | 0.93 | 0.24 | 3.55 | 0.889 | 1.11 | 0.46 | 2.69 | 0.765 | 1.14 | 0.55 | 2.36 | 0.644 |
| | | | | | | | | | | | | |
| Age | 0.98 | 0.96 | 0.99 | <0.001 | 0.98 | 0.96 | 0.99 | <0.001 | 0.98 | 0.97 | 0.99 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.92 | 1.28 | 2.88 | <0.001 | 1.73 | 1.27 | 2.35 | <0.001 | 1.61 | 1.23 | 2.10 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.83 | 0.51 | 1.37 | 0.340 | 0.83 | 0.56 | 1.24 | 0.244 | 0.82 | 0.58 | 1.14 | 0.119 |
| 2011 to 2015 | 0.48 | 0.27 | 0.85 | 0.001 | 0.52 | 0.33 | 0.82 | <0.001 | 0.48 | 0.33 | 0.71 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2016 to 2020 | 0.27 | 0.15 | 0.50 | <0.001 | 0.34 | 0.20 | 0.56 | <0.001 | 0.31 | 0.20 | 0.48 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.76 | 0.15 | 3.78 | 0.659 | 0.57 | 0.14 | 2.29 | 0.297 | 0.58 | 0.18 | 1.91 | 0.242 |
| Stroke | 1.18 | 0.21 | 6.67 | 0.801 | 1.19 | 0.33 | 4.35 | 0.725 | 0.92 | 0.28 | 2.96 | 0.846 |
| Diabetes | 0.88 | 0.23 | 3.41 | 0.811 | 0.92 | 0.31 | 2.75 | 0.850 | 0.68 | 0.26 | 1.83 | 0.319 |
| Epilepsy | 1.00 | 0.21 | 4.69 | 0.995 | 0.92 | 0.23 | 3.58 | 0.870 | 1.63 | 0.59 | 4.49 | 0.217 |
| Hypothyroidism | 1.00 | | | | 0.18 | 0.01 | 2.38 | 0.088 | 0.12 | 0.01 | 1.58 | 0.034 |
| Arthritis | 1.81 | 0.74 | 4.45 | 0.088 | 1.23 | 0.56 | 2.73 | 0.493 | 1.14 | 0.58 | 2.25 | 0.606 |
| Anxiety | 0.67 | 0.32 | 1.40 | 0.158 | 0.83 | 0.51 | 1.35 | 0.318 | 0.93 | 0.62 | 1.41 | 0.668 |
| Migraine | 0.19 | 0.03 | 1.20 | 0.021 | 0.35 | 0.12 | 0.99 | 0.009 | 0.50 | 0.24 | 1.03 | 0.013 |
| Cancer | 0.96 | 0.36 | 2.53 | 0.908 | 1.14 | 0.53 | 2.46 | 0.671 | 1.24 | 0.68 | 2.26 | 0.355 |
| Asthma | 0.97 | 0.57 | 1.64 | 0.872 | 1.15 | 0.77 | 1.74 | 0.371 | 1.04 | 0.72 | 1.48 | 0.805 |
| Renal failure | 1.00 | | | | | | | | 0.95 | 0.07 | 12.91 | 0.957 |
| Liver failure | 3.12 | 0.83 | 11.68 | 0.027 | 1.84 | 0.50 | 6.75 | 0.228 | 1.66 | 0.51 | 5.39 | 0.269 |
| Osteoporosis | 0.92 | 0.03 | 24.09 | 0.946 | 1.28 | 0.15 | 11.29 | 0.768 | 1.33 | 0.25 | 7.22 | 0.661 |
| Suicidality | 7.10 | 4.27 | 11.79 | <0.001 | 6.10 | 4.02 | 9.26 | <0.001 | 5.76 | 4.01 | 8.29 | <0.001 |
| Antihypertensive | 1.21 | 0.45 | 3.26 | 0.624 | 1.02 | 0.45 | 2.32 | 0.948 | 0.89 | 0.45 | 1.76 | 0.657 |
| Aspirin | 0.82 | 0.18 | 3.79 | 0.745 | 1.24 | 0.42 | 3.65 | 0.601 | 1.09 | 0.43 | 2.78 | 0.803 |
| Anticoagulants | 0.86 | 0.06 | 12.44 | 0.882 | 0.56 | 0.04 | 7.69 | 0.571 | 0.38 | 0.03 | 5.14 | 0.340 |
| NSAIDs | 0.92 | 0.34 | 2.48 | 0.832 | 1.14 | 0.56 | 2.33 | 0.640 | 1.00 | 0.54 | 1.88 | 0.986 |
| Anticonvulsants | 1.85 | 0.46 | 7.46 | 0.257 | 1.80 | 0.54 | 5.93 | 0.207 | 1.16 | 0.38 | 3.52 | 0.726 |
| Hypnotics | 2.02 | 1.23 | 3.32 | <0.001 | 2.33 | 1.60 | 3.39 | <0.001 | 2.42 | 1.77 | 3.32 | <0.001 |
| Bisphosphonates | 3.99 | 0.15 | 104.21 | 0.275 | 1.92 | 0.09 | 41.21 | 0.585 | 1.14 | 0.06 | 21.11 | 0.906 |
| Contraceptives | 1.15 | 0.49 | 2.69 | 0.668 | 0.75 | 0.36 | 1.59 | 0.331 | 0.73 | 0.39 | 1.37 | 0.199 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 |

***Table A5.4g*** *Regression analyses for safety (all-cause mortality) at 2 months, 6 months, and 12 months; complete case analysis (CCA) and full set analysis (FSA)*

| | **Safety, all-cause mortality *(CCA)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months *(N= 63,282)*** | | | | **6 months *(N= 63,282)*** | | | | **12 months *(N= 63,706)*** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 0.66 | 0.36 | 1.19 | 0.066 | 0.66 | 0.36 | 1.19 | 0.066 | 0.69 | 0.52 | 0.92 | 0.001 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 0.49 | 0.07 | 3.27 | 0.331 | 0.49 | 0.07 | 3.27 | 0.331 | 1.03 | 0.54 | 1.96 | 0.919 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 1.53 | 0.76 | 3.09 | 0.118 | 1.53 | 0.76 | 3.09 | 0.118 | 1.01 | 0.68 | 1.52 | 0.943 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.07 | 1.02 | 1.11 | <0.001 | 1.07 | 1.02 | 1.11 | <0.001 | 1.05 | 1.02 | 1.07 | <0.001 |
| BMI | 0.95 | 0.90 | 1.00 | 0.010 | 0.95 | 0.90 | 1.00 | 0.010 | 0.96 | 0.93 | 0.99 | <0.001 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.69 | 0.40 | 1.20 | 0.087 | 0.69 | 0.40 | 1.20 | 0.087 | 0.95 | 0.73 | 1.24 | 0.603 |
| Other | 2.00 | 0.59 | 6.74 | 0.141 | 2.00 | 0.59 | 6.74 | 0.141 | 1.65 | 0.82 | 3.33 | 0.066 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.14 | 0.64 | 2.03 | 0.572 | 1.14 | 0.64 | 2.03 | 0.572 | 1.38 | 1.01 | 1.89 | 0.007 |
| 3 | 1.26 | 0.70 | 2.26 | 0.308 | 1.26 | 0.70 | 2.26 | 0.308 | 1.30 | 0.94 | 1.80 | 0.039 |
| 4 | 0.62 | 0.26 | 1.47 | 0.155 | 0.62 | 0.26 | 1.47 | 0.155 | 1.39 | 0.96 | 2.02 | 0.021 |
| 5, most deprived | 1.06 | 0.45 | 2.52 | 0.856 | 1.06 | 0.45 | 2.52 | 0.856 | 1.05 | 0.68 | 1.62 | 0.774 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.77 | 0.13 | 4.72 | 0.710 | 0.77 | 0.13 | 4.72 | 0.710 | 0.90 | 0.38 | 2.15 | 0.759 |
| London | 1.34 | 0.34 | 5.32 | 0.580 | 1.34 | 0.34 | 5.32 | 0.580 | 1.27 | 0.67 | 2.42 | 0.334 |
| North East | 0.67 | 0.09 | 4.74 | 0.594 | 0.67 | 0.09 | 4.74 | 0.594 | 0.83 | 0.28 | 2.46 | 0.655 |
| North West | 0.97 | 0.24 | 3.86 | 0.948 | 0.97 | 0.24 | 3.86 | 0.948 | 1.16 | 0.63 | 2.15 | 0.535 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South Central | 1.03 | 0.26 | 4.05 | 0.955 | 1.03 | 0.26 | 4.05 | 0.955 | 1.01 | 0.53 | 1.92 | 0.973 |
| South East | 0.63 | 0.13 | 3.05 | 0.447 | 0.63 | 0.13 | 3.05 | 0.447 | 0.77 | 0.39 | 1.49 | 0.302 |
| South West | 0.63 | 0.13 | 3.01 | 0.448 | 0.63 | 0.13 | 3.01 | 0.448 | 0.88 | 0.44 | 1.75 | 0.624 |
| West Midlands | 1.66 | 0.43 | 6.44 | 0.335 | 1.66 | 0.43 | 6.44 | 0.335 | 1.25 | 0.65 | 2.39 | 0.378 |
| Yorkshire & Humber | 1.16 | 0.25 | 5.44 | 0.809 | 1.16 | 0.25 | 5.44 | 0.809 | 1.09 | 0.50 | 2.35 | 0.782 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.15 | 0.68 | 1.94 | 0.482 | 1.15 | 0.68 | 1.94 | 0.482 | 1.20 | 0.91 | 1.59 | 0.083 |
| Light-smoker | 1.05 | 0.54 | 2.03 | 0.852 | 1.05 | 0.54 | 2.03 | 0.852 | 1.73 | 1.24 | 2.41 | <0.001 |
| Moderate-smoker | 0.82 | 0.05 | 12.90 | 0.851 | 0.82 | 0.05 | 12.90 | 0.851 | 1.18 | 0.33 | 4.18 | 0.738 |
| Heavy-smoker | 1.00 | | | | 1.00 | | | | 1.32 | 0.27 | 6.34 | 0.651 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.13 | 0.68 | 1.89 | 0.537 | 1.13 | 0.68 | 1.89 | 0.537 | 1.28 | 0.98 | 1.66 | 0.018 |
| Medium | 0.86 | 0.37 | 1.99 | 0.652 | 0.86 | 0.37 | 1.99 | 0.652 | 1.31 | 0.89 | 1.92 | 0.068 |
| Heavy | 1.28 | 0.20 | 8.27 | 0.729 | 1.28 | 0.20 | 8.27 | 0.729 | 1.28 | 0.51 | 3.21 | 0.492 |
| Very heavy | 1.74 | 0.42 | 7.17 | 0.316 | 1.74 | 0.42 | 7.17 | 0.316 | 2.09 | 1.05 | 4.17 | 0.006 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.47 | 0.04 | 5.93 | 0.442 | 0.47 | 0.04 | 5.93 | 0.442 | 0.73 | 0.25 | 2.08 | 0.434 |
| Asian | 0.44 | 0.04 | 5.39 | 0.399 | 0.44 | 0.04 | 5.39 | 0.399 | 0.70 | 0.24 | 1.98 | 0.371 |
| Other | 1.23 | 0.17 | 8.88 | 0.784 | 1.23 | 0.17 | 8.88 | 0.784 | 0.77 | 0.27 | 2.22 | 0.522 |
| | | | | | | | | | | | | |
| Age | 1.09 | 1.07 | 1.11 | <0.001 | 1.09 | 1.07 | 1.11 | <0.001 | 1.09 | 1.08 | 1.10 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.69 | 1.01 | 2.82 | 0.008 | 1.69 | 1.01 | 2.82 | 0.008 | 1.64 | 1.27 | 2.11 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.27 | 0.57 | 2.85 | 0.449 | 1.27 | 0.57 | 2.85 | 0.449 | 0.73 | 0.53 | 1.02 | 0.017 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2011 to 2015 | 1.17 | 0.52 | 2.65 | 0.612 | 1.17 | 0.52 | 2.65 | 0.612 | 0.78 | 0.56 | 1.08 | 0.050 |
| 2016 to 2020 | 1.00 | | | | 1.00 | | | | 1.00 | | | |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.00 | 0.50 | 2.01 | 0.993 | 1.00 | 0.50 | 2.01 | 0.993 | 1.32 | 0.95 | 1.82 | 0.029 |
| Stroke | 1.40 | 0.74 | 2.65 | 0.180 | 1.40 | 0.74 | 2.65 | 0.180 | 1.40 | 1.00 | 1.96 | 0.010 |
| Diabetes | 1.16 | 0.62 | 2.16 | 0.552 | 1.16 | 0.62 | 2.16 | 0.552 | 1.47 | 1.07 | 2.03 | 0.002 |
| Epilepsy | 2.62 | 0.53 | 13.11 | 0.122 | 2.62 | 0.53 | 13.11 | 0.122 | 1.00 | 0.38 | 2.61 | 0.991 |
| Hypothyroidism | 1.02 | 0.42 | 2.48 | 0.954 | 1.02 | 0.42 | 2.48 | 0.954 | 0.98 | 0.62 | 1.55 | 0.910 |
| Arthritis | 0.81 | 0.45 | 1.47 | 0.365 | 0.81 | 0.45 | 1.47 | 0.365 | 0.94 | 0.71 | 1.25 | 0.576 |
| Anxiety | 0.53 | 0.22 | 1.26 | 0.059 | 0.53 | 0.22 | 1.26 | 0.059 | 0.74 | 0.50 | 1.10 | 0.052 |
| Migraine | 0.84 | 0.24 | 2.91 | 0.720 | 0.84 | 0.24 | 2.91 | 0.720 | 1.25 | 0.77 | 2.05 | 0.240 |
| Cancer | 2.11 | 1.29 | 3.47 | <0.001 | 2.11 | 1.29 | 3.47 | <0.001 | 2.51 | 1.94 | 3.24 | <0.001 |
| Asthma | 1.16 | 0.67 | 2.02 | 0.489 | 1.16 | 0.67 | 2.02 | 0.489 | 1.24 | 0.93 | 1.65 | 0.054 |
| Renal failure | 3.40 | 1.00 | 11.55 | 0.010 | 3.40 | 1.00 | 11.55 | 0.010 | 2.99 | 1.48 | 6.04 | <0.001 |
| Liver failure | 2.23 | 0.58 | 8.54 | 0.124 | 2.23 | 0.58 | 8.54 | 0.124 | 1.94 | 0.95 | 3.95 | 0.017 |
| Osteoporosis | 0.95 | 0.28 | 3.22 | 0.922 | 0.95 | 0.28 | 3.22 | 0.922 | 1.27 | 0.74 | 2.20 | 0.259 |
| Suicidality | 1.57 | 0.35 | 7.11 | 0.444 | 1.57 | 0.35 | 7.11 | 0.444 | 0.69 | 0.24 | 2.05 | 0.384 |
| Antihypertensive | 1.32 | 0.75 | 2.32 | 0.201 | 1.32 | 0.75 | 2.32 | 0.201 | 1.19 | 0.90 | 1.57 | 0.116 |
| Aspirin | 1.31 | 0.67 | 2.55 | 0.302 | 1.31 | 0.67 | 2.55 | 0.302 | 1.26 | 0.90 | 1.76 | 0.081 |
| Anticoagulants | 2.71 | 1.28 | 5.74 | 0.001 | 2.71 | 1.28 | 5.74 | 0.001 | 2.17 | 1.39 | 3.36 | <0.001 |
| NSAIDs | 1.93 | 0.73 | 5.07 | 0.081 | 1.93 | 0.73 | 5.07 | 0.081 | 1.12 | 0.65 | 1.91 | 0.601 |
| Anticonvulsants | 0.51 | 0.08 | 3.32 | 0.350 | 0.51 | 0.08 | 3.32 | 0.350 | 1.35 | 0.59 | 3.11 | 0.348 |
| Hypnotics | 1.31 | 0.67 | 2.53 | 0.298 | 1.31 | 0.67 | 2.53 | 0.298 | 0.98 | 0.67 | 1.42 | 0.874 |
| Bisphosphonates | 0.50 | 0.03 | 8.98 | 0.538 | 0.50 | 0.03 | 8.98 | 0.538 | 0.68 | 0.21 | 2.16 | 0.386 |
| Contraceptives | 1.21 | 0.08 | 18.00 | 0.858 | 1.21 | 0.08 | 18.00 | 0.858 | 0.57 | 0.09 | 3.59 | 0.426 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 |

| | **Safety, all-cause mortality *(FSA, N = 673,177)*** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | **6 months** | | | **12 months** | | |
| | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Statins*** | 0.69 | 0.62 | 0.78 | <0.001 | 0.69 | 0.62 | 0.78 | <0.001 | 0.72 | 0.67 | 0.77 | <0.001 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 0.92 | 0.79 | 1.07 | 0.144 | 0.92 | 0.79 | 1.07 | 0.144 | 0.96 | 0.88 | 1.06 | 0.297 |
| MAOIs | 1.50 | 0.08 | 28.09 | 0.719 | 1.50 | 0.08 | 28.09 | 0.719 | 0.77 | 0.11 | 5.19 | 0.719 |
| Other antidepressants | 1.22 | 1.09 | 1.38 | <0.001 | 1.22 | 1.09 | 1.38 | <0.001 | 1.18 | 1.09 | 1.27 | <0.001 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.01 | 0.99 | 1.02 | 0.117 | 1.01 | 0.99 | 1.02 | 0.117 | 1.01 | 1.00 | 1.01 | 0.008 |
| BMI | 0.98 | 0.97 | 0.99 | <0.001 | 0.98 | 0.97 | 0.99 | <0.001 | 0.99 | 0.98 | 0.99 | <0.001 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 1.23 | 1.11 | 1.35 | <0.001 | 1.23 | 1.11 | 1.35 | <0.001 | 1.25 | 1.18 | 1.33 | <0.001 |
| Other | 0.96 | 0.73 | 1.28 | 0.738 | 0.96 | 0.73 | 1.28 | 0.738 | 1.15 | 0.98 | 1.33 | 0.021 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 1.08 | 0.96 | 1.21 | 0.092 | 1.08 | 0.96 | 1.21 | 0.092 | 1.04 | 0.96 | 1.11 | 0.225 |
| 3 | 1.14 | 1.00 | 1.29 | 0.008 | 1.14 | 1.00 | 1.29 | 0.008 | 1.09 | 1.00 | 1.18 | 0.011 |
| 4 | 1.07 | 0.92 | 1.24 | 0.274 | 1.07 | 0.92 | 1.24 | 0.274 | 1.08 | 0.98 | 1.19 | 0.036 |
| 5, most deprived | 1.14 | 0.95 | 1.36 | 0.071 | 1.14 | 0.95 | 1.36 | 0.071 | 1.11 | 1.00 | 1.24 | 0.012 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.92 | 0.63 | 1.33 | 0.547 | 0.92 | 0.63 | 1.33 | 0.547 | 0.94 | 0.74 | 1.19 | 0.495 |
| London | 0.80 | 0.59 | 1.09 | 0.064 | 0.80 | 0.59 | 1.09 | 0.064 | 0.82 | 0.67 | 1.00 | 0.008 |
| North East | 0.83 | 0.60 | 1.16 | 0.154 | 0.83 | 0.60 | 1.16 | 0.154 | 0.97 | 0.76 | 1.24 | 0.766 |
| North West | 1.01 | 0.76 | 1.34 | 0.949 | 1.01 | 0.76 | 1.34 | 0.949 | 1.03 | 0.85 | 1.25 | 0.660 |
| South Central | 0.91 | 0.67 | 1.23 | 0.405 | 0.91 | 0.67 | 1.23 | 0.405 | 0.88 | 0.72 | 1.08 | 0.113 |
| South East | 0.88 | 0.64 | 1.21 | 0.297 | 0.88 | 0.64 | 1.21 | 0.297 | 0.84 | 0.68 | 1.04 | 0.040 |
| South West | 1.03 | 0.76 | 1.39 | 0.790 | 1.03 | 0.76 | 1.39 | 0.790 | 0.99 | 0.81 | 1.21 | 0.913 |
| West Midlands | 0.97 | 0.72 | 1.30 | 0.791 | 0.97 | 0.72 | 1.30 | 0.791 | 0.96 | 0.79 | 1.17 | 0.624 |
| Yorkshire & Humber | 0.96 | 0.69 | 1.34 | 0.743 | 0.96 | 0.69 | 1.34 | 0.743 | 0.93 | 0.75 | 1.17 | 0.435 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 0.97 | 0.87 | 1.08 | 0.469 | 0.97 | 0.87 | 1.08 | 0.469 | 1.03 | 0.97 | 1.10 | 0.250 |
| Light-smoker | 1.18 | 1.03 | 1.37 | 0.002 | 1.18 | 1.03 | 1.37 | 0.002 | 1.36 | 1.26 | 1.46 | <0.001 |
| Moderate-smoker | 1.41 | 0.89 | 2.23 | 0.052 | 1.41 | 0.89 | 2.23 | 0.052 | 1.37 | 1.06 | 1.78 | 0.002 |
| Heavy-smoker | 1.01 | 0.50 | 2.03 | 0.965 | 1.01 | 0.50 | 2.03 | 0.965 | 1.45 | 1.04 | 2.02 | 0.004 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 0.99 | 0.87 | 1.13 | 0.903 | 0.99 | 0.87 | 1.13 | 0.903 | 1.02 | 0.95 | 1.10 | 0.441 |
| Medium | 1.10 | 0.92 | 1.33 | 0.164 | 1.10 | 0.92 | 1.33 | 0.164 | 1.15 | 1.03 | 1.27 | 0.001 |
| Heavy | 1.12 | 0.61 | 2.06 | 0.612 | 1.12 | 0.61 | 2.06 | 0.612 | 1.08 | 0.84 | 1.40 | 0.406 |
| Very heavy | 1.20 | 0.76 | 1.89 | 0.291 | 1.20 | 0.76 | 1.89 | 0.291 | 1.38 | 1.09 | 1.75 | 0.001 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.26 | 0.90 | 1.77 | 0.065 | 1.26 | 0.90 | 1.77 | 0.065 | 1.37 | 1.14 | 1.64 | <0.001 |
| Asian | 0.75 | 0.50 | 1.12 | 0.068 | 0.75 | 0.50 | 1.12 | 0.068 | 0.61 | 0.49 | 0.77 | <0.001 |
| Other | 0.75 | 0.42 | 1.34 | 0.203 | 0.75 | 0.42 | 1.34 | 0.203 | 0.67 | 0.49 | 0.92 | 0.001 |
| | | | | | | | | | | | | |
| Age | 1.10 | 1.10 | 1.10 | <0.001 | 1.10 | 1.10 | 1.10 | <0.001 | 1.10 | 1.10 | 1.10 | <0.001 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 1.74 | 1.58 | 1.91 | <0.001 | 1.74 | 1.58 | 1.91 | <0.001 | 1.72 | 1.63 | 1.81 | <0.001 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.12 | 0.99 | 1.28 | 0.017 | 1.12 | 0.99 | 1.28 | 0.017 | 1.01 | 0.93 | 1.09 | 0.791 |
| 2011 to 2015 | 0.96 | 0.84 | 1.10 | 0.424 | 0.96 | 0.84 | 1.10 | 0.424 | 0.89 | 0.81 | 0.97 | <0.001 |
| 2016 to 2020 | 0.79 | 0.69 | 0.91 | <0.001 | 0.79 | 0.69 | 0.91 | <0.001 | 0.74 | 0.68 | 0.82 | <0.001 |
| | | | | | | | | | | | | |
| Coronary heart disease | 1.17 | 1.04 | 1.32 | 0.001 | 1.17 | 1.04 | 1.32 | 0.001 | 1.21 | 1.12 | 1.31 | <0.001 |
| Stroke | 1.07 | 0.94 | 1.22 | 0.204 | 1.07 | 0.94 | 1.22 | 0.204 | 1.22 | 1.13 | 1.31 | <0.001 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Diabetes | 1.27 | 1.11 | 1.44 | <0.001 | 1.27 | 1.11 | 1.44 | <0.001 | 1.37 | 1.28 | 1.48 | <0.001 |
| Epilepsy | 0.85 | 0.61 | 1.18 | 0.209 | 0.85 | 0.61 | 1.18 | 0.209 | 0.94 | 0.77 | 1.15 | 0.452 |
| Hypothyroidism | 0.88 | 0.75 | 1.03 | 0.040 | 0.88 | 0.75 | 1.03 | 0.040 | 1.00 | 0.91 | 1.09 | 0.978 |
| Arthritis | 0.75 | 0.67 | 0.83 | <0.001 | 0.75 | 0.67 | 0.83 | <0.001 | 0.78 | 0.73 | 0.83 | <0.001 |
| Anxiety | 0.80 | 0.69 | 0.93 | <0.001 | 0.80 | 0.69 | 0.93 | <0.001 | 0.79 | 0.73 | 0.86 | <0.001 |
| Migraine | 0.50 | 0.37 | 0.69 | <0.001 | 0.50 | 0.37 | 0.69 | <0.001 | 0.64 | 0.55 | 0.74 | <0.001 |
| Cancer | 1.93 | 1.75 | 2.13 | <0.001 | 1.93 | 1.75 | 2.13 | <0.001 | 2.17 | 2.04 | 2.31 | <0.001 |
| Asthma | 1.09 | 0.98 | 1.21 | 0.041 | 1.09 | 0.98 | 1.21 | 0.041 | 1.21 | 1.13 | 1.29 | <0.001 |
| Renal failure | 1.91 | 1.46 | 2.51 | <0.001 | 1.91 | 1.46 | 2.51 | <0.001 | 2.33 | 1.96 | 2.78 | <0.001 |
| Liver failure | 1.74 | 1.25 | 2.43 | <0.001 | 1.74 | 1.25 | 2.43 | <0.001 | 1.86 | 1.52 | 2.27 | <0.001 |
| Osteoporosis | 1.04 | 0.87 | 1.25 | 0.578 | 1.04 | 0.87 | 1.25 | 0.578 | 1.12 | 1.01 | 1.25 | 0.004 |
| Suicidality | 1.36 | 0.96 | 1.93 | 0.023 | 1.36 | 0.96 | 1.93 | 0.023 | 1.28 | 1.03 | 1.59 | 0.003 |
| Antihypertensive | 0.78 | 0.70 | 0.86 | <0.001 | 0.78 | 0.70 | 0.86 | <0.001 | 0.87 | 0.81 | 0.93 | <0.001 |
| Aspirin | 1.10 | 0.97 | 1.24 | 0.053 | 1.10 | 0.97 | 1.24 | 0.053 | 1.15 | 1.07 | 1.24 | <0.001 |
| Anticoagulants | 1.53 | 1.29 | 1.80 | <0.001 | 1.53 | 1.29 | 1.80 | <0.001 | 1.58 | 1.43 | 1.75 | <0.001 |
| NSAIDs | 1.35 | 1.13 | 1.62 | <0.001 | 1.35 | 1.13 | 1.62 | <0.001 | 1.19 | 1.07 | 1.32 | <0.001 |
| Anticonvulsants | 1.71 | 1.36 | 2.14 | <0.001 | 1.71 | 1.36 | 2.14 | <0.001 | 1.76 | 1.53 | 2.02 | <0.001 |
| Hypnotics | 1.31 | 1.16 | 1.48 | <0.001 | 1.31 | 1.16 | 1.48 | <0.001 | 1.40 | 1.31 | 1.51 | <0.001 |
| Bisphosphonates | 1.19 | 0.90 | 1.58 | 0.110 | 1.19 | 0.90 | 1.58 | 0.110 | 1.26 | 1.04 | 1.52 | 0.002 |
| Contraceptives | 0.61 | 0.23 | 1.63 | 0.194 | 0.61 | 0.23 | 1.63 | 0.194 | 0.48 | 0.27 | 0.84 | 0.001 |
| *Constant* | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | <0.001 |

