

Supplementary Material

Appendix 1

CPRD medcodes, corresponding Read codes and Read terms used to define dementia

medcode	Read code	Read term
1350	E00..12	Senile/presenile dementia
1916	E00..11	Senile dementia
1917	F110.00	Alzheimer's disease
2882	E00z.00	Senile or presenile psychoses NOS
4357	Eu02z14	[X] Senile dementia NOS
4693	Eu02z00	[X] Unspecified dementia
6578	Eu01.00	[X]Vascular dementia
7323	E000.00	Uncomplicated senile dementia
7572	F116.00	Lewy body disease
7664	Eu00.00	[X]Dementia in Alzheimer's disease
8195	Eu00z11	[X]Alzheimer's dementia unspec
8634	E004.11	Multi infarct dementia
8934	Eu01200	[X]Subcortical vascular dementia
9509	Eu02300	[X]Dementia in Parkinson's disease
9565	Eu01.11	[X]Arteriosclerotic dementia
11136	F111.00	Pick's disease
11175	Eu01100	[X]Multi-infarct dementia
11379	Eu00112	[X]Senile dementia,Alzheimer's type
12621	Eu02.00	[X]Dementia in other diseases classified elsewhere
15165	E001.00	Presenile dementia
15249	E00y.00	Other senile and presenile organic psychoses
16797	F110000	Alzheimer's disease with early onset
18386	E002000	Senile dementia with paranoia
19393	Eu01z00	[X]Vascular dementia, unspecified
19477	E004.00	Arteriosclerotic dementia
21887	E002100	Senile dementia with depression
25386	E041.00	Dementia in conditions EC
25704	Eu00011	[X]Presenile dementia,Alzheimer's type
26270	Eu02500	[X]Lewy body dementia
27677	E001300	Presenile dementia with depression
27759	Eu02z16	[X] Senile dementia, depressed or paranoid type
27935	Eu02z15	[X] Senile psychosis NOS
28402	Eu02000	[X]Dementia in Pick's disease
29386	Eu00z00	[X]Dementia in Alzheimer's disease, unspecified
29512	F112.00	Senile degeneration of brain
30032	E001200	Presenile dementia with paranoia
30706	Eu00200	[X]Dementia in Alzheimer's dis, atypical or mixed type
31016	Eu01300	[X]Mixed cortical and subcortical vascular dementia
32057	F110100	Alzheimer's disease with late onset
33707	E00..00	Senile and presenile organic psychotic conditions
34944	Eu02z13	[X] Primary degenerative dementia NOS

37014	Eu02200	[X]Dementia in Huntington's disease
37015	E003.00	Senile dementia with delirium
38438	E001z00	Presenile dementia NOS
38678	Eu00100	[X]Dementia in Alzheimer's disease with late onset
41089	E002z00	Senile dementia with depressive or paranoid features NOS
42279	E004z00	Arteriosclerotic dementia NOS
42602	E001000	Uncomplicated presenile dementia
43089	E004000	Uncomplicated arteriosclerotic dementia
43292	E004300	Arteriosclerotic dementia with depression
43346	Eu00113	[X]Primary degen dementia of Alzheimer's type, senile onset
44674	E002.00	Senile dementia with depressive or paranoid features
46488	Eu01000	[X]Vascular dementia of acute onset
46762	Eu00111	[X]Alzheimer's disease type 1
47619	Eu02z12	[X] Presenile psychosis NOS
48501	Eu02z11	[X] Presenile dementia NOS
49263	Eu00000	[X]Dementia in Alzheimer's disease with early onset
49513	E001100	Presenile dementia with delirium
51494	E00y.11	Presbyophrenic psychosis
53446	Eu04100	[X]Delirium superimposed on dementia
54106	Eu02100	[X]Dementia in Creutzfeldt-Jakob disease
55313	Eu01y00	[X]Other vascular dementia
55467	E004200	Arteriosclerotic dementia with paranoia
55838	Eu01111	[X]Predominantly cortical dementia
56912	E004100	Arteriosclerotic dementia with delirium
59122	Fyu3000	[X]Other Alzheimer's disease
60059	Eu00012	[X]Primary degen dementia, Alzheimer's type, presenile onset
61528	Eu00013	[X]Alzheimer's disease type 2
62132	E02y100	Drug-induced dementia
64267	Eu02y00	[X]Dementia in other specified diseases classif elsewhere
109288	A411000	