***Table A5.4h*** *Regression analyses for efficacy (response) at 2 months, 6 months, and 12 months; complete case analysis (CCA) and full set analysis (FSA)*

| | **Efficacy, response *(CCA)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months (*N= 22,804*)** | | | | **6 months (*N= 5,035*)** | | | | **12 months (*N= 2,938*)** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 1.10 | 0.93 | 1.29 | 0.155 | 1.06 | 0.74 | 1.52 | 0.685 | 1.47 | 0.87 | 2.49 | 0.057 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 0.60 | 0.45 | 0.81 | <0.001 | 0.74 | 0.42 | 1.30 | 0.166 | 0.85 | 0.43 | 1.67 | 0.526 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 0.77 | 0.65 | 0.92 | <0.001 | 0.77 | 0.53 | 1.13 | 0.083 | 0.80 | 0.48 | 1.35 | 0.282 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.02 | 1.01 | 1.03 | <0.001 | 1.04 | 1.02 | 1.05 | <0.001 | 1.05 | 1.03 | 1.07 | <0.001 |
| BMI | 0.99 | 0.99 | 1.00 | <0.001 | 0.98 | 0.97 | 1.00 | 0.001 | 0.99 | 0.97 | 1.01 | 0.243 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.93 | 0.84 | 1.02 | 0.044 | 0.86 | 0.72 | 1.03 | 0.035 | 0.88 | 0.67 | 1.15 | 0.204 |
| Other | 0.93 | 0.66 | 1.31 | 0.584 | 0.69 | 0.34 | 1.38 | 0.169 | 0.86 | 0.40 | 1.87 | 0.622 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.91 | 0.82 | 1.01 | 0.014 | 0.90 | 0.71 | 1.15 | 0.277 | 0.77 | 0.55 | 1.06 | 0.037 |
| 3 | 0.77 | 0.69 | 0.86 | <0.001 | 0.86 | 0.67 | 1.09 | 0.097 | 0.66 | 0.48 | 0.92 | 0.001 |
| 4 | 0.73 | 0.65 | 0.83 | <0.001 | 0.64 | 0.50 | 0.84 | <0.001 | 0.61 | 0.43 | 0.86 | <0.001 |
| 5, most deprived | 0.67 | 0.57 | 0.77 | <0.001 | 0.68 | 0.51 | 0.91 | 0.001 | 0.79 | 0.53 | 1.18 | 0.134 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.89 | 0.57 | 1.41 | 0.525 | 1.23 | 0.65 | 2.36 | 0.404 | 0.66 | 0.30 | 1.45 | 0.176 |
| London | 0.97 | 0.72 | 1.29 | 0.756 | 1.16 | 0.68 | 1.97 | 0.472 | 0.90 | 0.47 | 1.72 | 0.673 |
| North East | 0.95 | 0.67 | 1.34 | 0.708 | 1.00 | 0.53 | 1.89 | 0.999 | 0.75 | 0.26 | 2.12 | 0.470 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| North West | 0.88 | 0.66 | 1.18 | 0.257 | 1.05 | 0.62 | 1.79 | 0.797 | 0.91 | 0.47 | 1.75 | 0.707 |
| South Central | 1.10 | 0.81 | 1.48 | 0.430 | 1.20 | 0.69 | 2.09 | 0.405 | 0.92 | 0.46 | 1.82 | 0.745 |
| South East | 0.99 | 0.74 | 1.32 | 0.937 | 1.01 | 0.57 | 1.76 | 0.981 | 0.72 | 0.36 | 1.41 | 0.204 |
| South West | 0.98 | 0.73 | 1.31 | 0.859 | 0.86 | 0.49 | 1.52 | 0.501 | 0.77 | 0.38 | 1.57 | 0.339 |
| West Midlands | 0.94 | 0.68 | 1.29 | 0.602 | 1.04 | 0.60 | 1.79 | 0.864 | 1.06 | 0.54 | 2.09 | 0.831 |
| Yorkshire & Humber | 0.86 | 0.62 | 1.20 | 0.255 | 1.05 | 0.57 | 1.93 | 0.843 | 1.20 | 0.46 | 3.10 | 0.623 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.05 | 0.97 | 1.14 | 0.136 | 1.03 | 0.83 | 1.27 | 0.737 | 1.02 | 0.78 | 1.34 | 0.831 |
| Light-smoker | 0.75 | 0.68 | 0.83 | <0.001 | 0.69 | 0.57 | 0.84 | <0.001 | 0.75 | 0.58 | 0.97 | 0.004 |
| Moderate-smoker | 0.60 | 0.43 | 0.83 | <0.001 | 0.77 | 0.43 | 1.38 | 0.248 | 0.27 | 0.09 | 0.78 | 0.002 |
| Heavy-smoker | 0.66 | 0.40 | 1.08 | 0.029 | 0.74 | 0.31 | 1.78 | 0.377 | 0.45 | 0.12 | 1.73 | 0.125 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.11 | 1.03 | 1.20 | 0.001 | 1.13 | 0.95 | 1.35 | 0.074 | 1.06 | 0.86 | 1.31 | 0.466 |
| Medium | 1.10 | 0.96 | 1.25 | 0.085 | 1.02 | 0.77 | 1.37 | 0.830 | 0.69 | 0.46 | 1.03 | 0.018 |
| Heavy | 1.01 | 0.74 | 1.39 | 0.923 | 0.64 | 0.34 | 1.23 | 0.080 | 0.45 | 0.16 | 1.27 | 0.047 |
| Very heavy | 0.86 | 0.61 | 1.20 | 0.240 | 0.72 | 0.39 | 1.34 | 0.172 | 0.85 | 0.35 | 2.06 | 0.644 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.64 | 0.47 | 0.89 | 0.001 | 0.79 | 0.47 | 1.34 | 0.254 | 0.61 | 0.27 | 1.41 | 0.130 |
| Asian | 0.76 | 0.58 | 0.98 | 0.005 | 0.80 | 0.49 | 1.31 | 0.246 | 0.81 | 0.39 | 1.67 | 0.447 |
| Other | 0.79 | 0.63 | 0.99 | 0.007 | 0.59 | 0.35 | 1.01 | 0.012 | 0.55 | 0.26 | 1.20 | 0.048 |
| | | | | | | | | | | | | |
| Age | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.00 | 1.02 | <0.001 | 1.01 | 1.00 | 1.02 | 0.013 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.85 | 0.79 | 0.93 | <0.001 | 0.89 | 0.74 | 1.06 | 0.087 | 1.06 | 0.85 | 1.33 | 0.479 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2006 to 2010 | 1.85 | 0.46 | 7.50 | 0.259 | 1.04 | 0.03 | 38.72 | 0.977 | 1.81 | 0.07 | 45.84 | 0.636 |
| 2011 to 2015 | 1.72 | 0.43 | 6.95 | 0.317 | 1.06 | 0.03 | 39.14 | 0.969 | 1.84 | 0.07 | 46.67 | 0.629 |
| 2016 to 2020 | 1.46 | 0.36 | 6.00 | 0.490 | 1.09 | 0.03 | 40.94 | 0.952 | 1.81 | 0.07 | 46.83 | 0.639 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.65 | 0.50 | 0.84 | <0.001 | 0.76 | 0.41 | 1.41 | 0.251 | 0.76 | 0.36 | 1.62 | 0.346 |
| Stroke | 0.90 | 0.68 | 1.20 | 0.348 | 0.91 | 0.50 | 1.65 | 0.678 | 0.67 | 0.26 | 1.70 | 0.266 |
| Diabetes | 0.91 | 0.76 | 1.09 | 0.195 | 0.72 | 0.46 | 1.12 | 0.053 | 0.90 | 0.52 | 1.57 | 0.628 |
| Epilepsy | 1.06 | 0.74 | 1.51 | 0.694 | 0.66 | 0.31 | 1.40 | 0.150 | 0.99 | 0.40 | 2.46 | 0.968 |
| Hypothyroidism | 0.95 | 0.78 | 1.17 | 0.527 | 1.00 | 0.62 | 1.62 | 0.999 | 1.18 | 0.63 | 2.19 | 0.495 |
| Arthritis | 0.98 | 0.84 | 1.13 | 0.693 | 0.95 | 0.67 | 1.33 | 0.671 | 1.08 | 0.71 | 1.66 | 0.622 |
| Anxiety | 0.96 | 0.87 | 1.07 | 0.351 | 1.06 | 0.84 | 1.33 | 0.518 | 0.94 | 0.66 | 1.33 | 0.634 |
| Migraine | 0.94 | 0.81 | 1.08 | 0.224 | 0.99 | 0.73 | 1.33 | 0.924 | 0.85 | 0.56 | 1.28 | 0.300 |
| Cancer | 1.06 | 0.93 | 1.21 | 0.264 | 1.01 | 0.74 | 1.37 | 0.958 | 1.17 | 0.78 | 1.74 | 0.325 |
| Asthma | 0.99 | 0.90 | 1.09 | 0.777 | 0.98 | 0.80 | 1.20 | 0.767 | 1.04 | 0.76 | 1.41 | 0.770 |
| Renal failure | 0.47 | 0.21 | 1.03 | 0.013 | 0.37 | 0.05 | 2.96 | 0.217 | 1.98 | 0.28 | 14.04 | 0.367 |
| Liver failure | 0.88 | 0.58 | 1.35 | 0.450 | 1.09 | 0.50 | 2.35 | 0.776 | 0.92 | 0.26 | 3.34 | 0.874 |
| Osteoporosis | 0.93 | 0.62 | 1.41 | 0.671 | 0.64 | 0.22 | 1.86 | 0.278 | 0.50 | 0.10 | 2.49 | 0.266 |
| Suicidality | 0.82 | 0.65 | 1.04 | 0.031 | 1.11 | 0.72 | 1.72 | 0.530 | 0.64 | 0.32 | 1.27 | 0.095 |
| Antihypertensive | 0.98 | 0.85 | 1.14 | 0.756 | 1.05 | 0.74 | 1.48 | 0.724 | 0.95 | 0.59 | 1.51 | 0.759 |
| Aspirin | 1.11 | 0.89 | 1.38 | 0.232 | 1.01 | 0.59 | 1.71 | 0.974 | 0.75 | 0.38 | 1.50 | 0.288 |
| Anticoagulants | 0.90 | 0.58 | 1.40 | 0.527 | 1.06 | 0.28 | 4.01 | 0.903 | 0.90 | 0.22 | 3.72 | 0.846 |
| NSAIDs | 0.79 | 0.63 | 0.98 | 0.005 | 0.95 | 0.61 | 1.49 | 0.774 | 0.87 | 0.45 | 1.71 | 0.603 |
| Anticonvulsants | 0.71 | 0.49 | 1.03 | 0.019 | 0.87 | 0.36 | 2.12 | 0.695 | 0.78 | 0.26 | 2.35 | 0.568 |
| Hypnotics | 0.96 | 0.84 | 1.09 | 0.394 | 0.76 | 0.57 | 1.01 | 0.013 | 0.99 | 0.68 | 1.44 | 0.930 |
| Bisphosphonates | 1.44 | 0.66 | 3.14 | 0.224 | 1.39 | 0.22 | 8.82 | 0.643 | 1.26 | 0.13 | 12.25 | 0.792 |
| Contraceptives | 1.10 | 0.95 | 1.28 | 0.105 | 1.09 | 0.81 | 1.47 | 0.454 | 1.34 | 0.88 | 2.04 | 0.077 |
| *Constant* | 0.37 | 0.09 | 1.55 | 0.073 | 0.49 | 0.01 | 19.45 | 0.618 | 0.19 | 0.01 | 5.47 | 0.202 |

| | **Efficacy, response *(FSA, N = 673,177)*** | | |
|---|---|---|---|
| | **2 months** | **6 months** | **12 months** |

| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Statins*** | 1.01 | 0.94 | 1.09 | 0.715 | 1.01 | 0.95 | 1.06 | 0.723 | 1.00 | 0.96 | 1.04 | 0.992 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 0.95 | 0.92 | 0.99 | 0.001 | 0.98 | 0.94 | 1.03 | 0.307 | 0.99 | 0.94 | 1.04 | 0.550 |
| MAOIs | 0.82 | 0.31 | 2.20 | 0.594 | 0.99 | 0.39 | 2.50 | 0.969 | 0.83 | 0.34 | 2.00 | 0.565 |
| Other antidepressants | 0.97 | 0.94 | 1.01 | 0.027 | 0.99 | 0.93 | 1.04 | 0.481 | 0.99 | 0.94 | 1.03 | 0.398 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 1.00 | 0.99 | 1.01 | 0.944 | 1.04 | 1.03 | 1.04 | <0.001 | 1.04 | 1.03 | 1.05 | <0.001 |
| BMI | 1.00 | 0.99 | 1.00 | 0.002 | 0.99 | 0.98 | 1.00 | 0.005 | 0.99 | 0.99 | 1.00 | 0.054 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.98 | 0.96 | 1.00 | 0.009 | 0.99 | 0.97 | 1.01 | 0.068 | 0.99 | 0.96 | 1.02 | 0.427 |
| Other | 0.98 | 0.93 | 1.04 | 0.355 | 0.99 | 0.93 | 1.05 | 0.628 | 0.99 | 0.93 | 1.05 | 0.678 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.90 | 0.85 | 0.96 | <0.001 | 0.87 | 0.78 | 0.97 | 0.003 | 0.86 | 0.70 | 1.05 | 0.039 |
| 3 | 0.78 | 0.74 | 0.82 | <0.001 | 0.76 | 0.70 | 0.81 | <0.001 | 0.73 | 0.65 | 0.83 | <0.001 |
| 4 | 0.69 | 0.66 | 0.73 | <0.001 | 0.67 | 0.60 | 0.75 | <0.001 | 0.69 | 0.59 | 0.81 | <0.001 |
| 5, most deprived | 0.62 | 0.59 | 0.66 | <0.001 | 0.63 | 0.56 | 0.72 | <0.001 | 0.74 | 0.63 | 0.86 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.01 | 0.95 | 1.08 | 0.653 | 1.00 | 0.93 | 1.07 | 0.932 | 1.00 | 0.92 | 1.09 | 0.881 |
| London | 1.01 | 0.95 | 1.08 | 0.615 | 1.01 | 0.95 | 1.07 | 0.754 | 1.00 | 0.93 | 1.08 | 0.897 |
| North East | 1.00 | 0.92 | 1.08 | 0.970 | 1.00 | 0.94 | 1.06 | 0.855 | 0.99 | 0.92 | 1.07 | 0.809 |
| North West | 1.00 | 0.95 | 1.06 | 0.905 | 1.00 | 0.95 | 1.05 | 0.920 | 1.00 | 0.93 | 1.07 | 0.964 |
| South Central | 1.03 | 0.96 | 1.09 | 0.287 | 1.00 | 0.94 | 1.07 | 0.875 | 1.01 | 0.93 | 1.09 | 0.755 |
| South East | 1.01 | 0.94 | 1.09 | 0.607 | 1.00 | 0.94 | 1.06 | 0.972 | 1.00 | 0.94 | 1.06 | 0.961 |
| South West | 1.01 | 0.95 | 1.07 | 0.666 | 1.00 | 0.95 | 1.06 | 0.897 | 1.00 | 0.93 | 1.08 | 0.874 |
| West Midlands | 1.02 | 0.96 | 1.08 | 0.505 | 1.00 | 0.94 | 1.06 | 0.947 | 1.00 | 0.93 | 1.08 | 0.859 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yorkshire & Humber | 1.01 | 0.94 | 1.08 | 0.796 | 1.00 | 0.92 | 1.09 | 0.990 | 1.00 | 0.93 | 1.08 | 0.880 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.07 | 1.02 | 1.13 | 0.001 | 1.02 | 0.92 | 1.13 | 0.574 | 1.02 | 0.90 | 1.15 | 0.707 |
| Light-smoker | 0.75 | 0.71 | 0.80 | <0.001 | 0.66 | 0.58 | 0.76 | <0.001 | 0.67 | 0.57 | 0.78 | <0.001 |
| Moderate-smoker | 0.67 | 0.54 | 0.82 | <0.001 | 0.69 | 0.49 | 0.96 | 0.006 | 0.57 | 0.35 | 0.92 | 0.004 |
| Heavy-smoker | 0.77 | 0.60 | 0.99 | 0.008 | 0.50 | 0.24 | 1.04 | 0.014 | 0.42 | 0.22 | 0.81 | 0.002 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.04 | 0.97 | 1.12 | 0.079 | 1.02 | 0.92 | 1.13 | 0.555 | 1.13 | 1.05 | 1.22 | 0.001 |
| Medium | 1.02 | 0.92 | 1.12 | 0.600 | 0.96 | 0.78 | 1.16 | 0.474 | 1.03 | 0.83 | 1.29 | 0.660 |
| Heavy | 1.00 | 0.85 | 1.17 | 0.947 | 0.86 | 0.56 | 1.31 | 0.282 | 1.00 | 0.64 | 1.58 | 0.974 |
| Very heavy | 0.94 | 0.72 | 1.24 | 0.525 | 0.94 | 0.69 | 1.29 | 0.573 | 1.03 | 0.59 | 1.78 | 0.869 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.69 | 0.60 | 0.80 | <0.001 | 0.70 | 0.53 | 0.93 | 0.003 | 0.86 | 0.61 | 1.21 | 0.180 |
| Asian | 0.65 | 0.61 | 0.69 | <0.001 | 0.78 | 0.69 | 0.89 | <0.001 | 0.89 | 0.72 | 1.10 | 0.107 |
| Other | 0.70 | 0.62 | 0.78 | <0.001 | 0.72 | 0.59 | 0.87 | <0.001 | 0.76 | 0.63 | 0.93 | 0.001 |
| | | | | | | | | | | | | |
| Age | 1.00 | 1.00 | 1.00 | 0.006 | 1.00 | 1.00 | 1.00 | 0.104 | 1.00 | 1.00 | 1.00 | 0.154 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.99 | 0.97 | 1.01 | 0.167 | 1.00 | 0.97 | 1.02 | 0.729 | 1.00 | 0.97 | 1.02 | 0.754 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.01 | 0.98 | 1.04 | 0.346 | 1.01 | 0.97 | 1.04 | 0.576 | 1.00 | 0.98 | 1.03 | 0.727 |
| 2011 to 2015 | 1.02 | 0.99 | 1.05 | 0.064 | 1.01 | 0.98 | 1.04 | 0.407 | 1.01 | 0.98 | 1.03 | 0.434 |
| 2016 to 2020 | 0.99 | 0.96 | 1.02 | 0.335 | 1.00 | 0.97 | 1.04 | 0.858 | 1.00 | 0.97 | 1.03 | 0.898 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.97 | 0.90 | 1.05 | 0.262 | 0.99 | 0.94 | 1.05 | 0.687 | 0.99 | 0.92 | 1.06 | 0.673 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stroke | 1.00 | 0.92 | 1.08 | 0.906 | 1.01 | 0.94 | 1.08 | 0.750 | 1.00 | 0.91 | 1.10 | 0.930 |
| Diabetes | 1.00 | 0.95 | 1.05 | 0.807 | 0.99 | 0.93 | 1.05 | 0.614 | 1.00 | 0.95 | 1.07 | 0.862 |
| Epilepsy | 1.00 | 0.92 | 1.10 | 0.893 | 1.00 | 0.93 | 1.08 | 0.913 | 1.01 | 0.93 | 1.10 | 0.789 |
| Hypothyroidism | 1.01 | 0.94 | 1.07 | 0.810 | 1.01 | 0.96 | 1.06 | 0.653 | 1.01 | 0.93 | 1.09 | 0.836 |
| Arthritis | 1.00 | 0.96 | 1.04 | 0.982 | 1.00 | 0.96 | 1.04 | 0.983 | 1.00 | 0.96 | 1.05 | 0.997 |
| Anxiety | 1.00 | 0.98 | 1.03 | 0.826 | 1.00 | 0.97 | 1.03 | 0.967 | 0.99 | 0.96 | 1.03 | 0.658 |
| Migraine | 1.00 | 0.96 | 1.04 | 0.898 | 1.00 | 0.95 | 1.04 | 0.806 | 1.00 | 0.96 | 1.04 | 0.876 |
| Cancer | 1.01 | 0.97 | 1.05 | 0.585 | 1.00 | 0.97 | 1.04 | 0.799 | 1.01 | 0.97 | 1.05 | 0.528 |
| Asthma | 1.00 | 0.97 | 1.03 | 0.922 | 1.00 | 0.97 | 1.02 | 0.750 | 1.00 | 0.98 | 1.03 | 0.998 |
| Renal failure | 0.99 | 0.82 | 1.19 | 0.857 | 1.01 | 0.81 | 1.25 | 0.913 | 1.01 | 0.81 | 1.25 | 0.917 |
| Liver failure | 0.97 | 0.87 | 1.08 | 0.424 | 1.00 | 0.88 | 1.13 | 0.954 | 1.00 | 0.89 | 1.13 | 0.953 |
| Osteoporosis | 0.99 | 0.90 | 1.08 | 0.682 | 1.00 | 0.90 | 1.10 | 0.917 | 1.00 | 0.91 | 1.10 | 0.949 |
| Suicidality | 0.98 | 0.92 | 1.05 | 0.482 | 0.99 | 0.94 | 1.04 | 0.574 | 0.98 | 0.92 | 1.05 | 0.465 |
| Antihypertensive | 1.01 | 0.96 | 1.05 | 0.725 | 1.00 | 0.95 | 1.05 | 0.894 | 1.00 | 0.95 | 1.05 | 0.909 |
| Aspirin | 0.99 | 0.91 | 1.07 | 0.753 | 0.99 | 0.93 | 1.05 | 0.601 | 1.00 | 0.94 | 1.06 | 0.833 |
| Anticoagulants | 1.00 | 0.90 | 1.10 | 0.968 | 1.00 | 0.91 | 1.11 | 0.915 | 0.98 | 0.90 | 1.07 | 0.565 |
| NSAIDs | 0.97 | 0.92 | 1.02 | 0.102 | 0.98 | 0.93 | 1.03 | 0.266 | 0.99 | 0.93 | 1.05 | 0.665 |
| Anticonvulsants | 0.97 | 0.87 | 1.07 | 0.371 | 0.99 | 0.91 | 1.07 | 0.731 | 0.99 | 0.92 | 1.07 | 0.742 |
| Hypnotics | 0.99 | 0.94 | 1.03 | 0.359 | 0.99 | 0.96 | 1.03 | 0.522 | 1.00 | 0.96 | 1.04 | 0.792 |
| Bisphosphonates | 1.03 | 0.88 | 1.22 | 0.586 | 0.98 | 0.84 | 1.15 | 0.739 | 0.97 | 0.79 | 1.18 | 0.650 |
| Contraceptives | 1.03 | 0.99 | 1.07 | 0.082 | 1.02 | 0.97 | 1.06 | 0.315 | 1.01 | 0.96 | 1.06 | 0.598 |