Appendix 2. Definition of covariates

We extracted and coded the following covariates at the start and end of each patient's Drug Exposure Period (DEP), unless stated otherwise, from the patient's record:

Diagnosis of cardiovascular and related diseases: any previous diagnosis of diabetes, diabetes complications, hyperlipidemia, hypertension, stroke/ Transient Ischaemic Attack, congestive heart disease, heart failure, peripheral arterial disease, atrial fibrillation, angina, myocardial infarction, coronary artery operations, deep vein thrombosis.

Depression: Depression was measured in terms of its maximum severity (for diagnosed depression), the presence of depressive symptoms, and its duration. Maximum severity was defined as 'mild' 'moderate' or 'severe' using published classifications of Read codes for depression (1,2), with additional classification by members of the study team (KR, NS) for Read codes not included in those studies. The Read codes used for depression severity and depressive symptoms are given below. Duration is defined as the time between first record of diagnosis and the relevant cut-off date for measurement of covariates.

Other potential dementia risk factors or correlates: anxiety, anxiety symptoms, Parkinson's disease, severe mental illness, epilepsy, drug abuse, cancer, insomnia, sleep problems, migraine, headache, pain, neuropathy, Meniere's disease, restless leg syndrome

Other indications for anticholinergics: Chronic obstructive pulmonary disease, asthma, rhinitis, Gastroesophageal reflux disease, peptic/gastric ulcer, Irritable bowel syndrome, Inflammatory Bowel disease, intestinal surgery, liver disease, arthritis, dermatitis, eczema, psoriasis, incontinence, chronic kidney disease, or prostatism.

Other factors: GP practice region (Scotland, Northern Ireland, Wales and 10 health regions of England), smoking status (never, former, current or unknown), body mass index (<20, 20-24.9, 25-29.9, 30+ kg/m², or missing), and problematic alcohol use (categorised as more than 49 units per week for men and more than 35 units per week for women, or missing). In the 12 months prior to the DEP: any falls, any fractures, and number of GP consultations.

Other medication: Number of prescriptions during the DEP of other medications rated without anticholinergic activity from the following classes: benzodiazepines (ATC N05BA, N05CD, N03AE), z-drugs (ATC N05CF), antidepressants (ATC N06A), anti-nausea and anti-vertigo preparations (ATC N07C, A03F), antiepileptics (ATC N03), and anti-Parkinson drugs (ATC N04).

References

1. Martinez C, Rietbrock S, Wise L, Ashby D, Chick J, Moseley J, et al. Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study. *BMJ*. 2005 Feb 17;330(7488):389.
2. Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J. Antidepressant use and risk of cardiovascular outcomes in people aged 20 to 64: cohort study using primary care database. *BMJ*. 2016 Mar 22;352:i1350.

Appendix 3. CPRD medcodes, corresponding Read codes and Read terms used to define depression