***Table A5.4i*** *Regression analyses for efficacy (remission) at 2 months, 6 months, and 12 months; complete case analysis (CCA) and full set analysis (FSA)*

| | **Efficacy, remission *(CCA)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months (*N= 22,804*)** | | | | **6 months (*N= 5,025*)** | | | | **12 months (*N= 2,935*)** | | | |
| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
| ***Statins*** | 1.16 | 0.95 | 1.41 | 0.052 | 0.99 | 0.63 | 1.54 | 0.938 | 1.37 | 0.73 | 2.55 | 0.199 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 0.57 | 0.38 | 0.86 | <0.001 | 0.82 | 0.41 | 1.65 | 0.461 | 0.91 | 0.41 | 2.05 | 0.768 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 0.81 | 0.63 | 1.05 | 0.034 | 0.72 | 0.42 | 1.22 | 0.110 | 1.05 | 0.57 | 1.94 | 0.838 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 0.89 | 0.88 | 0.91 | <0.001 | 0.93 | 0.91 | 0.96 | <0.001 | 0.93 | 0.90 | 0.96 | <0.001 |
| BMI | 0.99 | 0.98 | 1.00 | 0.002 | 0.98 | 0.96 | 1.00 | 0.020 | 0.99 | 0.97 | 1.01 | 0.194 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.90 | 0.79 | 1.01 | 0.023 | 0.86 | 0.68 | 1.08 | 0.091 | 1.01 | 0.75 | 1.36 | 0.939 |
| Other | 1.06 | 0.70 | 1.61 | 0.705 | 1.08 | 0.46 | 2.56 | 0.816 | 0.90 | 0.39 | 2.07 | 0.735 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.91 | 0.80 | 1.04 | 0.080 | 0.82 | 0.62 | 1.08 | 0.060 | 1.00 | 0.66 | 1.52 | 0.981 |
| 3 | 0.77 | 0.67 | 0.90 | <0.001 | 0.79 | 0.59 | 1.06 | 0.038 | 0.80 | 0.53 | 1.21 | 0.166 |
| 4 | 0.75 | 0.64 | 0.88 | <0.001 | 0.64 | 0.47 | 0.86 | <0.001 | 0.77 | 0.49 | 1.21 | 0.138 |
| 5, most deprived | 0.70 | 0.58 | 0.84 | <0.001 | 0.65 | 0.46 | 0.92 | 0.001 | 0.86 | 0.51 | 1.46 | 0.470 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.91 | 0.47 | 1.74 | 0.695 | 1.09 | 0.53 | 2.23 | 0.764 | 0.65 | 0.25 | 1.72 | 0.253 |
| London | 0.97 | 0.59 | 1.60 | 0.883 | 0.98 | 0.55 | 1.75 | 0.937 | 0.80 | 0.41 | 1.59 | 0.411 |
| North East | 1.06 | 0.62 | 1.82 | 0.773 | 1.22 | 0.60 | 2.48 | 0.460 | 1.04 | 0.35 | 3.10 | 0.931 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| North West | 0.86 | 0.53 | 1.42 | 0.446 | 0.87 | 0.48 | 1.57 | 0.539 | 0.86 | 0.43 | 1.72 | 0.577 |
| South Central | 1.16 | 0.70 | 1.94 | 0.450 | 1.00 | 0.53 | 1.91 | 0.994 | 0.88 | 0.44 | 1.78 | 0.640 |
| South East | 0.97 | 0.59 | 1.61 | 0.896 | 0.86 | 0.46 | 1.60 | 0.533 | 0.54 | 0.27 | 1.07 | 0.020 |
| South West | 0.98 | 0.59 | 1.64 | 0.925 | 0.73 | 0.37 | 1.41 | 0.214 | 0.55 | 0.25 | 1.20 | 0.048 |
| West Midlands | 0.94 | 0.55 | 1.59 | 0.760 | 1.00 | 0.53 | 1.87 | 0.985 | 0.97 | 0.45 | 2.09 | 0.920 |
| Yorkshire & Humber | 0.79 | 0.46 | 1.35 | 0.255 | 0.91 | 0.46 | 1.78 | 0.705 | 0.77 | 0.31 | 1.92 | 0.468 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.10 | 0.99 | 1.23 | 0.022 | 1.00 | 0.78 | 1.29 | 0.984 | 1.16 | 0.83 | 1.62 | 0.254 |
| Light-smoker | 0.84 | 0.74 | 0.94 | <0.001 | 0.73 | 0.57 | 0.94 | 0.001 | 0.76 | 0.54 | 1.07 | 0.038 |
| Moderate-smoker | 0.71 | 0.45 | 1.12 | 0.052 | 0.67 | 0.31 | 1.44 | 0.175 | 0.22 | 0.03 | 1.32 | 0.029 |
| Heavy-smoker | 0.74 | 0.36 | 1.51 | 0.278 | 0.62 | 0.17 | 2.23 | 0.333 | 0.22 | 0.01 | 3.25 | 0.145 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.03 | 0.93 | 1.14 | 0.455 | 1.03 | 0.83 | 1.27 | 0.750 | 1.20 | 0.92 | 1.55 | 0.072 |
| Medium | 1.03 | 0.87 | 1.23 | 0.626 | 0.88 | 0.61 | 1.25 | 0.336 | 0.91 | 0.56 | 1.46 | 0.597 |
| Heavy | 0.91 | 0.58 | 1.42 | 0.579 | 0.65 | 0.27 | 1.57 | 0.205 | 0.35 | 0.07 | 1.68 | 0.084 |
| Very heavy | 0.89 | 0.55 | 1.44 | 0.540 | 0.70 | 0.29 | 1.71 | 0.309 | 0.45 | 0.08 | 2.40 | 0.220 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.73 | 0.46 | 1.16 | 0.079 | 0.52 | 0.21 | 1.28 | 0.061 | 0.96 | 0.31 | 2.98 | 0.917 |
| Asian | 0.63 | 0.44 | 0.92 | 0.002 | 0.71 | 0.39 | 1.29 | 0.139 | 0.94 | 0.38 | 2.33 | 0.871 |
| Other | 0.94 | 0.68 | 1.30 | 0.620 | 0.61 | 0.31 | 1.20 | 0.058 | 0.39 | 0.11 | 1.38 | 0.054 |
| | | | | | | | | | | | | |
| Age | 1.01 | 1.00 | 1.01 | <0.001 | 1.01 | 1.00 | 1.02 | 0.002 | 1.00 | 0.99 | 1.01 | 0.451 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.87 | 0.79 | 0.97 | 0.001 | 0.95 | 0.77 | 1.18 | 0.566 | 1.01 | 0.78 | 1.32 | 0.915 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2006 to 2010 | 1.02 | 0.25 | 4.18 | 0.975 | 0.80 | 0.27 | 2.34 | 0.596 | 0.93 | 0.55 | 1.58 | 0.738 |
| 2011 to 2015 | 0.92 | 0.22 | 3.78 | 0.881 | 0.78 | 0.27 | 2.27 | 0.552 | 0.89 | 0.54 | 1.47 | 0.560 |
| 2016 to 2020 | 0.76 | 0.18 | 3.12 | 0.614 | 0.78 | 0.26 | 2.32 | 0.554 | 1.00 | | | |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.55 | 0.40 | 0.78 | <0.001 | 0.88 | 0.43 | 1.79 | 0.638 | 0.79 | 0.32 | 1.95 | 0.505 |
| Stroke | 0.85 | 0.59 | 1.24 | 0.274 | 0.72 | 0.30 | 1.69 | 0.319 | 0.17 | 0.04 | 0.73 | 0.002 |
| Diabetes | 0.83 | 0.65 | 1.07 | 0.060 | 0.63 | 0.38 | 1.07 | 0.025 | 1.20 | 0.63 | 2.28 | 0.469 |
| Epilepsy | 0.86 | 0.54 | 1.37 | 0.395 | 0.59 | 0.24 | 1.49 | 0.143 | 1.32 | 0.53 | 3.31 | 0.437 |
| Hypothyroidism | 1.03 | 0.81 | 1.31 | 0.730 | 0.92 | 0.52 | 1.61 | 0.692 | 1.45 | 0.72 | 2.92 | 0.173 |
| Arthritis | 1.04 | 0.87 | 1.25 | 0.582 | 1.20 | 0.80 | 1.79 | 0.255 | 0.94 | 0.53 | 1.68 | 0.800 |
| Anxiety | 0.93 | 0.81 | 1.07 | 0.202 | 1.10 | 0.85 | 1.43 | 0.351 | 0.93 | 0.63 | 1.37 | 0.626 |
| Migraine | 0.80 | 0.66 | 0.98 | 0.004 | 0.89 | 0.62 | 1.28 | 0.414 | 0.83 | 0.50 | 1.37 | 0.344 |
| Cancer | 1.00 | 0.84 | 1.18 | 0.961 | 0.97 | 0.67 | 1.41 | 0.832 | 1.16 | 0.67 | 2.01 | 0.490 |
| Asthma | 0.99 | 0.88 | 1.12 | 0.895 | 0.95 | 0.74 | 1.22 | 0.596 | 1.11 | 0.76 | 1.62 | 0.466 |
| Renal failure | 0.55 | 0.19 | 1.63 | 0.157 | 1.00 | | | | 0.46 | 0.02 | 10.01 | 0.513 |
| Liver failure | 0.80 | 0.46 | 1.40 | 0.310 | 1.32 | 0.51 | 3.38 | 0.448 | 0.91 | 0.17 | 5.01 | 0.889 |
| Osteoporosis | 1.15 | 0.72 | 1.83 | 0.451 | 0.84 | 0.24 | 2.96 | 0.720 | 0.70 | 0.13 | 3.71 | 0.578 |
| Suicidality | 0.79 | 0.58 | 1.09 | 0.060 | 1.04 | 0.60 | 1.82 | 0.842 | 0.58 | 0.22 | 1.57 | 0.163 |
| Antihypertensive | 0.96 | 0.80 | 1.14 | 0.533 | 1.17 | 0.78 | 1.77 | 0.314 | 0.63 | 0.32 | 1.21 | 0.068 |
| Aspirin | 1.11 | 0.83 | 1.49 | 0.336 | 0.95 | 0.53 | 1.73 | 0.840 | 1.58 | 0.71 | 3.50 | 0.138 |
| Anticoagulants | 0.85 | 0.49 | 1.47 | 0.456 | 1.28 | 0.36 | 4.61 | 0.616 | 1.27 | 0.21 | 7.61 | 0.728 |
| NSAIDs | 0.82 | 0.60 | 1.12 | 0.100 | 0.99 | 0.56 | 1.73 | 0.955 | 1.21 | 0.55 | 2.70 | 0.532 |
| Anticonvulsants | 0.77 | 0.47 | 1.28 | 0.188 | 1.30 | 0.45 | 3.72 | 0.523 | 0.82 | 0.26 | 2.62 | 0.661 |
| Hypnotics | 0.98 | 0.82 | 1.17 | 0.796 | 0.81 | 0.56 | 1.18 | 0.150 | 1.06 | 0.67 | 1.67 | 0.758 |
| Bisphosphonates | 0.85 | 0.34 | 2.13 | 0.644 | 1.77 | 0.27 | 11.81 | 0.437 | 2.53 | 0.38 | 17.03 | 0.209 |
| Contraceptives | 1.08 | 0.90 | 1.30 | 0.289 | 1.03 | 0.70 | 1.51 | 0.864 | 1.05 | 0.60 | 1.81 | 0.836 |
| *Constant* | 1.79 | 0.40 | 8.00 | 0.315 | 1.74 | 0.48 | 6.29 | 0.270 | 1.23 | 0.41 | 3.71 | 0.635 |

| | **Efficacy, remission *(FSA, N = 673,177)*** | | |
|---|---|---|---|
| | **2 months** | **6 months** | **12 months** |

| | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* | *OR* | *99% CI* | | *P* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Statins*** | 1.02 | 0.95 | 1.08 | 0.502 | 1.01 | 0.95 | 1.08 | 0.541 | 1.00 | 0.92 | 1.08 | 0.973 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 0.95 | 0.89 | 1.02 | 0.060 | 0.99 | 0.93 | 1.05 | 0.532 | 0.98 | 0.93 | 1.04 | 0.451 |
| MAOIs | 0.81 | 0.17 | 3.78 | 0.703 | 1.01 | 0.30 | 3.41 | 0.975 | 0.77 | 0.17 | 3.58 | 0.650 |
| Other antidepressants | 0.97 | 0.92 | 1.03 | 0.178 | 0.99 | 0.94 | 1.04 | 0.559 | 0.99 | 0.93 | 1.04 | 0.521 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | 0.87 | 0.86 | 0.87 | <0.001 | 0.91 | 0.90 | 0.92 | <0.001 | 0.92 | 0.91 | 0.93 | <0.001 |
| BMI | 1.00 | 0.99 | 1.00 | 0.011 | 0.99 | 0.98 | 1.00 | 0.004 | 0.99 | 0.99 | 1.00 | 0.073 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.95 | 0.93 | 0.98 | <0.001 | 0.99 | 0.95 | 1.02 | 0.281 | 0.99 | 0.94 | 1.04 | 0.481 |
| Other | 0.99 | 0.91 | 1.07 | 0.650 | 1.00 | 0.91 | 1.09 | 0.984 | 1.00 | 0.92 | 1.08 | 0.933 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.90 | 0.83 | 0.98 | 0.002 | 0.88 | 0.79 | 0.98 | 0.004 | 0.87 | 0.69 | 1.08 | 0.068 |
| 3 | 0.78 | 0.74 | 0.82 | <0.001 | 0.76 | 0.71 | 0.82 | <0.001 | 0.73 | 0.64 | 0.85 | <0.001 |
| 4 | 0.70 | 0.65 | 0.74 | <0.001 | 0.67 | 0.60 | 0.75 | <0.001 | 0.69 | 0.57 | 0.84 | <0.001 |
| 5, most deprived | 0.62 | 0.58 | 0.67 | <0.001 | 0.63 | 0.56 | 0.71 | <0.001 | 0.74 | 0.62 | 0.88 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 1.04 | 0.93 | 1.16 | 0.323 | 0.99 | 0.89 | 1.11 | 0.853 | 1.00 | 0.90 | 1.10 | 0.991 |
| London | 1.04 | 0.95 | 1.14 | 0.231 | 1.02 | 0.93 | 1.11 | 0.606 | 1.01 | 0.93 | 1.10 | 0.690 |
| North East | 1.03 | 0.92 | 1.15 | 0.455 | 1.01 | 0.90 | 1.13 | 0.815 | 1.00 | 0.87 | 1.16 | 0.940 |
| North West | 1.02 | 0.94 | 1.10 | 0.520 | 1.01 | 0.92 | 1.10 | 0.841 | 1.00 | 0.92 | 1.09 | 0.939 |
| South Central | 1.05 | 0.96 | 1.16 | 0.142 | 1.01 | 0.92 | 1.11 | 0.792 | 1.01 | 0.92 | 1.11 | 0.728 |
| South East | 1.03 | 0.94 | 1.14 | 0.364 | 1.00 | 0.91 | 1.10 | 0.917 | 1.00 | 0.92 | 1.08 | 0.977 |
| South West | 1.03 | 0.93 | 1.14 | 0.473 | 1.00 | 0.91 | 1.10 | 0.987 | 1.01 | 0.92 | 1.11 | 0.792 |
| West Midlands | 1.04 | 0.96 | 1.12 | 0.250 | 1.01 | 0.92 | 1.11 | 0.824 | 1.01 | 0.92 | 1.11 | 0.808 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yorkshire & Humber | 1.01 | 0.90 | 1.13 | 0.814 | 1.01 | 0.88 | 1.14 | 0.908 | 1.01 | 0.91 | 1.11 | 0.888 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | 1.08 | 1.01 | 1.15 | 0.003 | 1.02 | 0.91 | 1.13 | 0.653 | 1.02 | 0.88 | 1.17 | 0.727 |
| Light-smoker | 0.75 | 0.71 | 0.80 | <0.001 | 0.66 | 0.57 | 0.76 | <0.001 | 0.66 | 0.56 | 0.78 | <0.001 |
| Moderate-smoker | 0.66 | 0.53 | 0.82 | <0.001 | 0.69 | 0.49 | 0.99 | 0.009 | 0.56 | 0.33 | 0.95 | 0.006 |
| Heavy-smoker | 0.76 | 0.56 | 1.05 | 0.026 | 0.47 | 0.19 | 1.13 | 0.021 | 0.38 | 0.17 | 0.87 | 0.004 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | 1.04 | 0.97 | 1.11 | 0.108 | 1.02 | 0.92 | 1.14 | 0.547 | 1.14 | 1.05 | 1.24 | 0.001 |
| Medium | 1.01 | 0.90 | 1.13 | 0.846 | 0.95 | 0.77 | 1.18 | 0.486 | 1.04 | 0.83 | 1.30 | 0.635 |
| Heavy | 0.97 | 0.82 | 1.15 | 0.659 | 0.85 | 0.53 | 1.34 | 0.277 | 1.00 | 0.61 | 1.65 | 0.986 |
| Very heavy | 0.94 | 0.67 | 1.30 | 0.551 | 0.94 | 0.65 | 1.36 | 0.614 | 1.01 | 0.55 | 1.86 | 0.945 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 0.68 | 0.58 | 0.79 | <0.001 | 0.69 | 0.52 | 0.93 | 0.003 | 0.86 | 0.59 | 1.24 | 0.211 |
| Asian | 0.64 | 0.59 | 0.71 | <0.001 | 0.78 | 0.67 | 0.91 | <0.001 | 0.90 | 0.74 | 1.10 | 0.131 |
| Other | 0.71 | 0.63 | 0.80 | <0.001 | 0.71 | 0.56 | 0.91 | 0.001 | 0.76 | 0.60 | 0.96 | 0.004 |
| | | | | | | | | | | | | |
| Age | 1.00 | 1.00 | 1.00 | 0.035 | 1.00 | 1.00 | 1.00 | 0.118 | 1.00 | 1.00 | 1.00 | 0.360 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.99 | 0.96 | 1.02 | 0.438 | 0.99 | 0.97 | 1.02 | 0.385 | 0.99 | 0.96 | 1.03 | 0.639 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 1.08 | 1.03 | 1.13 | <0.001 | 1.02 | 0.99 | 1.07 | 0.101 | 1.02 | 0.98 | 1.07 | 0.184 |
| 2011 to 2015 | 1.08 | 1.03 | 1.13 | <0.001 | 1.02 | 0.98 | 1.06 | 0.175 | 1.02 | 0.97 | 1.06 | 0.341 |
| 2016 to 2020 | 1.01 | 0.96 | 1.05 | 0.743 | 1.01 | 0.97 | 1.05 | 0.642 | 1.01 | 0.97 | 1.05 | 0.609 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.96 | 0.88 | 1.05 | 0.206 | 0.98 | 0.88 | 1.10 | 0.680 | 0.99 | 0.90 | 1.08 | 0.727 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stroke | 0.98 | 0.89 | 1.08 | 0.607 | 1.00 | 0.91 | 1.10 | 0.967 | 0.99 | 0.91 | 1.08 | 0.806 |
| Diabetes | 0.98 | 0.92 | 1.05 | 0.482 | 0.99 | 0.91 | 1.07 | 0.681 | 1.01 | 0.95 | 1.08 | 0.651 |
| Epilepsy | 1.01 | 0.88 | 1.16 | 0.885 | 1.01 | 0.90 | 1.13 | 0.863 | 1.00 | 0.88 | 1.13 | 0.980 |
| Hypothyroidism | 1.00 | 0.92 | 1.09 | 0.885 | 1.01 | 0.91 | 1.11 | 0.822 | 1.02 | 0.91 | 1.14 | 0.642 |
| Arthritis | 1.01 | 0.94 | 1.08 | 0.786 | 1.00 | 0.93 | 1.07 | 0.959 | 0.99 | 0.92 | 1.07 | 0.851 |
| Anxiety | 1.00 | 0.95 | 1.06 | 0.879 | 1.00 | 0.97 | 1.04 | 0.840 | 0.99 | 0.95 | 1.03 | 0.641 |
| Migraine | 1.00 | 0.95 | 1.06 | 0.951 | 0.99 | 0.93 | 1.06 | 0.802 | 1.00 | 0.94 | 1.06 | 0.869 |
| Cancer | 1.01 | 0.95 | 1.06 | 0.782 | 1.00 | 0.95 | 1.05 | 0.892 | 1.01 | 0.96 | 1.07 | 0.630 |
| Asthma | 1.00 | 0.96 | 1.05 | 0.838 | 1.00 | 0.97 | 1.03 | 0.965 | 1.00 | 0.97 | 1.04 | 0.931 |
| Renal failure | 0.98 | 0.78 | 1.24 | 0.840 | 0.98 | 0.73 | 1.32 | 0.876 | 1.01 | 0.74 | 1.38 | 0.936 |
| Liver failure | 0.96 | 0.82 | 1.12 | 0.518 | 1.00 | 0.84 | 1.19 | 0.990 | 1.00 | 0.80 | 1.26 | 0.998 |
| Osteoporosis | 0.99 | 0.85 | 1.16 | 0.914 | 0.98 | 0.88 | 1.10 | 0.691 | 1.01 | 0.89 | 1.14 | 0.884 |
| Suicidality | 0.99 | 0.87 | 1.12 | 0.817 | 0.99 | 0.92 | 1.08 | 0.856 | 0.99 | 0.91 | 1.07 | 0.695 |
| Antihypertensive | 1.00 | 0.93 | 1.08 | 0.979 | 1.00 | 0.95 | 1.06 | 0.848 | 1.00 | 0.93 | 1.07 | 0.946 |
| Aspirin | 0.99 | 0.91 | 1.06 | 0.624 | 0.99 | 0.92 | 1.07 | 0.663 | 1.00 | 0.91 | 1.09 | 0.880 |
| Anticoagulants | 0.99 | 0.86 | 1.14 | 0.818 | 1.01 | 0.89 | 1.15 | 0.843 | 0.98 | 0.86 | 1.11 | 0.649 |
| NSAIDs | 0.97 | 0.89 | 1.07 | 0.416 | 0.98 | 0.91 | 1.05 | 0.363 | 0.99 | 0.90 | 1.08 | 0.757 |
| Anticonvulsants | 0.97 | 0.86 | 1.10 | 0.518 | 0.99 | 0.87 | 1.12 | 0.783 | 0.99 | 0.88 | 1.10 | 0.761 |
| Hypnotics | 0.98 | 0.93 | 1.02 | 0.190 | 0.99 | 0.94 | 1.05 | 0.680 | 1.00 | 0.94 | 1.05 | 0.879 |
| Bisphosphonates | 1.01 | 0.79 | 1.28 | 0.951 | 0.98 | 0.74 | 1.28 | 0.805 | 0.99 | 0.75 | 1.32 | 0.955 |
| Contraceptives | 1.02 | 0.95 | 1.10 | 0.409 | 1.01 | 0.94 | 1.08 | 0.768 | 1.01 | 0.92 | 1.11 | 0.734 |
| *Constant* | 1.77 | 1.57 | 2.00 | <0.001 | 1.28 | 0.94 | 1.74 | 0.031 | 0.83 | 0.61 | 1.14 | 0.094 |