severity and depressive symptoms

medcode	Read code	Read term	Depression severity
595	E112.14	Endogenous depression	Severe
1055	E135.00	Agitated depression	Severe
2560	E11..12	Depressive psychoses	Severe
5879	E112.11	Agitated depression	Severe
6932	E113.11	Endogenous depression - recurrent	Severe
8478	E130.00	Reactive depressive psychosis	Severe
9667	Eu32200	[X]Severe depressive episode without psychotic symptoms	Severe
11329	Eu33311	[X]Endogenous depression with psychotic symptoms	Severe
12099	Eu32300	[X]Severe depressive episode with psychotic symptoms	Severe
15099	E113.00	Recurrent major depressive episode	Severe
16861	Eu33315	[X]Recurrent severe episodes of psychotic depression	Severe
16861	Eu33315	[X]Recurrent severe episodes of psychotic depression	Severe
17770	E130.11	Psychotic reactive depression	Severe
22806	Eu32212	[X]Single episode major depression w'out psychotic symptoms	Severe
24112	Eu32313	[X]Single episode of psychotic depression	Severe
24117	Eu32311	[X]Single episode of major depression and psychotic symptoms	Severe
24171	E113400	Recurrent major depressive episodes, severe, with psychosis	Severe
25563	E113z00	Recurrent major depressive episode NOS	Severe
25697	E113300	Recurrent major depressive episodes, severe, no psychosis	Severe
28863	Eu32314	[X]Single episode of reactive depressive psychosis	Severe
29784	Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp	Severe
31757	Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis	Severe
32159	E112400	Single major depressive episode, severe, with psychosis	Severe
32941	Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom	Severe
33469	Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt	Severe
33469	Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt	Severe
34390	E112000	Single major depressive episode, unspecified	Severe
35671	E113000	Recurrent major depressive episodes, unspecified	Severe
37764	Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis	Severe
37764	Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis	Severe
41989	Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms	Severe
52678	Eu32312	[X]Single episode of psychogenic depressive psychosis	Severe
98414	Eu32700	[X]Major depression, severe without psychotic symptoms	Severe
98417	Eu32800	[X]Major depression, severe with psychotic symptoms	Severe
101153	Eu32A00	[X]Recurr major depr ep, severe with psych, psych in remiss	Severe
324	E2B..00	Depressive disorder NEC	Moderate
2970	Eu32z00	[X]Depressive episode, unspecified	Moderate
3292	Eu33.00	[X]Recurrent depressive disorder	Moderate
4323	E2B1.00	Chronic depression	Moderate
4639	Eu32.00	[X]Depressive episode	Moderate
6482	E113700	Recurrent depression	Moderate
6546	E112.12	Endogenous depression first episode	Moderate
6950	E112.13	Endogenous depression first episode	Moderate
7011	E112z00	Single major depressive episode NOS	Moderate

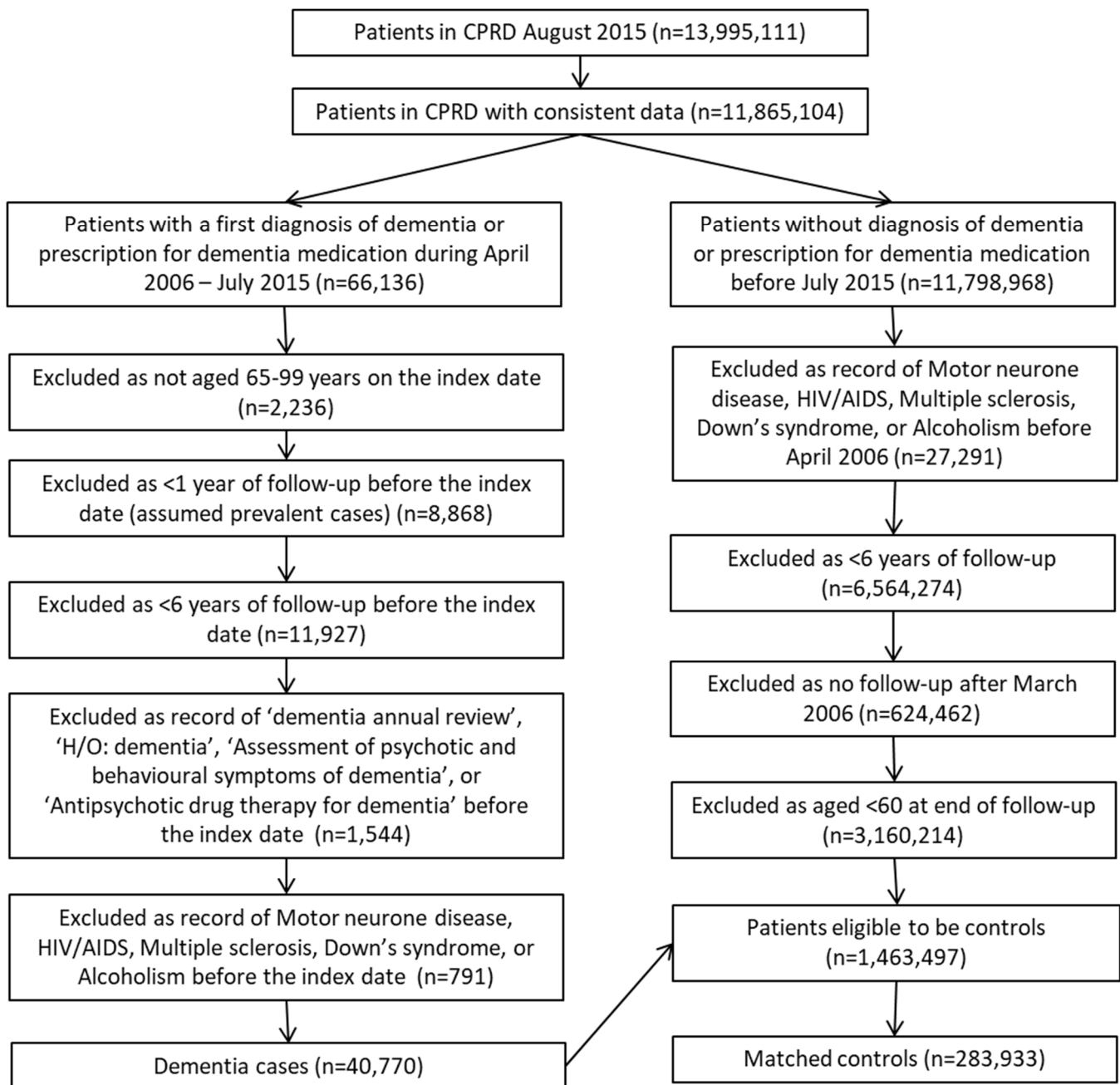
9183	E11z200	Masked depression	Moderate
9211	Eu32100	[X]Moderate depressive episode	Moderate
10610	E112.00	Single major depressive episode	Moderate
10720	Eu32y11	[X]Atypical depression	Moderate
11252	Eu33212	[X]Major depression, recurrent without psychotic symptoms	Moderate
11329	Eu33211	[X]Endogenous depression without psychotic symptoms	Moderate
11913	Eu41200	[X]Mixed anxiety and depressive disorder	Moderate
14709	E113200	Recurrent major depressive episodes, moderate	Moderate
15155	E112200	Single major depressive episode, moderate	Moderate
15219	E112300	Single major depressive episode, severe, without psychosis	Moderate
15220	Eu34114	[X]Persistant anxiety depression	Moderate
22116	Eu33400	[X]Recurrent depressive disorder, currently in remission	Moderate
27491	E11y200	Atypical depressive disorder	Moderate
28248	Eu32z13	[X]Prolonged single episode of reactive depression	Moderate
29520	Eu33100	[X]Recurrent depressive disorder, current episode moderate	Moderate
29520	Eu33100	[X]Recurrent depressive disorder, current episode moderate	Moderate
31757	Eu33214	[X]Vital depression, recurrent without psychotic symptoms	Moderate
36616	Eu33z11	[X]Monopolar depression NOS	Moderate
43324	E112500	Single major depressive episode, partial or unspec remission	Moderate
44300	Eu33z00	[X]Recurrent depressive disorder, unspecified	Moderate
47731	Eu33y00	[X]Other recurrent depressive disorders	Moderate
56273	E113500	Recurrent major depressive episodes,partial/unspec remission	Moderate
59386	Eu32213	[X]Single episode vital depression w'out psychotic symptoms	Moderate
98252	Eu32600	[X]Major depression, moderately severe	Moderate
101054	Eu32900	[X]Single major depr ep, severe with psych, psych in remiss	Moderate
543	Eu32z11	[X]Depression NOS	Mild
655	E200300	Anxiety with depression	Mild
1131	E204.00	Neurotic depression reactive type	Mild
1533	E290.00	Brief depressive reaction	Mild
2716	1465.00	H/O: depression	Mild
2972	E2B0.00	Postviral depression	Mild
3291	Eu32z12	[X]Depressive disorder NOS	Mild
5987	Eu32z14	[X] Reactive depression NOS	Mild
6854	Eu32y00	[X]Other depressive episodes	Mild
7604	Eu32.13	[X]Single episode of reactive depression	Mild
7737	Eu34113	[X]Neurotic depression	Mild
7749	Eu41211	[X]Mild anxiety depression	Mild
7953	Eu34100	[X]Dysthymia	Mild
8584	Eu34111	[X]Depressive neurosis	Mild
8826	Eu33.15	[X]SAD - Seasonal affective disorder	Mild
8851	Eu33.11	[X]Recurrent episodes of depressive reaction	Mild
8902	Eu33.13	[X]Recurrent episodes of reactive depression	Mild
9055	Eu32.11	[X]Single episode of depressive reaction	Mild
10290	Eu34112	[X]Depressive personality disorder	Mild
10455	E211200	Depressive personality disorder	Mild
10667	Eu32400	[X]Mild depression	Mild
10825	E118.00	Seasonal affective disorder	Mild
11717	Eu32000	[X]Mild depressive episode	Mild
12399	9H90.00	Depression annual review	Mild
16506	E112100	Single major depressive episode, mild	Mild