***Table A5.4j*** *Regression analyses for efficacy (change from baseline) at 2 months, 6 months, and 12 months; complete case analysis (CCA) and full set analysis (FSA)*

| | **Efficacy, change from baseline *(CCA)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months (*N= 22,804*)** | | | | **6 months (*N= 5,035*)** | | | | **12 months (*N= 2,938*)** | | | |
| | *MD* | *99% CI* | | *P* | *MD* | *99% CI* | | *P* | *MD* | *99% CI* | | *P* |
| ***Statins*** | -0.11 | -0.54 | 0.32 | 0.509 | -0.02 | -1.10 | 1.06 | 0.962 | -1.31 | -2.92 | 0.30 | 0.035 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |
| TCAs | 1.69 | 0.94 | 2.43 | <0.001 | 0.80 | -0.70 | 2.31 | 0.169 | 1.10 | -0.69 | 2.90 | 0.113 |
| MAOIs | | | | | | | | | | | | |
| Other antidepressants | 0.50 | 0.04 | 0.95 | 0.005 | 0.71 | -0.42 | 1.84 | 0.105 | 0.61 | -0.89 | 2.10 | 0.295 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | -0.53 | -0.55 | -0.50 | <0.001 | -0.64 | -0.70 | -0.59 | <0.001 | -0.67 | -0.74 | -0.60 | <0.001 |
| BMI | 0.03 | 0.01 | 0.05 | <0.001 | 0.06 | 0.02 | 0.10 | <0.001 | 0.04 | -0.02 | 0.10 | 0.054 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.30 | 0.03 | 0.57 | 0.004 | 0.46 | -0.09 | 1.02 | 0.031 | 0.34 | -0.44 | 1.11 | 0.259 |
| Other | 0.58 | -0.33 | 1.48 | 0.099 | 1.09 | -1.10 | 3.27 | 0.198 | 0.49 | -1.47 | 2.45 | 0.516 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.38 | 0.09 | 0.66 | 0.001 | 0.71 | -0.04 | 1.47 | 0.015 | 1.03 | 0.03 | 2.03 | 0.008 |
| 3 | 0.86 | 0.56 | 1.16 | <0.001 | 0.68 | -0.07 | 1.43 | 0.020 | 1.47 | 0.52 | 2.43 | <0.001 |
| 4 | 1.08 | 0.73 | 1.42 | <0.001 | 1.38 | 0.62 | 2.15 | <0.001 | 1.71 | 0.67 | 2.75 | <0.001 |
| 5, most deprived | 1.32 | 0.93 | 1.71 | <0.001 | 1.35 | 0.50 | 2.20 | <0.001 | 1.28 | 0.07 | 2.49 | 0.006 |
| | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | 0.15 | -1.25 | 1.54 | 0.785 | -0.06 | -2.09 | 1.97 | 0.940 | 0.46 | -2.09 | 3.01 | 0.644 |
| London | -0.15 | -1.13 | 0.83 | 0.692 | -0.39 | -1.94 | 1.16 | 0.514 | 0.16 | -1.83 | 2.16 | 0.833 |
| North East | 0.23 | -0.94 | 1.40 | 0.612 | 0.67 | -1.26 | 2.59 | 0.372 | 0.90 | -2.50 | 4.30 | 0.494 |
| North West | 0.28 | -0.71 | 1.28 | 0.463 | 0.00 | -1.59 | 1.59 | 1.000 | 0.35 | -1.63 | 2.34 | 0.644 |
| South Central | -0.49 | -1.48 | 0.51 | 0.205 | -0.52 | -2.18 | 1.15 | 0.423 | 0.13 | -1.91 | 2.17 | 0.869 |
| South East | -0.17 | -1.16 | 0.82 | 0.662 | 0.03 | -1.68 | 1.74 | 0.963 | 0.79 | -1.15 | 2.72 | 0.295 |
| South West | -0.25 | -1.23 | 0.74 | 0.519 | 0.49 | -1.23 | 2.20 | 0.465 | 1.23 | -0.95 | 3.41 | 0.144 |
| West Midlands | 0.01 | -1.02 | 1.05 | 0.972 | -0.15 | -1.75 | 1.45 | 0.811 | -0.29 | -2.38 | 1.80 | 0.723 |
| Yorkshire & Humber | 0.15 | -0.92 | 1.22 | 0.712 | -0.33 | -2.08 | 1.43 | 0.631 | -0.58 | -3.38 | 2.21 | 0.591 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | -0.12 | -0.35 | 0.12 | 0.206 | -0.21 | -0.84 | 0.43 | 0.400 | -0.04 | -0.84 | 0.76 | 0.903 |
| Light-smoker | 0.96 | 0.70 | 1.22 | <0.001 | 1.43 | 0.86 | 2.01 | <0.001 | 1.12 | 0.32 | 1.91 | <0.001 |
| Moderate-smoker | 1.43 | 0.60 | 2.27 | <0.001 | 0.97 | -0.87 | 2.81 | 0.175 | 2.87 | 0.67 | 5.06 | 0.001 |
| Heavy-smoker | 1.02 | -0.12 | 2.17 | 0.021 | 2.01 | -0.58 | 4.59 | 0.045 | 4.05 | 0.58 | 7.52 | 0.003 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | -0.27 | -0.48 | -0.07 | 0.001 | -0.30 | -0.79 | 0.19 | 0.112 | -0.32 | -0.98 | 0.34 | 0.213 |
| Medium | -0.34 | -0.71 | 0.02 | 0.016 | 0.02 | -0.85 | 0.90 | 0.942 | 0.74 | -0.34 | 1.83 | 0.075 |
| Heavy | 0.18 | -0.71 | 1.07 | 0.605 | 1.14 | -0.71 | 3.00 | 0.112 | 2.37 | -0.14 | 4.87 | 0.015 |
| Very heavy | 0.64 | -0.25 | 1.52 | 0.063 | 1.20 | -0.61 | 3.02 | 0.088 | 2.33 | -0.60 | 5.27 | 0.040 |
| | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.51 | 0.66 | 2.35 | <0.001 | 1.33 | -0.18 | 2.84 | 0.023 | 1.41 | -1.10 | 3.92 | 0.148 |
| Asian | 1.11 | 0.40 | 1.81 | <0.001 | 1.08 | -0.28 | 2.45 | 0.041 | 1.05 | -1.13 | 3.23 | 0.213 |
| Other | 0.96 | 0.37 | 1.54 | <0.001 | 1.71 | 0.36 | 3.05 | 0.001 | 1.75 | -0.24 | 3.73 | 0.023 |
| | | | | | | | | | | | | |
| Age | -0.02 | -0.03 | -0.01 | <0.001 | -0.04 | -0.06 | -0.02 | <0.001 | -0.03 | -0.05 | 0.00 | 0.014 |
| | | | | | | | | | | | | |
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.55 | 0.34 | 0.76 | <0.001 | 0.42 | -0.11 | 0.94 | 0.040 | -0.05 | -0.69 | 0.58 | 0.826 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | -0.83 | -3.64 | 1.98 | 0.447 | 3.66 | 0.09 | 7.23 | 0.008 | -4.64 | -12.85 | 3.57 | 0.145 |
| 2011 to 2015 | -0.75 | -3.55 | 2.06 | 0.492 | 3.64 | 0.09 | 7.18 | 0.008 | -4.81 | -12.99 | 3.37 | 0.129 |
| 2016 to 2020 | -0.06 | -2.89 | 2.76 | 0.955 | 3.68 | 0.07 | 7.29 | 0.009 | -4.39 | -12.66 | 3.87 | 0.170 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.99 | 0.31 | 1.67 | <0.001 | 0.30 | -1.42 | 2.01 | 0.655 | 0.45 | -1.77 | 2.68 | 0.598 |
| Stroke | 0.10 | -0.64 | 0.84 | 0.731 | 0.32 | -1.38 | 2.01 | 0.630 | 1.84 | -0.56 | 4.25 | 0.048 |
| Diabetes | 0.21 | -0.26 | 0.68 | 0.242 | 0.76 | -0.48 | 2.00 | 0.113 | 0.79 | -1.02 | 2.60 | 0.258 |
| Epilepsy | 0.34 | -0.63 | 1.31 | 0.368 | 2.00 | -0.35 | 4.36 | 0.029 | -0.15 | -2.71 | 2.42 | 0.883 |
| Hypothyroidism | 0.01 | -0.50 | 0.53 | 0.950 | 0.16 | -1.20 | 1.51 | 0.766 | -1.23 | -3.02 | 0.56 | 0.076 |
| Arthritis | -0.04 | -0.43 | 0.36 | 0.802 | 0.21 | -0.79 | 1.21 | 0.588 | -0.24 | -1.57 | 1.09 | 0.640 |
| Anxiety | 0.22 | -0.06 | 0.50 | 0.043 | -0.16 | -0.83 | 0.50 | 0.525 | 0.20 | -0.89 | 1.29 | 0.639 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Migraine | 0.40 | 0.01 | 0.79 | 0.008 | 0.27 | -0.62 | 1.16 | 0.431 | 0.22 | -0.99 | 1.44 | 0.635 |
| Cancer | -0.33 | -0.68 | 0.02 | 0.016 | -0.06 | -1.00 | 0.88 | 0.877 | -0.52 | -1.75 | 0.71 | 0.275 |
| Asthma | 0.02 | -0.23 | 0.28 | 0.818 | 0.19 | -0.40 | 0.77 | 0.407 | 0.10 | -0.80 | 1.00 | 0.774 |
| Renal failure | 1.24 | -0.39 | 2.86 | 0.050 | 5.49 | 1.19 | 9.80 | 0.001 | -2.51 | -7.79 | 2.76 | 0.219 |
| Liver failure | 0.12 | -0.99 | 1.23 | 0.779 | -0.42 | -2.75 | 1.91 | 0.639 | -0.15 | -3.81 | 3.50 | 0.914 |
| Osteoporosis | -0.35 | -1.40 | 0.69 | 0.381 | 0.72 | -2.10 | 3.54 | 0.508 | 1.37 | -2.27 | 5.00 | 0.332 |
| Suicidality | 0.72 | 0.13 | 1.31 | 0.002 | 0.35 | -1.16 | 1.86 | 0.550 | 1.70 | -0.31 | 3.70 | 0.029 |
| Antihypertensive | -0.11 | -0.48 | 0.26 | 0.452 | -0.36 | -1.44 | 0.72 | 0.392 | 0.28 | -1.11 | 1.66 | 0.606 |
| Aspirin | 0.03 | -0.57 | 0.64 | 0.890 | 0.49 | -1.00 | 1.99 | 0.394 | 1.31 | -0.66 | 3.27 | 0.086 |
| Anticoagulants | 0.37 | -0.72 | 1.46 | 0.384 | 0.57 | -3.35 | 4.48 | 0.708 | -0.12 | -4.11 | 3.88 | 0.940 |
| NSAIDs | 0.95 | 0.39 | 1.51 | <0.001 | 0.20 | -1.20 | 1.59 | 0.715 | 0.30 | -1.79 | 2.38 | 0.711 |
| Anticonvulsants | 0.91 | -0.02 | 1.85 | 0.012 | -0.12 | -2.87 | 2.63 | 0.907 | 0.96 | -2.24 | 4.15 | 0.439 |
| Hypnotics | 0.20 | -0.16 | 0.56 | 0.145 | 0.57 | -0.27 | 1.41 | 0.079 | -0.30 | -1.47 | 0.86 | 0.500 |
| Bisphosphonates | 0.52 | -1.52 | 2.57 | 0.509 | -0.89 | -4.21 | 2.43 | 0.489 | -2.06 | -5.52 | 1.41 | 0.126 |
| Contraceptives | -0.53 | -0.94 | -0.13 | 0.001 | -0.23 | -1.11 | 0.64 | 0.493 | -0.43 | -1.74 | 0.87 | 0.391 |
| *Constant* | 2.36 | -0.61 | 5.34 | 0.041 | -0.20 | -4.19 | 3.79 | 0.895 | 8.87 | 0.42 | 17.31 | 0.007 |

| | **Efficacy, change from baseline *(FSA, N= 673,177)*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 months** | | | | **6 months** | | | | **12 months** | | | |
| | *MD* | *99% CI* | | *P* | *MD* | *99% CI* | | *P* | *MD* | *99% CI* | | *P* |
| ***Statins*** | -0.01 | -0.16 | 0.14 | 0.846 | -0.02 | -0.20 | 0.16 | 0.748 | -0.01 | -0.12 | 0.11 | 0.855 |
| Antidepressant category (SSRIs) | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TCAs | 0.18 | 0.07 | 0.30 | <0.001 | 0.07 | -0.07 | 0.22 | 0.172 | 0.05 | -0.08 | 0.17 | 0.342 |
| MAOIs | 0.54 | -1.54 | 2.62 | 0.495 | 0.29 | -1.99 | 2.56 | 0.739 | 0.47 | -2.30 | 3.24 | 0.645 |
| Other antidepressants | 0.10 | -0.01 | 0.20 | 0.015 | 0.05 | -0.08 | 0.19 | 0.298 | 0.05 | -0.09 | 0.20 | 0.297 |
| | | | | | | | | | | | | |
| PHQ-9 baseline | -0.50 | -0.52 | -0.48 | <0.001 | -0.65 | -0.68 | -0.61 | <0.001 | -0.67 | -0.71 | -0.63 | <0.001 |
| BMI | 0.02 | 0.01 | 0.03 | 0.001 | 0.03 | 0.00 | 0.07 | 0.008 | 0.02 | -0.01 | 0.06 | 0.053 |
| | | | | | | | | | | | | |
| Read codes for depression (Major depression) | | | | | | | | | | | | |
| Minor depression | 0.07 | 0.01 | 0.12 | 0.001 | 0.05 | 0.00 | 0.10 | 0.015 | 0.03 | -0.03 | 0.09 | 0.158 |
| Other | 0.03 | -0.11 | 0.17 | 0.576 | 0.02 | -0.15 | 0.18 | 0.784 | 0.03 | -0.15 | 0.20 | 0.676 |
| | | | | | | | | | | | | |
| Townsend deprivation score in fifths (1, least deprived) | | | | | | | | | | | | |
| 2 | 0.38 | 0.12 | 0.64 | 0.001 | 0.52 | 0.09 | 0.94 | 0.004 | 0.58 | -0.45 | 1.62 | 0.073 |
| 3 | 0.88 | 0.72 | 1.04 | <0.001 | 1.06 | 0.76 | 1.37 | <0.001 | 1.20 | 0.67 | 1.73 | <0.001 |
| 4 | 1.28 | 1.14 | 1.42 | <0.001 | 1.52 | 1.07 | 1.96 | <0.001 | 1.40 | 0.71 | 2.09 | <0.001 |
| 5, most deprived | 1.64 | 1.45 | 1.83 | <0.001 | 1.73 | 1.22 | 2.23 | <0.001 | 1.19 | 0.55 | 1.82 | <0.001 |
| | | | | | | | | | | | | |
| Region of England (East Midlands) | | | | | | | | | | | | |
| East of England | -0.02 | -0.24 | 0.19 | 0.767 | 0.01 | -0.21 | 0.23 | 0.930 | -0.01 | -0.20 | 0.17 | 0.855 |
| London | -0.05 | -0.22 | 0.12 | 0.448 | -0.04 | -0.24 | 0.16 | 0.588 | -0.02 | -0.21 | 0.18 | 0.802 |
| North East | 0.02 | -0.21 | 0.25 | 0.796 | 0.02 | -0.23 | 0.26 | 0.845 | 0.02 | -0.27 | 0.31 | 0.836 |
| North West | -0.01 | -0.18 | 0.15 | 0.820 | 0.01 | -0.17 | 0.18 | 0.889 | 0.01 | -0.18 | 0.20 | 0.880 |
| South Central | -0.08 | -0.26 | 0.11 | 0.255 | -0.02 | -0.21 | 0.17 | 0.806 | -0.03 | -0.25 | 0.18 | 0.679 |
| South East | -0.03 | -0.21 | 0.15 | 0.656 | 0.00 | -0.21 | 0.20 | 0.995 | 0.00 | -0.17 | 0.17 | 0.977 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South West | -0.04 | -0.20 | 0.13 | 0.538 | 0.00 | -0.19 | 0.19 | 0.993 | -0.01 | -0.21 | 0.19 | 0.940 |
| West Midlands | -0.05 | -0.22 | 0.13 | 0.451 | 0.00 | -0.18 | 0.19 | 0.943 | -0.01 | -0.20 | 0.17 | 0.866 |
| Yorkshire & Humber | -0.02 | -0.23 | 0.18 | 0.743 | 0.00 | -0.22 | 0.23 | 0.979 | 0.00 | -0.23 | 0.23 | 0.999 |
| | | | | | | | | | | | | |
| Smoking status (Non-smoker) | | | | | | | | | | | | |
| Ex-smoker | -0.24 | -0.43 | -0.05 | 0.003 | -0.07 | -0.54 | 0.40 | 0.640 | -0.05 | -0.59 | 0.48 | 0.743 |
| Light-smoker | 0.99 | 0.81 | 1.16 | <0.001 | 1.54 | 0.99 | 2.08 | <0.001 | 1.51 | 0.84 | 2.19 | <0.001 |
| Moderate-smoker | 1.37 | 0.68 | 2.06 | <0.001 | 1.40 | -0.02 | 2.83 | 0.011 | 2.09 | 0.05 | 4.13 | 0.009 |
| Heavy-smoker | 0.86 | 0.02 | 1.69 | 0.009 | 2.55 | -0.45 | 5.54 | 0.020 | 3.13 | 0.61 | 5.64 | 0.004 |
| | | | | | | | | | | | | |
| Alcohol use (Non-drinker/trivial) | | | | | | | | | | | | |
| Light | -0.14 | -0.37 | 0.09 | 0.084 | -0.07 | -0.48 | 0.34 | 0.568 | -0.48 | -0.81 | -0.14 | 0.002 |
| Medium | -0.04 | -0.40 | 0.31 | 0.695 | 0.18 | -0.62 | 0.97 | 0.448 | -0.14 | -1.07 | 0.80 | 0.606 |
| Heavy | 0.05 | -0.45 | 0.56 | 0.746 | 0.60 | -1.21 | 2.41 | 0.278 | -0.04 | -2.04 | 1.95 | 0.937 |
| Very heavy | 0.20 | -0.61 | 1.02 | 0.436 | 0.22 | -1.03 | 1.47 | 0.567 | -0.11 | -2.55 | 2.32 | 0.863 |
| | | | | | | | | | | | | |
| Ethnic group (White) | | | | | | | | | | | | |
| African/Caribbean | 1.25 | 0.80 | 1.70 | <0.001 | 1.33 | 0.16 | 2.50 | 0.006 | 0.59 | -1.12 | 2.30 | 0.219 |
| Asian | 1.44 | 1.26 | 1.62 | <0.001 | 0.92 | 0.38 | 1.46 | <0.001 | 0.43 | -0.38 | 1.24 | 0.113 |
| Other | 1.24 | 0.86 | 1.62 | <0.001 | 1.23 | 0.42 | 2.03 | 0.001 | 1.01 | 0.26 | 1.76 | 0.002 |
| | | | | | | | | | | | | |
| Age | 0.00 | 0.00 | 0.00 | <0.001 | 0.00 | 0.00 | 0.00 | 0.010 | 0.00 | 0.00 | 0.00 | 0.057 |
| | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex (Female) | | | | | | | | | | | | |
| Male | 0.03 | -0.02 | 0.08 | 0.118 | 0.01 | -0.04 | 0.06 | 0.518 | 0.01 | -0.05 | 0.07 | 0.702 |
| | | | | | | | | | | | | |
| Year of diagnosis (1998-2005) | | | | | | | | | | | | |
| 2006 to 2010 | 0.01 | -0.06 | 0.08 | 0.816 | -0.01 | -0.09 | 0.06 | 0.646 | -0.01 | -0.09 | 0.07 | 0.788 |
| 2011 to 2015 | -0.03 | -0.10 | 0.04 | 0.312 | -0.02 | -0.13 | 0.08 | 0.522 | -0.02 | -0.10 | 0.05 | 0.379 |
| 2016 to 2020 | 0.05 | -0.02 | 0.12 | 0.046 | 0.00 | -0.11 | 0.10 | 0.923 | 0.00 | -0.09 | 0.08 | 0.878 |
| | | | | | | | | | | | | |
| Coronary heart disease | 0.09 | -0.14 | 0.32 | 0.268 | 0.03 | -0.12 | 0.19 | 0.579 | 0.04 | -0.14 | 0.22 | 0.586 |
| Stroke | 0.01 | -0.21 | 0.24 | 0.888 | -0.02 | -0.19 | 0.16 | 0.780 | 0.00 | -0.24 | 0.24 | 0.996 |
| Diabetes | 0.02 | -0.10 | 0.14 | 0.699 | 0.03 | -0.14 | 0.19 | 0.654 | 0.00 | -0.15 | 0.15 | 0.967 |
| Epilepsy | 0.00 | -0.20 | 0.19 | 0.951 | 0.02 | -0.22 | 0.26 | 0.811 | 0.00 | -0.27 | 0.28 | 0.975 |
| Hypothyroidism | -0.02 | -0.20 | 0.16 | 0.720 | -0.02 | -0.18 | 0.15 | 0.785 | -0.01 | -0.21 | 0.19 | 0.874 |
| Arthritis | -0.01 | -0.14 | 0.11 | 0.761 | 0.00 | -0.16 | 0.16 | 0.991 | 0.00 | -0.13 | 0.14 | 0.941 |
| Anxiety | 0.00 | -0.07 | 0.08 | 0.966 | 0.01 | -0.07 | 0.08 | 0.834 | 0.02 | -0.07 | 0.10 | 0.592 |
| Migraine | 0.02 | -0.09 | 0.12 | 0.670 | 0.01 | -0.14 | 0.17 | 0.806 | 0.00 | -0.11 | 0.12 | 0.970 |
| Cancer | -0.04 | -0.13 | 0.05 | 0.229 | -0.03 | -0.13 | 0.07 | 0.456 | -0.03 | -0.14 | 0.09 | 0.550 |
| Asthma | 0.00 | -0.07 | 0.07 | 0.990 | 0.01 | -0.07 | 0.10 | 0.684 | 0.00 | -0.08 | 0.09 | 0.900 |
| Renal failure | -0.02 | -0.41 | 0.36 | 0.871 | -0.03 | -0.57 | 0.52 | 0.899 | -0.02 | -0.66 | 0.62 | 0.935 |
| Liver failure | 0.04 | -0.21 | 0.29 | 0.674 | 0.03 | -0.28 | 0.35 | 0.784 | 0.01 | -0.32 | 0.34 | 0.944 |
| Osteoporosis | 0.00 | -0.21 | 0.21 | 0.999 | 0.03 | -0.23 | 0.29 | 0.762 | 0.00 | -0.29 | 0.29 | 0.977 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suicidality | 0.08 | -0.13 | 0.28 | 0.316 | 0.06 | -0.10 | 0.22 | 0.328 | 0.05 | -0.12 | 0.22 | 0.406 |
| Antihypertensive | -0.01 | -0.12 | 0.09 | 0.787 | -0.02 | -0.15 | 0.11 | 0.715 | -0.02 | -0.16 | 0.13 | 0.766 |
| Aspirin | 0.01 | -0.15 | 0.17 | 0.878 | 0.04 | -0.13 | 0.22 | 0.500 | 0.02 | -0.13 | 0.17 | 0.730 |
| Anticoagulants | -0.03 | -0.30 | 0.25 | 0.798 | -0.01 | -0.29 | 0.28 | 0.948 | 0.03 | -0.20 | 0.26 | 0.732 |
| NSAIDs | 0.12 | -0.05 | 0.28 | 0.064 | 0.06 | -0.10 | 0.22 | 0.309 | 0.04 | -0.16 | 0.24 | 0.587 |
| Anticonvulsants | 0.08 | -0.16 | 0.32 | 0.381 | 0.03 | -0.22 | 0.28 | 0.748 | 0.05 | -0.26 | 0.36 | 0.679 |
| Hypnotics | 0.06 | -0.06 | 0.17 | 0.197 | 0.03 | -0.09 | 0.15 | 0.459 | 0.01 | -0.12 | 0.15 | 0.772 |
| Bisphosphonates | -0.05 | -0.46 | 0.36 | 0.755 | 0.02 | -0.44 | 0.48 | 0.906 | 0.06 | -0.44 | 0.55 | 0.746 |
| Contraceptives | -0.09 | -0.24 | 0.05 | 0.078 | -0.06 | -0.17 | 0.06 | 0.199 | -0.04 | -0.15 | 0.08 | 0.427 |
| *Constant* | 2.00 | 1.58 | 2.42 | <0.001 | 3.27 | 2.19 | 4.35 | <0.001 | 4.93 | 3.82 | 6.04 | <0.001 |

## A5.5 Unadjusted and adjusted complete case analysis and full set analysis for all outcomes

***Table A5.5a*** *Unadjusted and adjusted odds ratios (any statin + antidepressant vs antidepressant-only) for acceptability and tolerability at 2 months, 6 months, and 12 months; complete case analysis and full set analysis.*

| | | **COMPLETE CASE ANALYSIS** | | | | | |
|---|---|---|---|---|---|---|---|
| | | Unadjusted analysis N= 673,177 | | | Adjusted analysis N= 63,801 | | |
| Outcome | Time point | *OR* | *99% CI* | *P* | *aOR* | *99% CI* | *P* |
| **Acceptability** | 2mo | 0.88 | 0.86 to 0.91 | <0.001 | 0.84 | 0.76 to 0.94 | <0.001 |
| | 6mo | 0.64 | 0.62 to 0.66 | <0.001 | 0.86 | 0.78 to 0.95 | <0.001 |
| | 12mo | 0.44 | 0.42 to 0.45 | <0.001 | 0.79 | 0.70 to 0.88 | <0.001 |
| **Tolerability** | 2mo | 1.44 | 1.37 to 1.51 | <0.001 | 1.02 | 0.83 to 1.26 | 0.795 |
| | 6mo | 1.43 | 1.37 to 1.48 | <0.001 | 1.07 | 0.90 to 1.26 | 0.316 |
| | 12mo | 1.65 | 1.60 to 1.71 | <0.001 | 1.11 | 0.97 to 1.28 | 0.052 |

| | | **FULL SET ANALYSIS** | | | | | |
|---|---|---|---|---|---|---|---|
| | | Unadjusted analysis N= 673,177 | | | Adjusted analysis N= 673,177 | | |
| Outcome | Time point | *OR* | *99% CI* | *P* | *aOR* | *99% CI* | *P* |
| **Acceptability** | 2mo | 0.88 | 0.86 to 0.91 | <0.001 | 0.88 | 0.85 to 0.91 | <0.001 |
| | 6mo | 0.64 | 0.62 to 0.66 | <0.001 | 0.81 | 0.79 to 0.84 | <0.001 |
| | 12mo | 0.44 | 0.42 to 0.45 | <0.001 | 0.78 | 0.75 to 0.81 | <0.001 |
| **Tolerability** | 2mo | 1.44 | 1.37 to 1.51 | <0.001 | 0.92 | 0.87 to 0.98 | 0.001 |
| | 6mo | 1.43 | 1.37 to 1.48 | <0.001 | 0.94 | 0.89 to 0.99 | 0.001 |
| | 12mo | 1.65 | 1.60 to 1.71 | <0.001 | 1.02 | 0.97 to 1.06 | 0.351 |

***Table A5.5b*** *Unadjusted and adjusted odds ratios (any statin + antidepressant vs antidepressant-only) for safety (any adverse event, self-harm, suicidality, completed suicide, and all-cause mortality) at 2 months, 6 months, and 12 months; complete case analysis and full set analysis.*

| | | **COMPLETE CASE ANALYSIS** | | | | | |
|---|---|---|---|---|---|---|---|
| | | Unadjusted analysis N= 673,177 | | | Adjusted analysis N= 63,801 | | |
| Outcome | Time point | *OR* | *99% CI* | *P* | *aOR* | *99% CI* | *P* |
| **Any adverse event** | 2mo | 1.33 | 1.28 to 1.37 | <0.001 | 0.94 | 0.85 to 1.06 | 0.140 |
| | 6mo | 1.51 | 1.45 to 1.56 | <0.001 | 0.98 | 0.88 to 1.09 | 0.605 |
| | 12mo | 1.75 | 1.68 to 1.82 | <0.001 | 1.00 | 0.89 to 1.12 | 0.961 |
| **Self-harm** | 2mo | 0.33 | 0.23 to 0.48 | <0.001 | 0.14 | 0.01 to 1.46 | 0.031 |
| | 6mo | 0.30 | 0.23 to 0.40 | <0.001 | 0.22 | 0.04 to 1.16 | 0.019 |
| | 12mo | 0.31 | 0.24 to 0.40 | <0.001 | 0.20 | 0.06 to 0.72 | 0.001 |
| **Suicidality** | 2mo | 0.78 | 0.65 to 0.93 | <0.001 | 1.07 | 0.70 to 1.64 | 0.684 |
| | 6mo | 0.74 | 0.64 to 0.87 | <0.001 | 0.94 | 0.63 to 1.40 | 0.693 |
| | 12mo | 0.71 | 0.62 to 0.82 | <0.001 | 0.97 | 0.66 to 1.43 | 0.840 |
| **Completed suicide** | 2mo | 0.49 | 0.18 to 1.32 | 0.064 | 0.81 | 0.01 to 81.94 | 0.908 |
| | 6mo | 0.42 | 0.18 to 0.95 | 0.006 | 0.36 | 0.01 to 13.65 | 0.473 |
| | 12mo | 0.48 | 0.25 to 0.92 | 0.004 | 0.32 | 0.01 to 10.19 | 0.394 |
| **All-cause mortality** | 2mo | 3.72 | 3.35 to 4.14 | <0.001 | 0.66 | 0.36 to 1.19 | 0.066 |
| | 6mo | 3.72 | 3.35 to 4.14 | <0.001 | 0.66 | 0.36 to 1.19 | 0.066 |
| | 12mo | 4.43 | 4.13 to 4.74 | <0.001 | 0.69 | 0.52 to 0.92 | 0.001 |

| | | **FULL SET ANALYSIS** | | | | | |
|---|---|---|---|---|---|---|---|
| | | Unadjusted analysis N= 673,177 | | | Adjusted analysis N= 673,177 | | |
| Outcome | Time point | *OR* | *99% CI* | *P* | *aOR* | *99% CI* | *P* |
| **Any adverse event** | 2mo | 1.33 | 1.28 to 1.37 | <0.001 | 0.96 | 0.92 to 0.99 | 0.001 |
| | 6mo | 1.51 | 1.45 to 1.56 | <0.001 | 0.98 | 0.95 to 1.02 | 0.174 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 12mo | 1.75 | 1.68 to 1.82 | <0.001 | 0.99 | 0.95 to 1.03 | 0.468 |
| **Self-harm** | 2mo | 0.33 | 0.23 to 0.48 | <0.001 | 0.70 | 0.44 to 1.12 | 0.049 |
| | 6mo | 0.30 | 0.23 to 0.40 | <0.001 | 0.73 | 0.51 to 1.05 | 0.026 |
| | 12mo | 0.31 | 0.24 to 0.40 | <0.001 | 0.81 | 0.60 to 1.09 | 0.068 |
| **Suicidality** | 2mo | 0.78 | 0.65 to 0.93 | <0.001 | 1.08 | 0.89 to 1.31 | 0.298 |
| | 6mo | 0.74 | 0.64 to 0.87 | <0.001 | 1.07 | 0.91 to 1.27 | 0.272 |
| | 12mo | 0.71 | 0.62 to 0.82 | <0.001 | 1.04 | 0.89 to 1.20 | 0.550 |
| **Completed suicide** | 2mo | 0.49 | 0.18 to 1.32 | 0.064 | 0.98 | 0.24 to 3.98 | 0.977 |
| | 6mo | 0.42 | 0.18 to 0.95 | 0.006 | 0.81 | 0.28 to 2.36 | 0.609 |
| | 12mo | 0.48 | 0.25 to 0.92 | 0.004 | 1.09 | 0.48 to 2.47 | 0.794 |
| **All-cause mortality** | 2mo | 3.72 | 3.35 to 4.14 | <0.001 | 0.69 | 0.62 to 0.78 | <0.001 |
| | 6mo | 3.72 | 3.35 to 4.14 | <0.001 | 0.69 | 0.62 to 0.78 | <0.001 |
| | 12mo | 4.43 | 4.13 to 4.74 | <0.001 | 0.72 | 0.67 to 0.77 | <0.001 |

***Table A5.5c*** *Unadjusted and adjusted odds ratios/mean differences (any statin + antidepressant vs antidepressant-only) for efficacy (response, remission, change in depressive score), as measured on the PHQ-9 at 2 months, 6 months, and 12 months; complete case analysis and full set analysis.*

| | | **COMPLETE CASE ANALYSIS** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Unadjusted analysis N= see below | | | | Adjusted analysis N= see below | | | |
| Outcome | Time point | *N* | *OR* | *99% CI* | *P* | *N* | *aOR* | *99% CI* | *P* |
| **Response** | 2mo | 47,720 | 1.09 | 0.99 to 1.19 | 0.017 | 22,804 | 1.10 | 0.93 to 1.29 | 0.155 |
| | 6mo | 10.580 | 1.12 | 0.91 to 1.37 | 0.160 | 5,035 | 1.06 | 0.74 to 1.52 | 0.685 |
| | 12mo | 6,289 | 1.25 | 0.93 to 1.70 | 0.054 | 2,938 | 1.47 | 0.87 to 2.49 | 0.057 |
| **Remission** | 2mo | 47,720 | 1.25 | 1.13 to 1.38 | <0.001 | 22,804 | 1.16 | 0.95 to 1.41 | 0.052 |
| | 6mo | 10.580 | 1.45 | 1.20 to 1.75 | <0.001 | 5,035 | 0.99 | 0.63 to 1.54 | 0.938 |
| | 12mo | 6,289 | 1.51 | 1.19 to 1.91 | <0.001 | 2,938 | 1.37 | 0.73 to 2.55 | 0.199 |
| | | *N* | *MD* | *99% CI* | *P* | *N* | *MD* | *99% CI* | *P* |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Change** | 2mo | 72,457 | 0.10 | -0.18 to 0.38 | 0.349 | 22,804 | -0.11 | -0.54 to 0.32 | 0.509 |
| **in depressive** | 6mo | 18,483 | 0.01 | -0.66 to 0.67 | 0.972 | 5,025 | -0.02 | -1.10 to 1.06 | 0.962 |
| **score** | 12mo | 11,764 | -0.03 | -1.05 to 0.98 | 0.932 | 2,935 | -1.31 | -2.92 to 0.30 | 0.035 |

| | | **FULL SET ANALYSIS** | | | | | |
|---|---|---|---|---|---|---|---|
| | | Unadjusted analysis N= 673,177 | | | Adjusted analysis N= 673,177 | | |
| Outcome | Time point | *OR* | *99% CI* | *P* | *aOR* | *99% CI* | *P* |
| **Response** | 2mo | 1.08 | 1.02 to 1.14 | <0.001 | 1.01 | 0.94 to 1.09 | 0.715 |
| | 6mo | 1.06 | 1.01 to 1.12 | <0.001 | 1.01 | 0.95 to 1.06 | 0.723 |
| | 12mo | 1.05 | 0.99 to 1.11 | 0.018 | 1.00 | 0.96 to 1.04 | 0.992 |
| **Remission** | 2mo | 1.13 | 1.06 to 1.19 | <0.001 | 1.02 | 0.95 to 1.08 | 0.502 |
| | 6mo | 1.10 | 1.04 to 1.17 | <0.001 | 1.01 | 0.95 to 1.08 | 0.541 |
| | 12mo | 1.09 | 1.01 to 1.17 | <0.001 | 1.00 | 0.92 to 1.08 | 0.973 |
| | | *MD* | *99% CI* | *P* | *MD* | *99% CI* | *P* |
| **Change** | 2mo | -0.08 | -0.23 to 0.07 | 0.136 | -0.01 | -0.16 to 0.14 | 0.846 |
| **in depressive** | 6mo | -0.05 | -0.26 to 0.15 | 0.462 | -0.02 | -0.20 to 0.16 | 0.748 |
| **score** | 12mo | -0.03 | -0.24 to 0.18 | 0.683 | -0.01 | -0.12 to 0.11 | 0.855 |

## A5.6 Sensitivity analysis on sample >65 years old

***Table A5.6a*** *Characteristics of subgroup sample >65 years old at baseline. Values are numbers (percentages) unless stated otherwise*

| **Characteristic** | **Antidepressant-only N= 59,124** | **Any statin + antidepressant N= 25,857** | **All sample N= 84,981** |
|---|---|---|---|
| Sex | | | |
| Male | 22,120 (37.41) | 12,699 (49.11) | 34,819 (40.97) |
| Mean age [SD] | 78.44 (8.44) | 77.77 (7.58) | 78.24 (8.19) |
| Read codes for depression | | | |

| | | | |
|---|---|---|---|
| Major depression | 38,799 (65.62) | 14,240 (55.07) | 53,039 (62.41) |
| Minor depression | 18,728 (31.68) | 10,783 (41.70) | 29,511 (34.73) |
| Other | 1,597 (2.70) | 834 (3.23) | 2,431 (2.86) |
| PHQ-9 baseline [SD] | 14.92 (5.18) | 14.93 (5.24) | 14.92 (5.20) |
| Year of diagnosis | | | |
| 1998 to 2005 | 23,656 (40.01) | 3,753 (14.51) | 27,409 (32.25) |
| 2006 to 2010 | 12,403 (20.98) | 6,772 (26.19) | 19,175 (22.56) |
| 2011 to 2015 | 11,951 (20.21) | 7,774 (30.07) | 19,725 (23.21) |
| 2016 to 2020 | 11,114 (18.80) | 7,558 (29.23) | 18,672 (21.97) |
| Body Mass Index [SD] | 26.15 (5.31) | 27.47 (5.49) | 26.59 (5.41) |
| Smoking | | | |
| Non-smoker | 28,571 (48.32) | 12,282 (47.50) | 40,853 (48.07) |
| Ex-smoker | 16,231 (27.45) | 9,319 (36.04) | 25,550 (30.07) |
| Light-smoker | 7,642 (12.93) | 3,316 (12.82) | 10,958 (12.89) |
| Moderate-smoker | 368 (0.62) | 110 (0.43) | 478 (0.56) |
| Heavy-smoker | 171 (0.29) | 60 (0.23) | 231 (0.27) |
| Alcohol (daily units) | | | |
| Non-drinker/trivial (< 1) | 16,681 (28.21) | 9,156 (35.41) | 25,837 (30.40) |
| Light (1-2) | 9,035 (15.28) | 4,692 (18.15) | 13,727 (16.15) |
| Medium (3-6) | 2,446 (4.14) | 1,514 (5.86) | 3,960 (4.66) |
| Heavy (7-9) | 275 (0.47) | 174 (0.67) | 449 (0.53) |
| Very heavy (> 9) | 226 (0.38) | 108 (0.42) | 334 (0.39) |
| Ethnic group | | | |
| White | 35,183 (59.51) | 19,170 (74.14) | 54,353 (63.96) |
| Indian | 309 (0.52) | 308 (1.19) | 617 (0.73) |
| Pakistani | 158 (0.27) | 182 (0.70) | 340 (0.40) |
| Bangladeshi | 96 (0.16) | 130 (0.50) | 226 (0.27) |
| Other Asian | 148 (0.25) | 145 (0.56) | 293 (0.34) |
| Caribbean | 285 (0.48) | 240 (0.93) | 525 (0.62) |

| | | | |
|---|---|---|---|
| Black African | 109 (0.18) | 67 (0.26) | 176 (0.21) |
| Chinese | 40 (0.07) | 28 (0.11) | 68 (0.08) |
| Other | 303 (0.51) | 202 (0.78) | 505 (0.59) |
| Townsend deprivation score in fifths | | | |
| 1 (Least deprived) | 18,031 (30.50) | 7,352 (28.43) | 25,383 (29.87) |
| 2 | 15,375 (26.00) | 6,439 (24.90) | 21,814 (25.67) |
| 3 | 12,180 (20.60) | 5,294 (20.47) | 17,474 (20.56) |
| 4 | 8,341 (14.11) | 4,110 (15.90) | 12,451 (14.65) |
| 5 (Most deprived) | 5,055 (8.55) | 2,631 (10.18) | 7,686 (9.04) |
| Region of England | | | |
| East Midlands | 1,787 (3.02) | 661 (2.56) | 2,448 (2.88) |
| East of England | 2,993 (5.06) | 1,069 (4.13) | 4,062 (4.78) |
| London | 7,381 (12.48) | 3,782 (14.63) | 11,163 (13.14) |
| North-East | 1,725 (2.92) | 872 (3.37) | 25,97 (3.06) |
| North-West | 11,831 (20.01) | 6,214 (24.03) | 18,045 (21.23) |
| South-Central | 8,223 (13.91) | 3,041 (11.76) | 11264 (13.25) |
| South-East | 7,575 (12.81) | 3,023 (11.69) | 10,598 (12.47) |
| South-West | 8,226 (13.91) | 2,903 (11.23) | 11,129 (13.10) |
| West Midlands | 6,583 (11.13) | 3,037 (11.75) | 9,620 (11.32) |
| Yorkshire & Humber | 2,800 (4.74) | 1,255 (4.85) | 4,055 (4.77) |
| Comorbidities at baseline | | | |
| Coronary heart disease | 7,015 (11.86) | 9,381 (36.28) | 16,396 (19.29) |
| Stroke | 6,451 (10.91) | 6,362 (24.60) | 12,813 (15.08) |
| Diabetes | 5,566 (9.41) | 7,223 (27.93) | 12,789 (15.05) |
| Epilepsy | 886 (1.50) | 513 (1.98) | 1,399 (1.65) |
| Hypothyroidism | 5,074 (8.58) | 2,816 (10.89) | 7,890 (9.28) |
| Arthritis | 17,657 (29.86) | 8,858 (34.26) | 26,515 (31.20) |
| Anxiety | 6,670 (11.28) | 2,868 (11.09) | 9,538 (11.22) |
| Migraine | 2,006 (3.39) | 1,032 (3.99) | 3,038 (3.57) |

| | | | |
|---|---|---|---|
| Cancer | 15,252 (25.80) | 6,918 (26.75) | 22,170 (26.09) |
| Asthma | 10,491 (17.74) | 5,086 (19.67) | 15,577 (18.33) |
| Renal failure | 763 (1.29) | 597 (2.31) | 1,360 (1.60) |
| Liver failure | 638 (1.08) | 425 (1.64) | 1,063 (1.25) |
| Osteoporosis | 4,490 (7.59) | 1,745 (6.75) | 6,235 (7.34) |
| Suicidality | 481 (0.81) | 224 (0.87) | 705 (0.83) |
| Antidepressant category at baseline | | | |
| SSRIs | 44,388 (75.08) | 20,103 (77.75) | 64,491 (75.89) |
| TCAs | 7,506 (12.70) | 1,721 (6.66) | 9,227 (10.86) |
| MAOIs | 13 (0.02) | 2 (0.01) | 15 (0.02) |
| other ADs | 7,217 (12.21) | 4,031 (15.59) | 1,1248 (13.24) |
| Use of other drugs at baseline | | | |
| Antihypertensive | 12,622 (21.35) | 14,006 (54.17) | 26,628 (31.33) |
| Aspirin | 9,293 (15.72) | 10,856 (41.98) | 20,149 (23.71) |
| Anticoagulants | 3,196 (5.41) | 2,943 (11.38) | 6,139 (7.22) |
| NSAIDs | 3,827 (6.47) | 1,117 (4.32) | 4,944 (5.82) |
| Anticonvulsants | 1,711 (2.89) | 1,240 (4.80) | 2,951 (3.47) |
| Hypnotics | 7,873 (13.32) | 2,926 (11.32) | 10,799 (12.71) |
| Bisphosphonates | 1,220 (2.06) | 585 (2.26) | 1,805 (2.12) |
| Contraceptives | 3 (0.01) | 3 (0.01) | 6 (0.01) |

***Table A5.6b*** *Unadjusted and adjusted odds ratios (any statin + antidepressant vs antidepressant-only) for acceptability and tolerability at 2 months, 6 months, and 12 months; subgroup sample >65 years old*

| | | **COMPLETE CASE ANALYSIS** | | | | | | **FULL SET ANALYSIS** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Unadjusted analysis N= 84,981 | | | Adjusted analysis N= 6,091 | | | Unadjusted analysis N= 84,981 | | | Adjusted analysis N= 84,981 | | |
| Outcome | Time point | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* |
| **Acceptability** | 2mo | 0.82 | 0.79 to 0.85 | <0.001 | 0.83 | 0.70 to 0.99 | 0.006 | 0.82 | 0.79 to 0.85 | <0.001 | 0.89 | 0.85 to 0.93 | <0.001 |
| | 6mo | 0.76 | 0.73 to 0.79 | <0.001 | 0.82 | 0.69 to 0.97 | 0.002 | 0.76 | 0.73 to 0.79 | <0.001 | 0.85 | 0.81 to 0.89 | <0.001 |
| | 12mo | 0.71 | 0.67 to 0.74 | <0.001 | 0.75 | 0.61 to 0.92 | <0.001 | 0.71 | 0.67 to 0.74 | <0.001 | 0.81 | 0.78 to 0.87 | <0.001 |
| **Tolerability** | 2mo | 0.93 | 0.87 to 0.99 | 0.002 | 0.90 | 0.67 to 1.22 | 0.381 | 0.93 | 0.87 to 0.99 | 0.002 | 0.92 | 0.86 to 0.99 | 0.006 |
| | 6mo | 0.97 | 0.92 to 1.02 | 0.089 | 0.98 | 0.76 to 1.25 | 0.800 | 0.97 | 0.92 to 1.02 | 0.089 | 0.94 | 0.88 to 1.00 | 0.011 |
| | 12mo | 1.06 | 1.01 to 1.11 | 0.001 | 1.03 | 0.83 to 1.27 | 0.757 | 1.06 | 1.01 to 1.11 | 0.001 | 0.98 | 0.93 to 1.04 | 0.476 |

***Table A5.6c*** *Unadjusted and adjusted odds ratios (any statin + antidepressant vs antidepressant-only) for safety (any adverse event, self-harm, suicidality, completed suicide, and all-cause mortality) at 2 months, 6 months, and 12 months; subgroup sample >65 years old*

| | | **COMPLETE CASE ANALYSIS** | | | | | | **FULL SET ANALYSIS** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Unadjusted analysis N= 84,981 | | | Adjusted analysis N= 6,091 | | | Unadjusted analysis N= 84,981 | | | Adjusted analysis N= 84,981 | | |
| Outcome | Time point | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* |
| **Any adverse event** | 2mo | 1.10 | 1.05 to 1.15 | <0.001 | 1.00 | 0.85 to 1.19 | 0.943 | 1.10 | 1.05 to 1.15 | <0.001 | 0.98 | 0.94 to 1.03 | 0.367 |
| | 6mo | 1.17 | 1.12 to 1.23 | <0.001 | 0.92 | 0.77 to 1.10 | 0.245 | 1.17 | 1.12 to 1.23 | <0.001 | 0.99 | 0.94 to 1.05 | 0.725 |
| | 12mo | 1.19 | 1.12 to 1.26 | <0.001 | 0.91 | 0.75 to 1.11 | 0.227 | 1.19 | 1.12 to 1.26 | <0.001 | 0.97 | 0.91 to 1.03 | 0.168 |
| **Self-harm** | 2mo | 0.59 | 0.33 to 1.05 | 0.018 | 0.00 | 0.00 to 1374.98 | 0.083 | 0.59 | 0.33 to 1.05 | 0.018 | 0.61 | 0.29 to 1.26 | 0.080 |
| | 6mo | 0.67 | 0.41 to 1.09 | 0.036 | 0.05 | 0.00 to 1.56 | 0.025 | 0.67 | 0.41 to 1.09 | 0.036 | 0.65 | 0.35 to 1.20 | 0.071 |
| | 12mo | 0.71 | 0.45 to 1.13 | 0.057 | 0.06 | 0.00 to 0.92 | 0.008 | 0.71 | 0.45 to 1.13 | 0.057 | 0.73 | 0.41 to 1.28 | 0.150 |
| **Suicidality** | 2mo | 1.53 | 1.16 to 2.02 | <0.001 | 0.87 | 0.39 to 1.96 | 0.659 | 1.53 | 1.16 to 2.02 | <0.001 | 1.15 | 0.83 to 1.59 | 0.275 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6mo | 1.45 | 1.15 to 1.83 | <0.001 | 0.73 | 0.34 to 1.56 | 0.284 | 1.45 | 1.14 to 1.83 | <0.001 | 1.14 | 0.87 to 1.49 | 0.208 |
| | 12mo | 1.39 | 1.22 to 1.73 | <0.001 | 0.67 | 0.33 to 1.34 | 0.135 | 1.39 | 1.12 to 1.73 | <0.001 | 1.13 | 0.88 to 1.44 | 0.201 |
| **Completed suicide** | 2mo | 0.57 | 0.07 to 4.39 | 0.480 | - | | | - | | | 1.77 | 0.13 to 24.52 | 0.577 |
| | 6mo | 0.43 | 0.09 to 1.99 | 0.155 | - | | | - | | | 0.82 | 0.13 to 5.06 | 0.774 |
| | 12mo | 0.69 | 0.22 to 2.17 | 0.400 | - | | | - | | | 1.59 | 0.38 to 6.63 | 0.400 |
| **All-cause mortality** | 2mo | 0.71 | 0.64 to 0.78 | <0.001 | 0.61 | 0.32 to 1.17 | 0.051 | 0.71 | 0.64 to 0.78 | <0.001 | 0.69 | 0.62 to 0.78 | <0.001 |
| | 6mo | 0.71 | 0.64 to 0.78 | <0.001 | 0.61 | 0.32 to 1.17 | 0.051 | 0.71 | 0.64 to 0.78 | <0.001 | 0.69 | 0.62 to 0.78 | <0.001 |
| | 12mo | 0.80 | 0.76 to 0.85 | <0.001 | 0.70 | 0.52 to 0.96 | 0.003 | 0.80 | 0.76 to 0.85 | <0.001 | 0.71 | 0.66 to 0.76 | <0.001 |

***Table A5.6d*** *Unadjusted and adjusted odds ratios/mean differences (any statin + antidepressant vs antidepressant-only) for efficacy (response, remission, change in depressive score), as measured on the PHQ-9 at 2 months, 6 months, and 12 months; subgroup sample >65 years old*

| | | **COMPLETE CASE ANALYSIS** | | | | | | | | **FULL SET ANALYSIS** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Unadjusted analysis N= see below | | | | Adjusted analysis N= see below | | | | Unadjusted analysis N= 84,981 | | | Adjusted analysis N= 84,981 | | |
| Outcome | Time point | *N* | *OR* | *99% CI* | *P* | *N* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* | *OR* | *99% CI* | *P* |
| **Response** | 2mo | 3,592 | 1.06 | 0.88 to 1.27 | 0.452 | 2,019 | 1.09 | 0.82 to 1.45 | 0.446 | 1.00 | 0.91 to 1.09 | 0.872 | 1.04 | 0.99 to 1.09 | 0.024 |
| | 6mo | 576 | 1.16 | 0.77 to 1.77 | 0.351 | 330 | 1.02 | 0.40 to 2.63 | 0.947 | 0.99 | 0.92 to 1.07 | 0.721 | 1.03 | 0.98 to 1.08 | 0.104 |
| | 12mo | 326 | 1.08 | 0.57 to 2.04 | 0.768 | 171 | 1.86 | 0.43 to 8.10 | 0.279 | 0.99 | 0.93 to 1.05 | 0.565 | 0.99 | 0.94 to 1.04 | 0.706 |
| **Remission** | 2mo | 5,570 | 0.99 | 0.83 to 1.18 | 0.864 | 2,019 | 1.26 | 0.91 to 1.75 | 0.062 | 1.02 | 0.92 to 1.12 | 0.605 | 1.05 | 0.98 to 1.13 | 0.049 |
| | 6mo | 1,119 | 1.41 | 0.99 to 2.03 | 0.013 | 319 | 1.12 | 0.40 to 3.15 | 0.784 | 1.01 | 0.92 to 1.11 | 0.720 | 1.04 | 0.97 to 1.10 | 0.131 |
| | 12mo | 695 | 1.26 | 0.79 to 2.00 | 0.204 | 152 | 1.68 | 0.34 to 8.20 | 0.402 | 1.00 | 0.91 to 1.09 | 0.953 | 1.02 | 0.96 to 1.09 | 0.391 |
| | | *N* | *MD* | *99% CI* | *P* | *N* | *MD* | *99% CI* | *P* | *MD* | *99% CI* | *P* | *MD* | *99% CI* | *P* |
| **Change** | 2mo | 3,592 | -0.17 | -0.70 to 0.35 | 0.390 | 2,020 | -0.25 | -0.97 to 0.47 | 0.366 | -0.08 | -0.20 to 0.35 | 0.421 | -0.01 | -0.25 to 0.28 | 0.901 |
| **in depression** | 6mo | 576 | -0.07 | -1.46 to 1.32 | 0.901 | 332 | 0.01 | -2.30 to 2.32 | 0.988 | -0.09 | -0.19 to 0.37 | 0.367 | -0.01 | -0.30 to 0.28 | 0.897 |
| **score** | 12mo | 326 | 0.18 | -2.12 to 2.48 | 0.839 | 178 | -1.36 | -4.62 to 1.89 | 0.276 | -0.09 | -0.13 to 0.31 | 0.250 | -0.02 | -0.20 to 0.23 | 0.840 |

## A5.7 Comparison with aspirin

***A5.7a*** *Background evidence for aspirin use in add-on to antidepressants for depression*

Small trials investigating acetylsalicylic acid (aspirin, a very commonly used anti-inflammatory and anti-platelet drug) in addition to antidepressant treatments sometimes showed a positive effect on depressive symptoms (Sepehrmanesh et al., 2017), sometimes no antidepressant effect but indeed more adverse events (Berk et al., 2020). Larger observational studies even suggested an increased association (OR = 1.10, 95% CI = 1.05 to 1.16) between the use of aspirin alone and depressive episodes (Kim et al., 2020).

Perhaps unsurprisingly, we could not identify any study that, akin to ours, explicitly assessed the acceptability and tolerability of antidepressant treatment in addition to aspirin. Our regression analyses did include data about aspirin (see Supplementary Material, S8), since it had been examined as a potential confounder. Overall, no significative effect for aspirin could be observed on acceptability and efficacy outcomes. Tolerability and safety (any adverse event and all-cause mortality) appeared worse. The general impression, compounded by more consistently positive clinical trials and meta-analyses (De Giorgi et al., 2021), is thus that statins may have an overall better profile for repurposing in depression. However, these observations should be considered with great caution since our study had not been conceived for assessing the effects of medications other than statins in add-on to antidepressants.

***Table A5.7b*** *Summary of regression analyses for aspirin*

CCA: complete case analysis; FSA: full set analysis

Acceptability

CCA

2 months: no effect

6 months: no effect

12 months: no effect

FSA

2 months: no effect

6 months: no effect

12 months: no effect

Tolerability

CCA
2 months: no effect
6 months: no effect
12 months: no effect
FSA
2 months: no effect
6 months: negative effect (OR 1.09, 95%CI 1.03 to 1.16, p <0.001)
12 months: negative effect (OR 1.08, 95%CI 1.03 to 1.14, p <0.001)
Any adverse event
CCA
2 months: no effect
6 months: no effect
12 months: no effect

FSA
2 months: negative effect (OR 1.07, 95%CI 1.07 to 1.11, p <0.001)
6 months: negative effect (OR 1.12, 95%CI 1.07 to 1.17, p <0.001)
12 months: negative effect (OR 1.18, 95%CI 1.12 to 1.24, p <0.001)
Self-harm
CCA
2 months: no effect
6 months: no effect
12 months: no effect
FSA
2 months: no effect
6 months: no effect
12 months: no effect
Suicidality

CCA
2 months: no effect
6 months: no effect
12 months: no effect
FSA
2 months: no effect
6 months: no effect
12 months: no effect
Completed suicide
CCA
2 months: no effect
6 months: no effect
12 months: no effect
FSA
2 months: no effect
6 months: no effect
12 months: no effect
All-cause mortality
CCA
2 months: no effect
6 months: no effect
12 months: no effect
FSA
2 months: no effect
6 months: no effect
12 months: negative effect (OR 1.15, 95%CI 1.07 to 1.24, p <0.001)
Response
CCA

2 months: no effect
6 months: no effect
12 months: no effect
FSA
2 months: no effect
6 months: no effect
12 months: no effect
Remission
CCA
2 months: no effect
6 months: no effect
12 months: no effect
FSA
2 months: no effect
6 months: no effect
12 months: no effect
Change in depressive score
*CCA*
2 months: no effect
6 months: no effect
12 months: no effect
*FSA*
2 months: no effect
6 months: no effect
12 months: no effect

***A5.7c** References*

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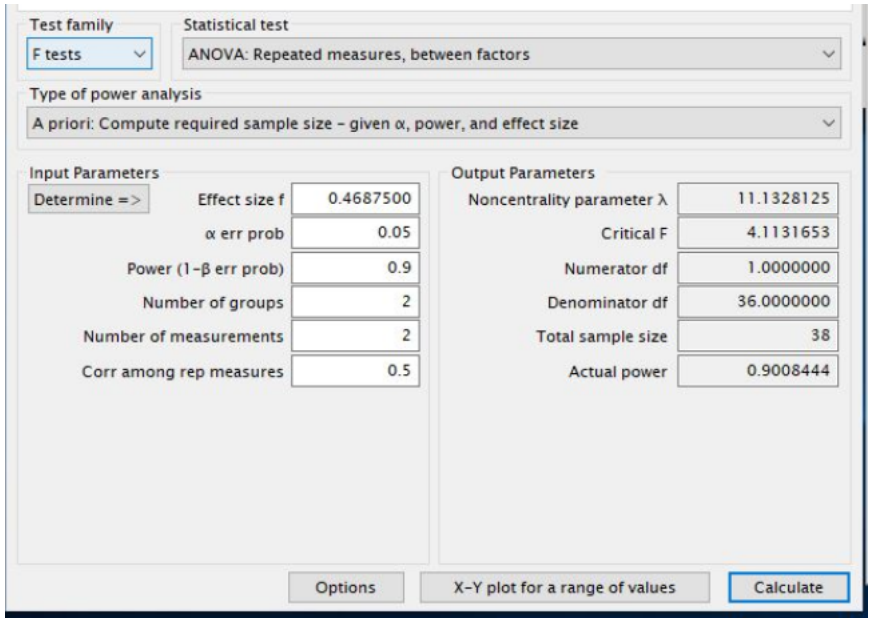
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A5.8 Infographic




**Appendix to Chapter 6**

## A6.1 Sample size calculation




## A6.2 Inclusion/exclusion criteria

Inclusion criteria

- Male or female
- Aged 18-50 years
- Sufficiently fluent English to understand and complete the tasks
- Body Mass Index in the range of 18-30
- Participant is willing and able to give informed consent for participation in the study
- Not currently taking any regular medications (except the contraceptive pill)

Exclusion criteria

- Currently any regular medications (except the contraceptive pill)

- History or current significant psychiatric illness
- Current alcohol or substance misuse disorder
- History or current significant hepatic disease
- History or current significant neurological condition (e.g., epilepsy)
- History of haemorrhagic stroke or lacunar infarct
- Known hyperglycaemia/pre-diabetes
- Known hypersensitivity to the study drug (i.e., simvastatin) or sucrose
- Pregnant, breast feeding, women of child-bearing potential not using appropriate contraceptive measures
- Participation in a study that uses the same or similar computer tasks as those used in the present study
- Participation in a study that involves the use of a medication within the last three months

## A6.3 Participants' repeated Bond-Lader Visual Analog Scale (BL-VAS)

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS1AlertDrowsy | 19.9545 | 15.26427 | 22 | 33.0714 | 27.87130 | 28 |
| RV_VAS1AlertDrowsy | 28.1818 | 20.09889 | 22 | 32.0714 | 26.47700 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS2CalmExcited | 32.5000 | 18.77372 | 22 | 31.7857 | 26.30640 | 28 |
| RV_VAS2CalmExcited | 34.2273 | 21.83691 | 22 | 40.0000 | 27.11840 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS3StrongFeeble | 27.1364 | 20.44108 | 22 | 33.5000 | 27.29740 | 28 |
| RV_VAS3StrongFeeble | 25.2727 | 17.14138 | 22 | 26.9643 | 22.87402 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS4FuzzyClearheaded | 74.9091 | 24.00974 | 22 | 71.1071 | 28.41536 | 28 |
| RV_VAS4FuzzyClearheaded | 70.3182 | 27.11068 | 22 | 66.5714 | 25.86923 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS5WellcoordinatedClumsy | 22.8636 | 20.75319 | 22 | 26.0714 | 28.92638 | 28 |
| RV_VAS5WellcoordinatedClumsy | 31.0909 | 26.59379 | 22 | 38.0357 | 30.58017 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS6LethargicEnergetic | 69.0000 | 21.10067 | 22 | 68.2143 | 16.95606 | 28 |
| RV_VAS6LethargicEnergetic | 61.1818 | 26.94021 | 22 | 65.8571 | 24.17638 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS7ContentedDiscontented | 20.7727 | 18.85012 | 22 | 25.5000 | 27.59562 | 28 |
| RV_VAS7ContentedDiscontented | 19.4091 | 17.25622 | 22 | 27.2857 | 28.18045 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS8TroubledTranquil | 76.0000 | 20.79377 | 22 | 71.8929 | 29.31861 | 28 |
| RV_VAS8TroubledTranquil | 70.3636 | 22.79003 | 22 | 68.5000 | 27.83217 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS9MentallyslowQuick | 71.5455 | 21.27312 | 22 | 66.2857 | 24.55358 | 28 |
| RV_VAS9MentallyslowQuick | 63.5455 | 25.15992 | 22 | 65.0000 | 21.86152 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS10TenseRelaxed | 73.4091 | 20.74943 | 22 | 67.7857 | 29.22373 | 28 |
| RV_VAS10TenseRelaxed | 71.9091 | 23.16794 | 22 | 67.0357 | 25.41286 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS11AttentiveDreamy | 29.0909 | 22.95733 | 22 | 33.2500 | 27.75638 | 28 |
| RV_VAS11AttentiveDreamy | 28.7727 | 22.29015 | 22 | 33.1071 | 21.72955 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS12IncompetentProficient | 76.5455 | 17.21773 | 22 | 71.3571 | 24.99217 | 28 |
| RV_VAS12IncompetentProficient | 72.7273 | 15.85404 | 22 | 68.8571 | 25.00624 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS13HappySad | 15.2273 | 10.41031 | 22 | 32.5714 | 33.30046 | 28 |
| RV_VAS13HappySad | 24.0909 | 14.51734 | 22 | 24.9286 | 25.66151 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS14AntagonisticFriendly | 90.1364 | 9.37725 | 22 | 80.5357 | 28.35160 | 28 |
| RV_VAS14AntagonisticFriendly | 80.2727 | 18.84064 | 22 | 72.8571 | 33.26405 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS15InterestedBored | 24.4545 | 21.05939 | 22 | 25.9286 | 28.14766 | 28 |
| RV_VAS15InterestedBored | 23.8182 | 17.18980 | 22 | 29.9286 | 24.52803 | 28 |

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| SV_VAS16WithrawnSociable | 75.4545 | 15.25256 | 22 | 71.3929 | 28.50515 | 28 |
| RV_VAS16WithrawnSociable | 71.8182 | 20.75856 | 22 | 68.9286 | 26.25788 | 28 |

## A6.4 Descriptive statistics for neuropsychological tasks

Outcomes measured are defined in the Methods. Values are means and standard errors of the mean, unless indicated otherwise

***FERT***

FERT accuracy, all emotions

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| Sad | 65.2273 | 10.90841 | 22 | 63.4821 | 10.19121 | 28 |
| Fear | 40.3409 | 12.42347 | 22 | 29.3750 | 13.95471 | 28 |
| Happy | 74.0909 | 6.15018 | 22 | 70.8929 | 8.82479 | 28 |
| Surprise | 68.7500 | 10.28609 | 22 | 72.4107 | 4.43482 | 28 |
| Disgust | 45.2273 | 12.02451 | 22 | 42.7679 | 10.59217 | 28 |
| Anger | 55.9091 | 8.14838 | 22 | 58.3929 | 7.76430 | 28 |
| Neutral | 84.5455 | 17.38288 | 22 | 90.3571 | 12.31745 | 28 |

FERT accuracy, positive vs negative emotions

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| FERT_acc_Positive | 71.4205 | 4.23097 | 22 | 71.6518 | 5.29296 | 28 |
| FERT_acc_Negative | 51.6761 | 6.64072 | 22 | 48.5045 | 5.32329 | 28 |

FERT reaction times, all emotions

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| FERT_rt_sad_mea | 1.4447 | .25469 | 22 | 1.4396 | .25161 | 28 |
| FERT_rt_fea_mea | 1.9679 | .39124 | 22 | 1.9463 | .54552 | 28 |
| FERT_rt_hap_mea | 1.3730 | .24228 | 22 | 1.4397 | .35364 | 28 |
| FERT_rt_sur_mea | 1.4111 | .21511 | 22 | 1.3428 | .21903 | 28 |
| FERT_rt_dis_mea | 1.5862 | .28105 | 22 | 1.5605 | .20179 | 28 |
| FERT_rt_anger_mea | 1.5204 | .27341 | 22 | 1.5772 | .26675 | 28 |
| FERT_rt_neutral | 1.1629 | .23807 | 22 | 1.1295 | .23996 | 28 |

FERT reaction times, positive vs negative emotions

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| FERT_rt_Positive_Correct | 1.3920 | .20541 | 22 | 1.3912 | .24900 | 28 |
| FERT_rt_Negative_Correct | 1.6298 | .24632 | 22 | 1.6601 | .22407 | 28 |

FERT misclassifications, all emotions

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| misclas_ang_percll | 2.8355 | 1.48037 | 22 | 3.2823 | 1.84355 | 28 |
| misclas_dis_percll | 3.1818 | 1.79012 | 22 | 2.8401 | 2.45727 | 28 |
| misclas_fea_percll | 3.2900 | 2.18420 | 22 | 2.1429 | 1.69229 | 28 |
| misclas_hap_percll | .9524 | 1.05971 | 22 | .5102 | .62059 | 28 |
| misclas_sad_percll | 7.7273 | 4.60497 | 22 | 6.7177 | 2.76858 | 28 |
| misclas_sur_percll | 5.4113 | 2.34460 | 22 | 7.1429 | 2.61463 | 28 |
| misclas_neu_percll | 21.9129 | 2.92843 | 22 | 24.3750 | 4.53397 | 28 |

FERT sensitivity index (d'), all emotions

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| sigDet_dpri_ang | .8738 | .02322 | 22 | .8790 | .01769 | 28 |
| sigDet_dpri_dis | .8404 | .03602 | 22 | .8366 | .02980 | 28 |
| sigDet_dpri_fea | .8261 | .03296 | 22 | .7710 | .15863 | 28 |
| sigDet_dpri_hap | .9315 | .01488 | 22 | .9250 | .02284 | 28 |
| sigDet_dpri_sad | .8774 | .02825 | 22 | .8759 | .02948 | 28 |
| sigDet_dpri_sur | .8977 | .02910 | 22 | .9009 | .01779 | 28 |
| sigDet_dpri_neu | .8838 | .06797 | 22 | .9027 | .03557 | 28 |

FERT response bias (beta), all emotions

| | Atorvastatin | | | Placebo | | | |
|---|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N | Mean |
| sigDet_beta_ang | .7988 | .09759 | 22 | .7690 | .12082 | 28 | .7821 |
| sigDet_beta_dis | .7777 | .11625 | 22 | .8074 | .13560 | 28 | .7943 |
| sigDet_beta_fea | .7721 | .12908 | 22 | .7336 | .36934 | 28 | .7505 |
| sigDet_beta_hap | .8998 | .12138 | 22 | .9521 | .05736 | 28 | .9291 |
| sigDet_beta_sad | .5251 | .22282 | 22 | .5681 | .15496 | 28 | .5492 |
| sigDet_beta_sur | .6044 | .15427 | 22 | .5101 | .12420 | 28 | .5516 |
| sigDet_beta_neu | -.3815 | .46924 | 22 | -.5366 | .47630 | 28 | -.4683 |

***ECAT***

ECAT, accuracy

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| ECAT_pos_cor | 93.8636 | 8.15502 | 22 | 95.0000 | 4.51335 | 28 |
| ECAT_neg_cor | 96.3636 | 5.15978 | 22 | 95.3571 | 6.92935 | 28 |

ECAT, reaction times

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| ECAT_pos_RT | .8915 | .26007 | 22 | .9423 | .22517 | 28 |
| ECAT_neg_RT | .9105 | .22058 | 22 | .9734 | .23750 | 28 |

***EREC***

EREC, correctly recalled words

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| EREC_Positive_correct | 5.5000 | 2.24139 | 22 | 5.1786 | 2.37352 | 28 |
| EREC_Negative_correct | 4.8182 | 1.91824 | 22 | 3.7500 | 1.93649 | 28 |

EREC, incorrectly recalled words

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| EREC_Positive_incorrect | 2.3182 | 2.00918 | 22 | 2.3214 | 2.21198 | 28 |
| EREC_Negative_incorrect | 1.0455 | 1.36198 | 22 | 1.2143 | 1.37051 | 28 |

***EMEM***

EMEM, accuracy

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| EMEM_Acc_Pos_cor | 80.7095 | 8.93493 | 22 | 78.8328 | 8.04984 | 28 |
| EMEM_Acc_Neg_cor | 80.2661 | 8.87129 | 22 | 80.8362 | 6.03726 | 28 |

EMEM, reaction times

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| EMEM_RT_Pos_corr | 1.0447 | .18169 | 22 | 1.0630 | .15796 | 28 |
| EMEM_RT_Neg_cor | 1.0694 | .19447 | 22 | 1.0975 | .15363 | 28 |

EMEM, misclassifications

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| EMEM_Acc_Pos_Miscl | 19.2905 | 8.93493 | 22 | 21.0801 | 8.16292 | 28 |
| EMEM_Acc_Neg_Miscl | 19.7339 | 8.87129 | 22 | 19.1638 | 6.03726 | 28 |

***FDOT***

FDOT, attentional vigilance

| | | Atorvastatin | Placebo |
|---|---|---|---|
| Mean | FDOT_unmasked_Vig_score_hap | -.0337 | -.0159 |
| | FDOT_unmasked_Vig_score_fear | .0058 | .0211 |
| | FDOT_masked_Vig_score_hap | .0010 | -.0030 |
| | FDOT_masked_Vig_score_fear | -.0038 | .0106 |
| N | FDOT_unmasked_Vig_score_hap | 22 | 28 |
| | FDOT_unmasked_Vig_score_fear | 22 | 28 |
| | FDOT_masked_Vig_score_hap | 22 | 28 |
| | FDOT_masked_Vig_score_fear | 22 | 28 |
| Std. Deviation | FDOT_unmasked_Vig_score_hap | .05818 | .05373 |
| | FDOT_unmasked_Vig_score_fear | .07917 | .07329 |
| | FDOT_masked_Vig_score_hap | .04817 | .04915 |
| | FDOT_masked_Vig_score_fear | .06416 | .06330 |

***PILT***

PILT, amount won/lost

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| Rew | .7992 | .18902 | 22 | .8286 | .18910 | 28 |
| Los | .2061 | .13584 | 22 | .2464 | .13134 | 28 |

PILT, number of choice switches

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Mean | Std. Deviation | N | Mean | Std. Deviation | N |
| PILT_R_Switches_total | .2364 | .27020 | 22 | .2007 | .26981 | 28 |
| PILT_L_Switches_total | .4058 | .26488 | 22 | .5717 | .35847 | 28 |

***AVLT***

AVLT, total correct

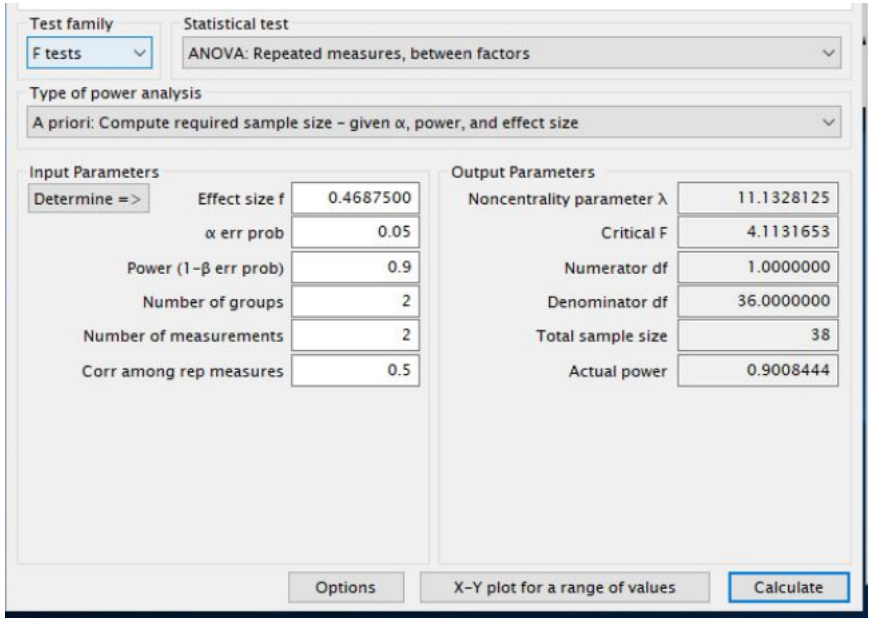
| | Atorvastatin | | | | Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | Std. Deviation | Std. Error Mean | N | Mean | Std. Deviation | Std. Error Mean |
| AVLT_Total_correct | 22 | 62.3636 | 6.62280 | 1.41199 | 28 | 60.8214 | 6.60557 | 1.24834 |

AVLT, short delay, long delay, recognition

| | Atorvastatin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | N | Mean Rank | Sum of Ranks | N | Mean Rank | Sum of Ranks |
| PID | 22 | 24.91 | 548.00 | 28 | 25.96 | 727.00 |
| AVLT_Short_delay | 22 | 25.48 | 560.50 | 28 | 25.52 | 714.50 |
| AVLT_Long_delay | 22 | 28.20 | 620.50 | 28 | 23.38 | 654.50 |
| AVLT_Recog_hits | 22 | 29.55 | 650.00 | 28 | 22.32 | 625.00 |

# Appendix to Chapter 7

## A7.1 Sample size calculation



# A7.2 Inclusion/exclusion criteria

## Inclusion criteria

- Male or female
- Aged 18-50 years
- Sufficiently fluent English to understand and complete the tasks
- Body Mass Index in the range of 18-30
- Participant is willing and able to give informed consent for participation in the study
- Not currently taking any regular medications (except the contraceptive pill)

## Exclusion criteria

- Currently any regular medications (except the contraceptive pill)
- History or current significant psychiatric illness
- Current alcohol or substance misuse disorder
- History or current significant hepatic disease
- History or current significant neurological condition (e.g., epilepsy)
- History of haemorrhagic stroke or lacunar infarct
- Known hyperglycaemia/pre-diabetes
- Known hypersensitivity to the study drug (i.e., simvastatin) or sucrose
- Pregnant, breast feeding, women of child-bearing potential not using appropriate contraceptive measures
- Participation in a study that uses the same or similar computer tasks as those used in the present study
- Participation in a study that involves the use of a medication within the last three months

## A7.3 Participants' repeated Bond-Lader Visual Analog Scale (BL-VAS)

| | **Placebo** | | **Simvastatin** | | *Visit* | | *Group x Visit* | |
|---|---|---|---|---|---|---|---|---|
| | *Screening visit* | *Research visit* | *Screening visit* | *Research visit* | *F* | *p* | *F* | *p* |
| Alert/Drowsy | 18.6 (21.3) | 25.6 (17.9) | 24.0 (17.7) | 32.4 (20.2) | 5.90 | *0.02 | 0.05 | >0.20 |
| Calm/Excited | 30.2 (24.2) | 34.4 (18.4) | 37.3 (23.1) | 40.6 (22.9) | 0.78 | >0.20 | 0.01 | >0.20 |
| Strong/Feeble | 25.0 (19.6) | 29.3 (18.3) | 29.7 (20.4) | 28.9 (17.5) | 0.38 | >0.20 | 0.85 | >0.20 |
| Fuzzy/Clear-headed | 77.0 (21.2) | 67.0 (31.5) | 75.6 (24.0) | 68.5 (27.4) | 4.77 | *0.03 | 0.14 | >0.20 |
| Well-coordinated/Clumsy | 25.3 (27.6) | 31.1 (26.4) | 26.2 (24.3) | 31.8 (28.0) | 1.66 | >0.20 | 0.00 | >0.20 |
| Lethargic/Energetic | 65.3 (18.3) | 58.5 (23.5) | 61.1 (17.8) | 49.6 (27.4) | 7.03 | *0.01 | 0.45 | >0.20 |
| Contented/Discontented | 25.2 (25.0) | 27.8 (24.6) | 18.7 (16.1) | 29.6 (22.4) | 4.88 | *0.03 | 1.79 | >0.20 |
| Troubled/Tranquil | 69.8 (23.0) | 68.8 (25.3) | 75.6 (20.9) | 60.1 (28.2) | 5.36 | *0.03 | 4.10 | 0.06 |
| Mentally-slow/Quick-witted | 76.1 (16.9) | 66.7 (22.9) | 67.0 (21.6) | 60.1 (24.4) | 7.89 | *0.01 | 0.20 | >0.20 |
| Tense/Relaxed | 71.0 (22.9) | 68.0 (23.3) | 71.5 (23.6) | 63.0 (24.4) | 3.99 | 0.05 | 0.89 | >0.20 |
| Attentive/Dreamy | 22.9 (16.3) | 32.1 (19.2) | 25.0 (20.0) | 36.5 (22.2) | 10.87 | *0.00 | 0.14 | >0.20 |
| Incompetent/Proficient | 76.6 (19.0) | 67.1 (22.3) | 73.4 (21.2) | 69.3 (19.2) | 6.51 | *0.01 | 1.00 | >0.20 |
| Happy/Sad | 24.3 (22.0) | 25.0 (18.2) | 19.2 (16.1) | 31.8 (23.7) | 3.68 | 0.06 | 2.92 | 0.09 |
| Antagonistic/Friendly | 78.2 (18.3) | 71.6 (27.4) | 82.4 (23.8) | 71.8 (29.4) | 4.58 | *0.04 | 0.25 | >0.20 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Interested/Bored | 18.8 (18.5) | 27.5 (23.7) | 23.0 (21.9) | 26.6 (19.5) | 4.27 | *0.04 | 0.74 | >0.20 |
| Withdrawn/Sociable | 74.6 (18.5) | 63.7 (24.5) | 71.6 (25.6) | 69.0 (25.3) | 3.07 | 0.09 | 1.18 | >0.20 |

Values are means with (standard deviations). An asterisk (*) highlights a statistically significant difference between the simvastatin and placebo groups.

## A7.4 Descriptive statistics for neuropsychological tasks

Outcomes measured are defined in the Methods. Values are means and standard errors of the mean, unless indicated otherwise.

***FERT***

**FERT, accuracy**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 26 | | | |
| Sad | 66.33 | 2.02 | 63.57 | 2.02 | | |
| Fear | 32.79 | 3.16 | 34.81 | 3.16 | | |
| Happy | 71.82 | 1.47 | 74.89 | 1.47 | | |
| Surprise | 69.72 | 1.47 | 72.56 | 1.47 | | |
| Disgust | 44.02 | 1.93 | 41.96 | 1.93 | | |
| Anger | 59.05 | 2.29 | 57.86 | 2.29 | *F* | *p* |
| Neutral | 83.85 | 2.62 | 87.09 | 2.62 | 0.79 | 0.56 |

**FERT, reaction times**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Sad | 1.48 | 0.07 | 1.51 | 0.07 | | |
| Fear | 2.15 | 0.11 | 2.14 | 0.10 | | |
| Happy | 1.50 | 0.06 | 1.46 | 0.06 | | |
| Surprise | 1.48 | 0.06 | 1.44 | 0.06 | | |
| Disgust | 1.57 | 0.06 | 1.66 | 0.06 | | |
| Anger | 1.69 | 0.07 | 1.69 | 0.07 | *F* | *p* |
| Neutral | 1.22 | 0.07 | 1.24 | 0.07 | 0.51 | 0.74 |

**FERT, misclassification**

| | **Placebo** | **Simvastatin** |
|---|---|---|

| | N= 25 | | N= 27 | | | |
|---|---|---|---|---|---|---|
| Sad | 14.55 | 1.15 | 12.34 | 1.10 | | |
| Fear | 5.57 | 0.77 | 5.13 | 0.74 | | |
| Happy | 1.53 | 0.49 | 1.81 | 0.47 | | |
| Surprise | 12.13 | 0.98 | 12.06 | 0.94 | | |
| Disgust | 5.33 | 0.86 | 6.20 | 0.82 | | |
| Anger | 7.00 | 0.77 | 7.85 | 0.74 | *F* | *p* |
| Neutral | 53.89 | 2.04 | 54.60 | 1.97 | 0.43 | 0.71 |

**FERT, accuracy pos/neg**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Positive | 70.77 | 1.30 | 72.66 | 1.28 | *F* | *p* |
| Negative | 50.55 | 1.47 | 49.33 | 1.45 | 1.40 | 0.24 |

**FERT, d'**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Sad | 0.88 | 0.01 | 0.88 | 0.01 | | |
| Fear | 0.80 | 0.01 | 0.81 | 0.01 | | |
| Happy | 0.93 | 0.01 | 0.93 | 0.01 | | |
| Surprise | 0.90 | 0.00 | 0.91 | 0.00 | | |
| Disgust | 0.84 | 0.01 | 0.83 | 0.01 | | |
| Anger | 0.88 | 0.01 | 0.87 | 0.01 | *F* | *p* |
| Neutral | 0.88 | 0.01 | 0.89 | 0.01 | 0.75 | 0.55 |

**FERT, beta**

| | **Placebo** | **Simvastatin** |
|---|---|---|

| | N= 26 | | N= 27 | | | |
|---|---|---|---|---|---|---|
| Sad | 0.53 | 0.04 | 0.60 | 0.04 | | |
| Fear | 0.73 | 0.04 | 0.79 | 0.04 | | |
| Happy | 0.90 | 0.03 | 0.91 | 0.03 | | |
| Surprise | 0.58 | 0.03 | 0.57 | 0.03 | | |
| Disgust | 0.82 | 0.03 | 0.79 | 0.03 | | |
| Anger | 0.75 | 0.03 | 0.73 | 0.02 | *F* | *p* |
| Neutral | -0.30 | 0.09 | -0.39 | 0.09 | 0.74 | 0.50 |

***FERT, subgroup analyses***

***Gender***

Males N= 26, Females N= 27

**FERT, gender, accuracy**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | Male | 2.34 | 3.80 | 0.54 |
| | Female | 3.18 | 3.80 | 0.41 |
| *Fear* | Male | 1.05 | 6.32 | 0.87 |
| | Female | -5.11 | 6.32 | 0.42 |
| *Happy* | Male | -1.69 | 2.97 | 0.57 |
| | Female | -4.45 | 2.97 | 0.14 |
| *Surprise* | Male | -3.11 | 2.99 | 0.30 |
| | Female | -2.57 | 2.99 | 0.40 |
| *Disgust* | Male | 2.79 | 3.92 | 0.48 |
| | Female | 1.35 | 3.92 | 0.73 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Anger* | Male | 2.64 | 4.56 | 0.57 | | |
| | Female | -0.26 | 4.56 | 0.96 | | |
| *Neutral* | Male | -1.11 | 5.32 | 0.84 | *F* | *p* |
| | Female | -5.39 | 5.32 | 0.32 | 0.18 | 0.96 |

**FERT, gender, reaction times**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | Male | -0.08 | 0.13 | 0.53 |
| | Female | 0.00 | 0.13 | 0.99 |
| *Fear* | Male | -0.09 | 0.19 | 0.63 |
| | Female | 0.07 | 0.18 | 0.69 |
| *Happy* | Male | 0.04 | 0.11 | 0.73 |
| | Female | 0.02 | 0.11 | 0.86 |
| *Surprise* | Male | 0.06 | 0.11 | 0.60 |
| | Female | 0.01 | 0.11 | 0.93 |
| *Disgust* | Male | -0.11 | 0.11 | 0.30 |
| | Female | -0.08 | 0.10 | 0.43 |
| *Anger* | Male | 0.03 | 0.13 | 0.85 |
| | Female | -0.05 | 0.13 | 0.72 |
| *Neutral* | Male | -0.12 | 0.13 | 0.36 |
| | Female | 0.07 | 0.12 | 0.58 |

| *F* | *p* |
|---|---|
| 0.73 | 0.58 |

**FERT, gender, misclassifications**

| | ***Placebo/Simvastatin*** | | |
|---|---|---|---|
| | *MD* | *SE* | *p* |

| | | | | | | |
|---|---|---|---|---|---|---|
| Sad | Male | -0.86 | 1.99 | 0.67 | | |
| | Female | 5.04 | 1.92 | 0.01 | | |
| Fear | Male | -0.42 | 1.56 | 0.79 | | |
| | Female | 1.23 | 1.50 | 0.42 | | |
| Happy | Male | -0.46 | 1.00 | 0.65 | | |
| | Female | -0.12 | 0.96 | 0.90 | | |
| Surprise | Male | -0.72 | 1.99 | 0.72 | | |
| | Female | 0.80 | 1.92 | 0.68 | | |
| Disgust | Male | -1.49 | 1.74 | 0.40 | | |
| | Female | -0.29 | 1.67 | 0.86 | | |
| Anger | Male | -0.93 | 1.54 | 0.55 | | |
| | Female | -0.77 | 1.48 | 0.60 | | |
| Neutral | Male | 4.87 | 3.99 | 0.23 | *F* | *p* |
| | Female | -5.88 | 3.84 | 0.13 | 2.50 | 0.07 |

| | *MD* | *SE* | F | *p* | $h^2$ |
|---|---|---|---|---|---|
| *Female, sad* | 5.04 | 1.92 | 6.91 | 0.01 | 0.07 |

**FERT, gender, accuracy positive/negative**

| | | ***Placebo/Simvastatin*** | | | | |
|---|---|---|---|---|---|---|
| | | *MD* | *SE* | *p* | | |
| *Positive* | Male | -2.40 | 2.60 | 0.36 | | |
| | Female | -1.50 | 2.55 | 0.56 | | |
| *Negative* | Male | 2.21 | 2.83 | 0.44 | *F* | *p* |
| | Female | 0.45 | 2.78 | 0.87 | 0.30 | 0.59 |

**FERT, gender, d'**

| | | ***Placebo/Simvastatin*** | | | | |
|---|---|---|---|---|---|---|
| | | *MD* | *SE* | *p* | | |
| *Sad* | Male | 0.01 | 0.01 | 0.46 | | |
| | Female | 0.00 | 0.01 | 0.88 | | |
| *Fear* | Male | 0.01 | 0.03 | 0.82 | | |
| | Female | -0.03 | 0.03 | 0.35 | | |
| *Happy* | Male | -0.01 | 0.01 | 0.57 | | |
| | Female | 0.00 | 0.01 | 0.72 | | |
| *Surprise* | Male | -0.01 | 0.01 | 0.60 | | |
| | Female | -0.01 | 0.01 | 0.41 | | |
| *Disgust* | Male | 0.01 | 0.02 | 0.46 | | |
| | Female | 0.01 | 0.01 | 0.55 | | |
| *Anger* | Male | 0.01 | 0.01 | 0.44 | | |
| | Female | 0.01 | 0.01 | 0.65 | | |
| *Neutral* | Male | -0.01 | 0.02 | 0.70 | *F* | *p* |
| | Female | -0.02 | 0.02 | 0.41 | 0.31 | 0.85 |

**FERT, gender, beta**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | Male | 0.01 | 0.06 | 0.85 |
| | Female | -0.17 | 0.06 | 0.01 |
| *Fear* | Male | -0.02 | 0.08 | 0.79 |
| | Female | -0.08 | 0.08 | 0.30 |
| *Happy* | Male | -0.02 | 0.06 | 0.66 |
| | Female | 0.00 | 0.06 | 0.95 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Surprise* | Male | 0.05 | 0.07 | 0.49 | | |
| | Female | -0.01 | 0.07 | 0.91 | | |
| *Disgust* | Male | 0.05 | 0.06 | 0.38 | | |
| | Female | 0.01 | 0.06 | 0.87 | | |
| *Anger* | Male | 0.01 | 0.05 | 0.79 | | |
| | Female | 0.03 | 0.05 | 0.58 | | |
| *Neutral* | Male | -0.03 | 0.17 | 0.87 | *F* | *p* |
| | Female | 0.21 | 0.17 | 0.23 | 1.01 | 0.37 |

**Subgroup analysis for females**

**FERT, female, accuracy**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 13 | | N= 13 | | | |
| Sad | 70.51 | 2.57 | 67.32 | 2.57 | | |
| Fear | 34.03 | 4.17 | 39.14 | 4.17 | | |
| Happy | 70.17 | 2.09 | 74.62 | 2.09 | | |
| Surprise | 69.19 | 1.85 | 71.76 | 1.85 | | |
| Disgust | 44.81 | 2.52 | 43.46 | 2.52 | | |
| Anger | 60.75 | 2.40 | 61.01 | 2.40 | *F* | *p* |
| Neutral | 82.31 | 3.23 | 87.69 | 3.23 | 0.82 | 0.54 |

**FERT, female, reaction times**

| | **Placebo** | | **Simvastatin** | |
|---|---|---|---|---|
| | N= 13 | | N= 14 | |
| Sad | 1.38 | 0.07 | 1.38 | 0.07 |
| Fear | 1.93 | 0.07 | 1.85 | 0.07 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Happy | 1.39 | 0.07 | 1.37 | 0.07 | | |
| Surprise | 1.39 | 0.07 | 1.38 | 0.06 | | |
| Disgust | 1.44 | 0.07 | 1.52 | 0.06 | | |
| Anger | 1.53 | 0.07 | 1.57 | 0.07 | *F* | *p* |
| Neutral | 1.14 | 0.06 | 1.07 | 0.05 | 0.92 | 0.48 |

**FERT, female, misclassifications**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 13 | | N= 14 | | | |
| Sad | 18.49 | 1.41 | 13.45 | 1.36 | | |
| Fear | 6.12 | 0.81 | 4.89 | 0.78 | | |
| Happy | 1.36 | 0.50 | 1.48 | 0.48 | | |
| Surprise | 12.28 | 1.40 | 11.48 | 1.35 | | |
| Disgust | 5.36 | 1.18 | 5.65 | 1.14 | | |
| Anger | 6.39 | 1.03 | 7.17 | 0.99 | *F* | *p* |
| Neutral | 50.00 | 2.32 | 55.88 | 2.24 | 2.57 | 0.05 |

| | *MD* | *SE* | F | *p* | $h^2$ |
|---|---|---|---|---|---|
| *Sad* | 5.04 | 1.96 | 6.60 | 0.02 | 0.21 |
| ***Positive as sad*** | 1.50 | 0.62 | 5.79 | 0.02 | 0.19 |

**FERT, female, accuracy pos/neg**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 13 | | N= 14 | | | |
| Positive | 69.68 | 2.00 | 71.18 | 1.93 | *F* | *p* |
| Negative | 52.52 | 1.74 | 52.08 | 1.67 | 0.46 | 0.50 |

**FERT, female, d'**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 13 | | N= 14 | | | |
| Sad | 0.89 | 0.01 | 0.89 | 0.01 | | |
| Fear | 0.80 | 0.02 | 0.83 | 0.02 | | |
| Happy | 0.92 | 0.01 | 0.93 | 0.01 | | |
| Surprise | 0.90 | 0.01 | 0.90 | 0.01 | | |
| Disgust | 0.84 | 0.01 | 0.83 | 0.01 | | |
| Anger | 0.89 | 0.01 | 0.88 | 0.01 | *F* | *p* |
| Neutral | 0.88 | 0.01 | 0.89 | 0.01 | 0.93 | 0.46 |

**FERT, female, beta**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 13 | | N= 14 | | | |
| Sad | 0.40 | 0.05 | 0.57 | 0.05 | | |
| Fear | 0.74 | 0.04 | 0.82 | 0.04 | | |
| Happy | 0.94 | 0.02 | 0.93 | 0.02 | | |
| Surprise | 0.59 | 0.05 | 0.60 | 0.04 | | |
| Disgust | 0.82 | 0.04 | 0.81 | 0.04 | | |
| Anger | 0.79 | 0.03 | 0.76 | 0.03 | *F* | *p* |
| Neutral | -0.17 | 0.10 | -0.38 | 0.10 | 2.42 | 0.08 |

***BMI***

Normoweight N= 44, Overweight N= 9

**FERT, BMI, accuracy**

| | | ***Placebo/Simvastatin*** | | | | |
|---|---|---|---|---|---|---|
| | | *MD* | *SE* | *p* | | |
| *Sad* | Normoweight | 1.27 | 3.11 | 0.69 | | |
| | Overweight | 8.74 | 6.84 | 0.21 | | |
| *Fear* | Normoweight | -2.50 | 4.95 | 0.62 | | |
| | Overweight | -1.27 | 10.89 | 0.91 | | |
| *Happy* | Normoweight | -3.13 | 2.31 | 0.18 | | |
| | Overweight | -2.10 | 5.08 | 0.68 | | |
| *Surprise* | Normoweight | -2.46 | 2.32 | 0.30 | | |
| | Overweight | -4.17 | 5.10 | 0.42 | | |
| *Disgust* | Normoweight | 1.47 | 3.05 | 0.63 | | |
| | Overweight | 4.45 | 6.71 | 0.51 | | |
| *Anger* | Normoweight | 2.40 | 3.34 | 0.48 | | |
| | Overweight | -7.10 | 7.35 | 0.34 | | |
| *Neutral* | Normoweight | -3.68 | 4.10 | 0.37 | *F* | *p* |
| | Overweight | 0.00 | 9.01 | 1.00 | 0.46 | 0.78 |

**FERT, BMI, reaction times**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | Normoweight | -0.03 | 0.11 | 0.77 |
| | Overweight | -0.05 | 0.24 | 0.82 |
| *Fear* | Normoweight | 0.02 | 0.17 | 0.91 |
| | Overweight | -0.04 | 0.37 | 0.90 |
| *Happy* | Normoweight | 0.05 | 0.09 | 0.63 |
| | Overweight | -0.02 | 0.21 | 0.94 |
| *Surprise* | Normoweight | 0.03 | 0.09 | 0.75 |
| | Overweight | 0.06 | 0.20 | 0.77 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Disgust* | Normoweight | -0.07 | 0.09 | 0.46 | | |
| | Overweight | -0.19 | 0.20 | 0.36 | | |
| *Anger* | Normoweight | 0.03 | 0.11 | 0.81 | | |
| | Overweight | -0.14 | 0.24 | 0.56 | | |
| *Neutral* | Normoweight | -0.01 | 0.11 | 0.94 | *F* | *p* |
| | Overweight | -0.07 | 0.24 | 0.78 | 0.15 | 0.96 |

**FERT, BMI, misclassifications**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | Normoweight | 2.50 | 1.78 | 0.17 |
| | Overweight | 0.68 | 3.91 | 0.86 |
| *Fear* | Normoweight | 0.83 | 1.19 | 0.49 |
| | Overweight | -1.45 | 2.61 | 0.58 |
| *Happy* | Normoweight | -0.61 | 0.74 | 0.41 |
| | Overweight | 1.49 | 1.63 | 0.37 |
| *Surprise* | Normoweight | 0.68 | 1.51 | 0.65 |
| | Overweight | -2.76 | 3.32 | 0.41 |
| *Disgust* | Normoweight | -2.38 | 1.22 | 0.06 |
| | Overweight | 6.51 | 2.69 | 0.02 |
| *Anger* | Normoweight | -0.78 | 1.17 | 0.51 |
| | Overweight | -1.48 | 2.57 | 0.57 |
| *Neutral* | Normoweight | -0.24 | 3.18 | 0.94 |
| | Overweight | -2.99 | 6.99 | 0.67 |

| *F* | *p* |
|---|---|
| 0.94 | 0.41 |

**FERT,BMI, accuracy positive/negative**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Positive* | Normoweight | -1.51 | 2.00 | 0.45 | | |
| | Overweight | -3.14 | 4.45 | 0.48 | | |
| *Negative* | Normoweight | 0.99 | 2.19 | 0.65 | *F* | *p* |
| | Overweight | 1.20 | 4.87 | 0.81 | 0.08 | 0.78 |

**FERT, BMI, d'**

| | | ***Placebo/Simvastatin*** | | | | |
|---|---|---|---|---|---|---|
| | | *MD* | *SE* | *p* | | |
| *Sad* | Normoweight | 0.00 | 0.01 | 0.84 | | |
| | Overweight | 0.03 | 0.02 | 0.22 | | |
| *Fear* | Normoweight | -0.01 | 0.02 | 0.54 | | |
| | Overweight | 0.00 | 0.05 | 0.95 | | |
| *Happy* | Normoweight | 0.00 | 0.01 | 0.65 | | |
| | Overweight | -0.01 | 0.02 | 0.66 | | |
| *Surprise* | Normoweight | -0.01 | 0.01 | 0.41 | | |
| | Overweight | -0.01 | 0.02 | 0.69 | | |
| *Disgust* | Normoweight | 0.01 | 0.01 | 0.20 | | |
| | Overweight | -0.02 | 0.03 | 0.53 | | |
| *Anger* | Normoweight | 0.01 | 0.01 | 0.25 | | |
| | Overweight | -0.02 | 0.02 | 0.47 | | |
| *Neutral* | Normoweight | -0.01 | 0.02 | 0.35 | *F* | *p* |
| | Overweight | 0.00 | 0.03 | 0.95 | 0.67 | 0.60 |

**FERT, BMI, beta**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | Normoweight | -0.08 | 0.06 | 0.13 |
| | Overweight | -0.04 | 0.12 | 0.77 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Fear* | Normoweight | -0.06 | 0.06 | 0.30 | | |
| | Overweight | -0.01 | 0.13 | 0.92 | | |
| *Happy* | Normoweight | 0.01 | 0.04 | 0.90 | | |
| | Overweight | -0.11 | 0.09 | 0.27 | | |
| *Surprise* | Normoweight | 0.00 | 0.05 | 0.95 | | |
| | Overweight | 0.12 | 0.12 | 0.30 | | |
| *Disgust* | Normoweight | 0.08 | 0.04 | 0.05 | | |
| | Overweight | -0.22 | 0.09 | 0.01 | | |
| *Anger* | Normoweight | 0.02 | 0.04 | 0.68 | | |
| | Overweight | 0.05 | 0.09 | 0.61 | | |
| *Neutral* | Normoweight | 0.09 | 0.14 | 0.53 | *F* | *p* |
| | Overweight | 0.08 | 0.30 | 0.79 | 0.67 | 0.52 |

***hs-CRP (research visit)***

hs-CRP<1 N= 38, hs-CRP≥1 N= 15

**FERT, hs-CRP, accuracy**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | hs-CRP<1 | 5.39 | 3.35 | 0.11 |
| | hs-CRP≥1 | -0.84 | 5.48 | 0.88 |
| *Fear* | hs-CRP<1 | -1.28 | 5.42 | 0.82 |
| | hs-CRP≥1 | -1.24 | 8.87 | 0.89 |
| *Happy* | hs-CRP<1 | -2.57 | 2.53 | 0.32 |
| | hs-CRP≥1 | -3.66 | 4.14 | 0.38 |
| *Surprise* | hs-CRP<1 | -4.33 | 2.49 | 0.09 |
| | hs-CRP≥1 | -0.70 | 4.07 | 0.86 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Disgust* | hs-CRP<1 | 2.43 | 3.31 | 0.47 | | |
| | hs-CRP≥1 | 1.21 | 5.42 | 0.83 | | |
| *Anger* | hs-CRP<1 | -1.24 | 3.88 | 0.75 | | |
| | hs-CRP≥1 | 9.11 | 6.34 | 0.16 | | |
| *Neutral* | hs-CRP<1 | -4.11 | 4.43 | 0.36 | *F* | *p* |
| | hs-CRP≥1 | -2.08 | 7.25 | 0.78 | 0.56 | 0.71 |

**FERT, hs-CRP, reaction times**

| | | ***Placebo/Simvastatin*** | | | | |
|---|---|---|---|---|---|---|
| | | *MD* | *SE* | *p* | | |
| *Sad* | hs-CRP<1 | 0.01 | 0.11 | 0.94 | | |
| | hs-CRP≥1 | -0.11 | 0.19 | 0.58 | | |
| *Fear* | hs-CRP<1 | -0.03 | 0.18 | 0.88 | | |
| | hs-CRP≥1 | 0.00 | 0.29 | 0.99 | | |
| *Happy* | hs-CRP<1 | 0.06 | 0.10 | 0.58 | | |
| | hs-CRP≥1 | -0.01 | 0.17 | 0.94 | | |
| *Surprise* | hs-CRP<1 | 0.10 | 0.10 | 0.32 | | |
| | hs-CRP≥1 | -0.03 | 0.16 | 0.84 | | |
| *Disgust* | hs-CRP<1 | 0.00 | 0.10 | 1.00 | | |
| | hs-CRP≥1 | -0.28 | 0.16 | 0.09 | | |
| *Anger* | hs-CRP<1 | 0.09 | 0.12 | 0.45 | | |
| | hs-CRP≥1 | -0.25 | 0.20 | 0.21 | | |
| *Neutral* | hs-CRP<1 | 0.03 | 0.11 | 0.82 | *F* | *p* |
| | hs-CRP≥1 | -0.04 | 0.19 | 0.84 | 0.86 | 0.49 |

**FERT, hs-CRP, misclassifications**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Sad* | hs-CRP<1 | 5.05 | 1.79 | 0.01 | | |
| | hs-CRP≥1 | -3.48 | 2.92 | 0.24 | | |
| *Fear* | hs-CRP<1 | 0.93 | 1.56 | 0.79 | | |
| | hs-CRP≥1 | 1.66 | 2.12 | 0.44 | | |
| *Happy* | hs-CRP<1 | -0.02 | 0.84 | 0.98 | | |
| | hs-CRP≥1 | -0.80 | 1.36 | 0.56 | | |
| *Surprise* | hs-CRP<1 | -0.34 | 1.66 | 0.84 | | |
| | hs-CRP≥1 | 0.57 | 2.71 | 0.84 | | |
| *Disgust* | hs-CRP<1 | -2.29 | 1.40 | 0.11 | | |
| | hs-CRP≥1 | 3.03 | 2.28 | 0.19 | | |
| *Anger* | hs-CRP<1 | -1.89 | 1.23 | 0.13 | | |
| | hs-CRP≥1 | 3.03 | 1.99 | 0.14 | | |
| *Neutral* | hs-CRP<1 | -0.64 | 3.40 | 0.85 | *F* | *p* |
| | hs-CRP≥1 | -4.02 | 5.54 | 0.47 | 1.64 | 0.19 |

**FERT, hs-CRP, accuracy positive/negative**

| | | ***Placebo/Simvastatin*** | | | | |
|---|---|---|---|---|---|---|
| | | *MD* | *SE* | *p* | | |
| *Positive* | hs-CRP<1 | -2.40 | 2.60 | 0.36 | | |
| | hs-CRP≥1 | -1.50 | 2.55 | 0.56 | | |
| *Negative* | hs-CRP<1 | 2.21 | 2.83 | 0.44 | *F* | *p* |
| | hs-CRP≥1 | 0.45 | 2.78 | 0.87 | 0.46 | 0.64 |

**FERT, hs-CRP, d'**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | hs-CRP<1 | 0.01 | 0.01 | 0.65 |
| | hs-CRP≥1 | 0.01 | 0.02 | 0.72 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Fear* | hs-CRP<1 | -0.01 | 0.02 | 0.78 | | |
| | hs-CRP≥1 | -0.02 | 0.04 | 0.67 | | |
| *Happy* | hs-CRP<1 | 0.00 | 0.01 | 0.69 | | |
| | hs-CRP≥1 | -0.01 | 0.01 | 0.60 | | |
| *Surprise* | hs-CRP<1 | -0.01 | 0.01 | 0.25 | | |
| | hs-CRP≥1 | 0.00 | 0.01 | 0.84 | | |
| *Disgust* | hs-CRP<1 | 0.02 | 0.01 | 0.16 | | |
| | hs-CRP≥1 | -0.01 | 0.02 | 0.59 | | |
| *Anger* | hs-CRP<1 | 0.00 | 0.01 | 0.71 | | |
| | hs-CRP≥1 | 0.02 | 0.02 | 0.33 | | |
| *Neutral* | hs-CRP<1 | -0.01 | 0.02 | 0.37 | *F* | *p* |
| | hs-CRP≥1 | 0.00 | 0.03 | 0.94 | 0.41 | 0.77 |

**FERT, hs-CRP, beta**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | hs-CRP<1 | -0.16 | 0.06 | 0.01 |
| | hs-CRP≥1 | 0.10 | 0.09 | 0.26 |
| *Fear* | hs-CRP<1 | -0.05 | 0.06 | 0.44 |
| | hs-CRP≥1 | -0.07 | 0.11 | 0.49 |
| *Happy* | hs-CRP<1 | -0.04 | 0.05 | 0.43 |
| | hs-CRP≥1 | 0.04 | 0.08 | 0.60 |
| *Surprise* | hs-CRP<1 | 0.04 | 0.06 | 0.50 |
| | hs-CRP≥1 | 0.01 | 0.09 | 0.91 |
| *Disgust* | hs-CRP<1 | 0.08 | 0.05 | 0.09 |
| | hs-CRP≥1 | -0.10 | 0.08 | 0.18 |
| *Anger* | hs-CRP<1 | 0.06 | 0.04 | 0.11 |
| | hs-CRP≥1 | -0.13 | 0.07 | 0.06 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Neutral* | hs-CRP<1 | 0.15 | 0.14 | 0.29 | *F* | *p* |
| | hs-CRP≥1 | -0.03 | 0.24 | 0.89 | 1.35 | 0.27 |

***Family history***

NoFamHx N= 32, PosFamHx N= 20

**FERT, famhx, accuracy**

| | | ***Placebo/Simvastatin*** | | | | |
|---|---|---|---|---|---|---|
| | | *MD* | *SE* | *p* | | |
| *Sad* | NoFamHx | 0.79 | 3.62 | 0.83 | | |
| | PosFamHx | 5.03 | 4.59 | 0.28 | | |
| *Fear* | NoFamHx | 0.61 | 5.60 | 0.91 | | |
| | PosFamHx | -7.87 | 7.11 | 0.27 | | |
| *Happy* | NoFamHx | 0.16 | 2.61 | 0.95 | | |
| | PosFamHx | -8.17 | 3.31 | 0.02 | | |
| *Surprise* | NoFamHx | -2.17 | 2.70 | 0.43 | | |
| | PosFamHx | -3.65 | 3.43 | 0.29 | | |
| *Disgust* | NoFamHx | -0.34 | 3.51 | 0.92 | | |
| | PosFamHx | 5.63 | 4.46 | 0.21 | | |
| *Anger* | NoFamHx | 1.87 | 4.19 | 0.66 | | |
| | PosFamHx | -0.41 | 5.32 | 0.94 | | |
| *Neutral* | NoFamHx | -0.90 | 4.69 | 0.85 | *F* | *p* |
| | PosFamHx | -5.85 | 5.94 | 0.33 | 0.87 | 0.49 |

**FERT, famhx, reaction times**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Sad* | NoFamHx | -0.02 | 0.12 | 0.87 | | |
| | PosFamHx | -0.08 | 0.16 | 0.62 | | |
| *Fear* | NoFamHx | 0.04 | 0.19 | 0.84 | | |
| | PosFamHx | -0.02 | 0.25 | 0.93 | | |
| *Happy* | NoFamHx | 0.08 | 0.11 | 0.46 | | |
| | PosFamHx | -0.03 | 0.14 | 0.85 | | |
| *Surprise* | NoFamHx | 0.12 | 0.10 | 0.25 | | |
| | PosFamHx | -0.11 | 0.13 | 0.43 | | |
| *Disgust* | NoFamHx | -0.02 | 0.11 | 0.89 | | |
| | PosFamHx | -0.20 | 0.14 | 0.15 | | |
| *Anger* | NoFamHx | -0.01 | 0.13 | 0.93 | | |
| | PosFamHx | 0.00 | 0.16 | 0.99 | | |
| *Neutral* | NoFamHx | 0.02 | 0.12 | 0.87 | *F* | *p* |
| | PosFamHx | -0.11 | 0.16 | 0.50 | 0.42 | 0.78 |

**FERT, famhx, misclassifications**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | NoFamHx | -0.50 | 1.82 | 0.79 |
| | PosFamHx | 6.10 | 2.39 | 0.01 |
| *Fear* | NoFamHx | 0.77 | 1.36 | 0.57 |
| | PosFamHx | -0.24 | 1.79 | 0.90 |
| *Happy* | NoFamHx | 0.37 | 0.86 | 0.67 |
| | PosFamHx | -1.47 | 1.13 | 0.20 |
| *Surprise* | NoFamHx | -1.03 | 1.70 | 0.55 |
| | PosFamHx | -1.03 | 1.70 | 0.55 |
| *Disgust* | NoFamHx | 0.35 | 1.50 | 0.82 |
| | PosFamHx | -2.82 | 1.97 | 0.16 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Anger* | NoFamHx | 0.40 | 1.33 | 0.76 | | |
| | PosFamHx | -2.97 | 1.75 | 0.10 | | |
| *Neutral* | NoFamHx | -0.36 | 3.62 | 0.92 | *F* | *p* |
| | PosFamHx | -0.86 | 4.75 | 0.86 | 1.14 | 0.33 |

**FERT, famhx, accuracy positive/negative**

| | | ***Placebo/Simvastatin*** | | | | |
|---|---|---|---|---|---|---|
| | | *MD* | *SE* | *p* | | |
| *Positive* | NoFamHx | 0.56 | 2.30 | 0.81 | | |
| | PosFamHx | -5.91 | 2.96 | 0.05 | | |
| *Negative* | NoFamHx | 0.98 | 2.57 | 0.70 | *F* | *p* |
| | PosFamHx | 0.45 | 2.78 | 0.87 | 1.30 | 0.26 |
| | | 0.594 | 3.303 | 0.858 | | |

**FERT, famhx, d'**

| | | ***Placebo/Simvastatin*** | | |
|---|---|---|---|---|
| | | *MD* | *SE* | *p* |
| *Sad* | NoFamHx | 0.00 | 0.01 | 0.76 |
| | PosFamHx | 0.00 | 0.01 | 0.89 |
| *Fear* | NoFamHx | -0.01 | 0.03 | 0.69 |
| | PosFamHx | -0.02 | 0.03 | 0.62 |
| *Happy* | NoFamHx | 0.01 | 0.01 | 0.49 |
| | PosFamHx | -0.02 | 0.01 | 0.06 |
| *Surprise* | NoFamHx | 0.00 | 0.01 | 0.93 |
| | PosFamHx | -0.02 | 0.01 | 0.15 |
| *Disgust* | NoFamHx | 0.00 | 0.01 | 0.85 |
| | PosFamHx | 0.03 | 0.02 | 0.11 |
| *Anger* | NoFamHx | 0.01 | 0.01 | 0.55 |
| | PosFamHx | 0.01 | 0.02 | 0.70 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Neutral* | NoFamHx | 0.00 | 0.02 | 0.99 | *F* | *p* |
| | PosFamHx | -0.03 | 0.02 | 0.21 | 0.90 | 0.45 |

**FERT, famhx, beta**

| | | ***Placebo/Simvastatin*** | | | | |
|---|---|---|---|---|---|---|
| | | *MD* | *SE* | *p* | | |
| *Sad* | NoFamHx | 0.02 | 0.06 | 0.67 | | |
| | PosFamHx | -0.22 | 0.07 | 0.01 | | |
| *Fear* | NoFamHx | -0.08 | 0.07 | 0.27 | | |
| | PosFamHx | -0.01 | 0.09 | 0.89 | | |
| *Happy* | NoFamHx | -0.03 | 0.05 | 0.60 | | |
| | PosFamHx | 0.02 | 0.06 | 0.73 | | |
| *Surprise* | NoFamHx | 0.05 | 0.06 | 0.37 | | |
| | PosFamHx | -0.06 | 0.08 | 0.47 | | |
| *Disgust* | NoFamHx | -0.02 | 0.05 | 0.75 | | |
| | PosFamHx | 0.09 | 0.06 | 0.16 | | |
| *Anger* | NoFamHx | -0.02 | 0.04 | 0.60 | | |
| | PosFamHx | 0.08 | 0.06 | 0.16 | | |
| *Neutral* | NoFamHx | 0.05 | 0.16 | 0.75 | *F* | *p* |
| | PosFamHx | 0.11 | 0.20 | 0.58 | 0.98 | 0.38 |

***ECAT***

**ECAT, correct**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 25 | | N= 27 | | | |
| Positive | 94.00 | 1.39 | 94.82 | 1.34 | *F* | *p* |
| Negative | 97.20 | 1.00 | 94.63 | 0.96 | 2.90 | 0.10 |

**ECAT, reaction times**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Positive | 0.88 | 0.05 | 0.99 | 0.04 | *F* | *p* |
| Negative | 1.00 | 0.05 | 1.07 | 0.04 | 2.48 | 0.12 |

***EREC***

**EREC, correct**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Positive | 5.46 | 0.39 | 6.11 | 0.38 | *F* | *p* |
| Negative | 4.12 | 0.45 | 4.89 | 0.44 | 0.04 | 0.84 |

**EREC, incorrect**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Positive | 1.77 | 0.30 | 2.70 | 0.29 | *F* | *p* |
| Negative | 1.19 | 0.24 | 1.15 | 0.24 | 4.86 | 0.03 |

| | *MD* | *SE* | *F* | *p* | $h^2$ |
|---|---|---|---|---|---|
| *Positive* | -0.93 | 0.42 | 4.99 | 0.03 | 0.09 |

***EMEM***

**EMEM, correct**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 24 | | N= 27 | | | |
| Positive | 79.98 | 1.65 | 81.93 | 1.55 | *F* | *p* |
| Negative | 81.81 | 1.55 | 83.65 | 1.47 | 0.00 | 0.96 |

**EMEM, reaction times**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 24 | | N= 27 | | | |
| Positive | 1.07 | 0.05 | 1.13 | 0.04 | *F* | *p* |
| Negative | 1.12 | 0.05 | 1.17 | 0.04 | 0.04 | 0.85 |

**EMEM, misclassification**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 24 | | N= 27 | | | |
| Positive | 18.80 | 1.70 | 17.34 | 1.60 | *F* | *p* |
| Negative | 17.48 | 1.53 | 15.90 | 1.44 | 0.00 | 0.96 |

***FDOT***

**FDOT, masked, congruent, accuracy**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Happy | 98.08 | 1.09 | 97.22 | 1.07 | *F* | *p* |
| Fear | 94.44 | 1.70 | 95.47 | 1.67 | 0.51 | 0.48 |

**FDOT, unmasked, congruent, accuracy**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Happy | 96.64 | 1.07 | 97.22 | 1.05 | *F* | *p* |
| Fear | 95.73 | 1.32 | 95.47 | 1.29 | 0.17 | 0.68 |

**FDOT, masked, congruent, reaction times**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Happy | 0.60 | 0.02 | 0.60 | 0.02 | *F* | *p* |
| Fear | 0.58 | 0.02 | 0.57 | 0.02 | 0.75 | 0.39 |

**FDOT, unmasked, congruent, reaction times**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Happy | 0.62 | 0.02 | 0.59 | 0.02 | *F* | *p* |
| Fear | 0.61 | 0.02 | 0.59 | 0.02 | 0.04 | 0.84 |

**FDOT, masked, vigilance**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Happy | -0.03 | 0.01 | -0.05 | 0.01 | *F* | *p* |
| Fear | 0.03 | 0.01 | 0.02 | 0.01 | 0.20 | 0.66 |

**FDOT, unmasked, vigilance**

| | Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | | |
| Happy | -0.02 | 0.01 | -0.02 | 0.01 | *F* | *p* |
| Fear | 0.01 | 0.01 | 0.04 | 0.01 | 0.97 | 0.33 |

***PILT***

**PILT, total won**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| 5.20 | 0.31 | 5.11 | 0.30 | 0.04 | 0.84 |

**PILT, rew**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| 0.82 | 0.04 | 0.81 | 0.04 | 0.13 | 0.72 |

**PILT, rew t16-30**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| 0.85 | 0.04 | 0.85 | 0.04 | 0.00 | 0.95 |

**PILT, won**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| 2.43 | 0.06 | 2.39 | 0.06 | 0.18 | 0.67 |

**PILT, won t16-30**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| 1.22 | 0.03 | 1.22 | 0.03 | 0.00 | 0.99 |

**PILT, los**

| Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 26 | | *F* | *p* |
| 0.25 | 0.03 | 0.23 | 0.03 | 0.19 | 0.67 |

**PILT, los t16-30**

| Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| 0.22 | 0.04 | 0.17 | 0.04 | 0.82 | 0.37 |

**PILT, lost**

| Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| -1.69 | 0.06 | -1.68 | 0.06 | 0.01 | 0.92 |

**PILT, lost t16-30**

| Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| -0.84 | 0.03 | -0.80 | 0.03 | 0.56 | 0.46 |

**PILT, rew switch**

| Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|
| N= 22 | | N= 25 | | *F* | *p* |
| 0.09 | 0.02 | 0.10 | 0.02 | 0.24 | 0.63 |

**PILT, rew switch t16-30**

| Placebo | | Simvastatin | | | |
|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| | N= 22 | | N= 25 | | *F* | *p* |
| | 0.04 | 0.02 | 0.07 | 0.02 | 1.04 | 0.31 |

**PILT, los switch**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | *F* | *p* |
| | 0.09 | 0.02 | 0.10 | 0.02 | 0.01 | 0.91 |

**PILT, los switch t16-30**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | *F* | *p* |
| | 0.25 | 0.04 | 0.24 | 0.04 | 0.03 | 0.88 |

**PILT, rew switch/rew switch t16-30**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 22 | | N= 25 | | *F* | *p* |
| Rew switch | 0.09 | 0.02 | 0.10 | 0.02 | 0.97 | 0.33 |
| Rew switch t16-30 | 0.04 | 0.02 | 0.07 | 0.02 | 0.97 | 0.33 |

**PILT, los switch/los switch t16-30**

| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 26 | | N= 27 | | *F* | *p* |
| Los switch | 0.28 | 0.03 | 0.27 | 0.03 | 0.04 | 0.85 |
| Los switch t16-30 | 0.25 | 0.04 | 0.24 | 0.04 | 0.04 | 0.85 |

***AVLT***

**AVLT, total correct**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| 58.19 | 1.42 | 60.26 | 1.40 | 1.07 | 0.31 |

**AVLT, short delay correct**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| 12.39 | 0.38 | 13.11 | 0.37 | 1.85 | 0.18 |

**AVLT, long delay correct**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| 12.65 | 0.38 | 13.11 | 0.38 | 0.73 | 0.40 |

**AVLT, intrusions**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 27 | | *F* | *p* |
| 1.28 | 0.39 | 1.31 | 0.39 | 0.00 | 0.96 |

**AVLT, repetitions**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 26 | | N= 26 | | *F* | *p* |
| 5.19 | 0.78 | 3.39 | 0.78 | 2.70 | 0.11 |

**AVLT, recognition hits**

| **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|
| N= 25 | | N= 26 | | *F* | *p* |

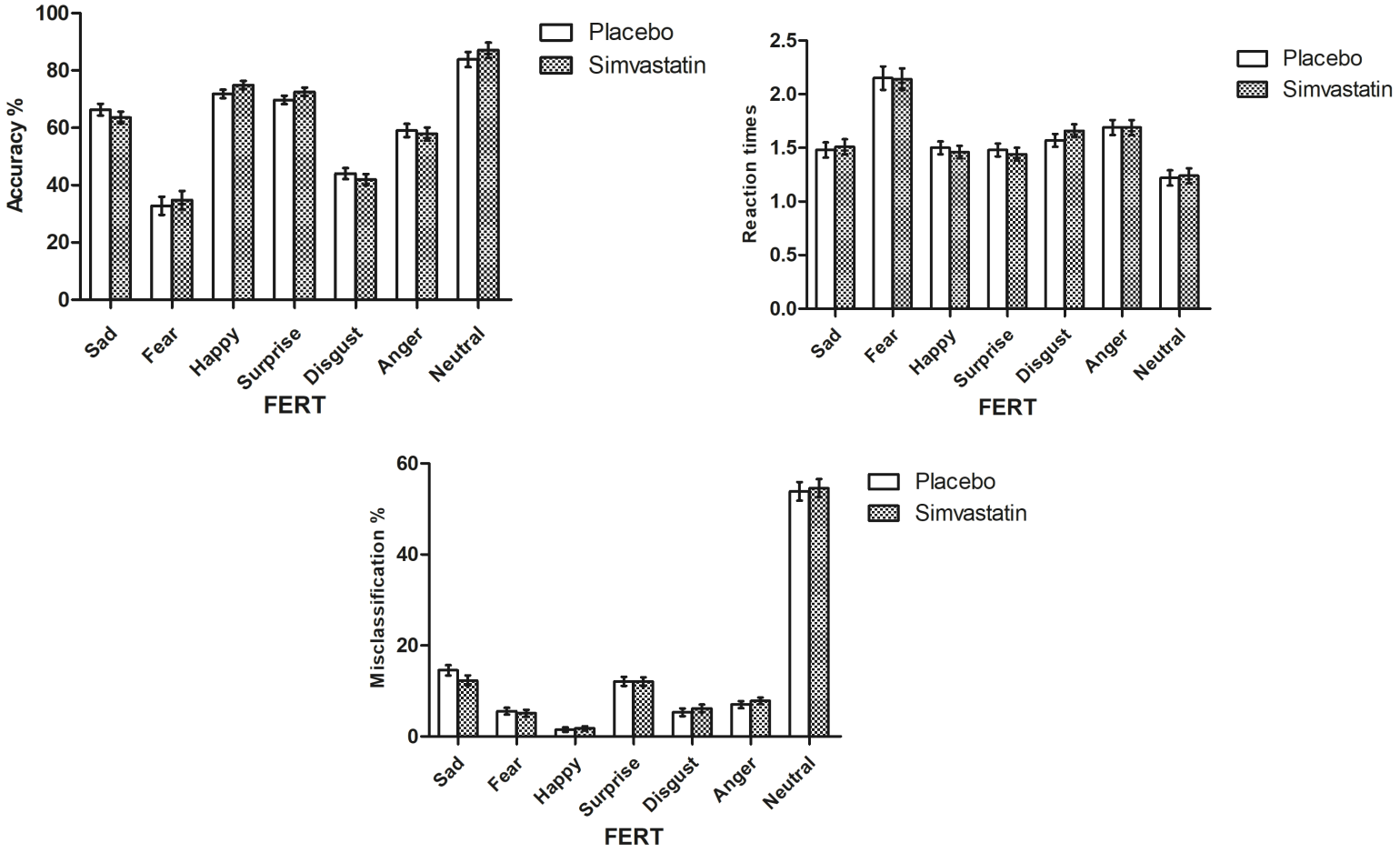
| | | | | | | |
|---|---|---|---|---|---|---|
| | 14.36 | 0.17 | 14.50 | 0.16 | 0.36 | 0.55 |

**AVLT, recognition false alarm**

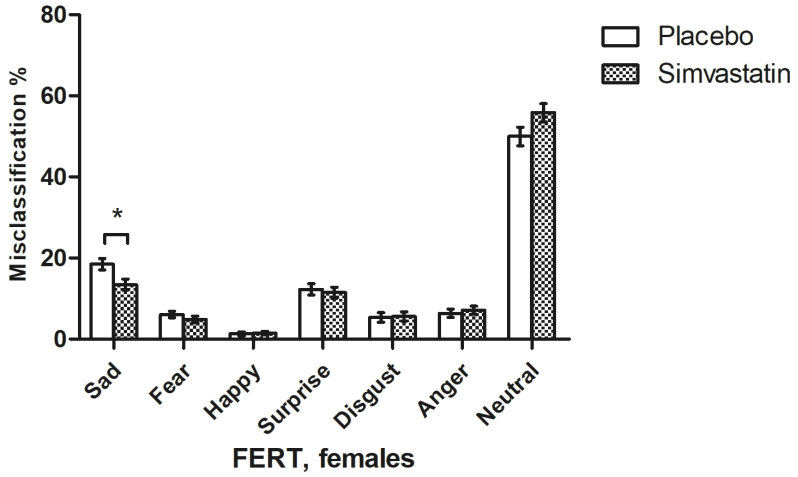
| | **Placebo** | | **Simvastatin** | | | |
|---|---|---|---|---|---|---|
| | N= 25 | | N= 27 | | *F* | *p* |
| | 0.40 | 0.12 | 0.22 | 0.11 | 1.23 | 0.27 |

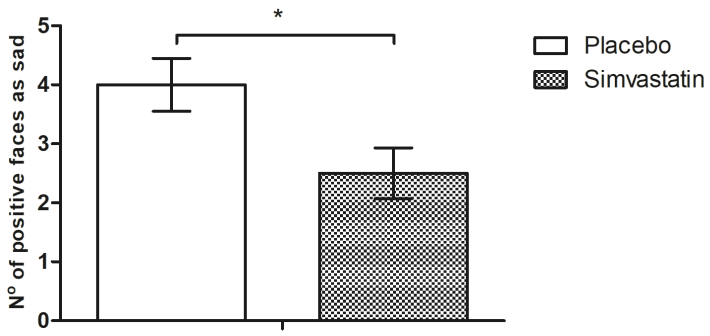
## A7.5 Outcome measures of the Facial Expression Recognition Task

***FERT.*** Effects of simvastatin on facial expression recognition (FERT). Results for accuracy, reaction times, and misclassifications for all seven facial expressions are shown. Values are means ± standard error of the mean bars, an asterisk (*) represents a statistically significant difference between the simvastatin (grey) and placebo (white) groups



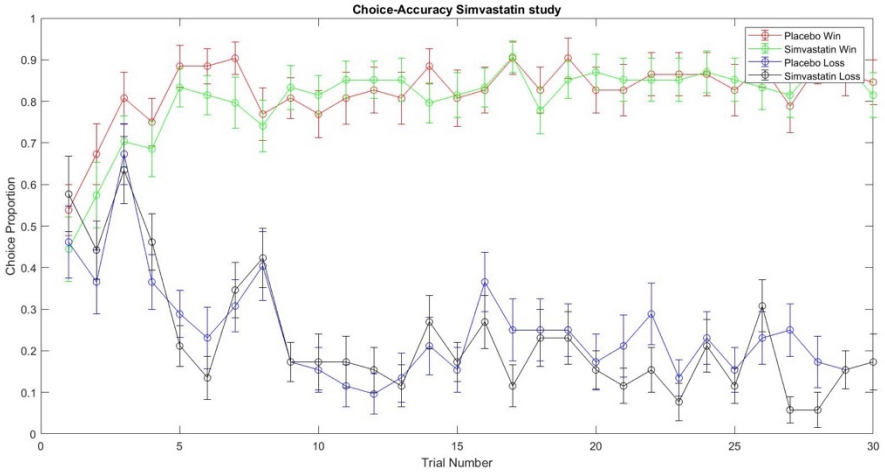
***FERT, females' subgroup.*** Effects of simvastatin on facial expression recognition in the females' subgroup. Results for misclassifications for all seven facial expressions, and for positive faces misclassified as sad facial expressions are shown. Values are means ± standard error of the mean bars, an asterisk (*) represents a statistically significant difference between the simvastatin (grey) and placebo (white) groups




**FERT, female, misclassification, positive faces as sad**

## A7.6 Probabilistic instrumental learning task, learning curves




# Appendix to Chapter 8

## A8.1 Inclusion/exclusion criteria

***Table A8.1*** *Participant eligibility criteria*

Inclusion criteria

- Male or female
- Aged 21-65 years
- At-risk for depression as measured by a score >6 on the UCLA 3-item Loneliness Scale
- Body Mass Index (BMI) in the range of 18-30
- Willing and able to give informed consent for participation in the study
- Registered with a GP and consenting to GP being informed of participation in the study
- Currently living in the UK and sufficiently fluent English to understand and complete the tasks

- Able to access and use a computer with internet
- Able to complete online questionnaires and tasks

Exclusion criteria

- Currently on any regular prescribed medications (except the contraceptive pill), unless unlikely to compromise safety or affect data quality in the opinion of the Investigator
- History or current significant psychiatric illness (other than past [>6 months] episodes of depression or anxiety)
- Current alcohol or substance misuse disorder (<6 months)
- History of, or current significant hepatic disease
- History of, or current significant neurological condition (e.g., epilepsy)
- History of haemorrhagic stroke or deep brain structures stroke
- Known hyperglycaemia/pre-diabetes
- Known hypersensitivity to the study drug (i.e., simvastatin) or sucrose
- Pregnant, breast feeding, women of child-bearing potential not using appropriate contraceptive measures
- Participation in a study that uses the same or similar computer tasks (apart from the N-back) as those used in the present study
- Participation in a study that involves the use of a medication within the last 3 months

# Appendix, miscellanea

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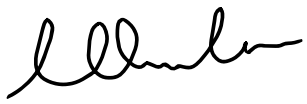
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- "An experimental medicine study of the effects of simvastatin on emotional processing, reward learning, verbal memory, and inflammation in healthy volunteers", De Giorgi et al., 2022; DOI:10.1007/s00213-022-06156-y

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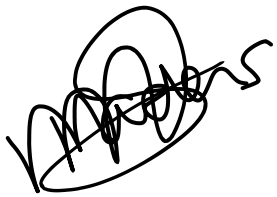
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- "The effects of statin monotherapy on depressive symptoms: a systematic review and meta-analysis", De Giorgi et al., 2022; DOI:10.1016/j.jad.2022.05.113
- "Statins for major depressive disorder: A systematic review and meta-analysis of randomized controlled trials", De Giorgi et al., 2021; DOI:10.1371/journal.pone.0249409
- "The effects of atorvastatin on emotional processing, reward learning, verbal memory and inflammation in healthy volunteers: An experimental medicine study", De Giorgi et al., 2021; DOI:10.1177/02698811211060307
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