16632	E291.00	Prolonged depressive reaction	Mild
18510	Eu32.12	[X]Single episode of psychogenic depression	Mild
19696	Eu33.12	[X]Recurrent episodes of psychogenic depression	Mild
28756	Eu33.14	[X]Seasonal depressive disorder	Mild
29342	E113100	Recurrent major depressive episodes, mild	Mild
29784	Eu33000	[X]Recurrent depressive disorder, current episode mild	Mild
42931	9HA0.00	On depression register	Mild
55384	E113600	Recurrent major depressive episodes, in full remission	Mild
56609	Eu32y12	[X]Single episode of masked depression NOS	Mild
57409	E112600	Single major depressive episode, in full remission	Mild
98346	Eu32500	[X]Major depression, mild	Mild
1449	1B1J.00	Emotional problem	Depressive symptoms
1908	2257.00	O/E – depressed	Depressive symptoms
1996	1B17.00	Depressed	Depressive symptoms
2639	E204.11	Postnatal depression	Depressive symptoms
2775	E290000	Grief reaction	Depressive symptoms
3489	E11z100	Rebound mood swings	Depressive symptoms
3502	1B1J.11	Emotional upset	Depressive symptoms
4824	1B17.11	C/O - feeling depressed	Depressive symptoms
4979	Eu53012	[X]Postpartum depression NOS	Depressive symptoms
6021	1BO..00	Mood swing	Depressive symptoms
7382	R007z14	[D]Work stress	Depressive symptoms
8928	1BT..11	Low mood	Depressive symptoms
9796	1B1U.00	Symptoms of depression	Depressive symptoms
10015	1BT..00	depressed mood	Depressive symptoms
10438	1B1U.11	Depressive symptoms	Depressive symptoms
10535	Eu43012	[[X]Acute reaction to stress	Depressive symptoms
10734	E290011	Bereavement reaction	Depressive symptoms
11098	Eu43.00	[X]Reaction to severe stress, and adjustment disorders	Depressive symptoms
11607	Eu43000	[X]Acute stress reaction	Depressive symptoms
12122	9H91.00	Depression medication review	Depressive symptoms
12416	1S4..00	Mood observations	Depressive symptoms
13307	Eu53011	[X]Postnatal depression NOS	Depressive symptoms

13307	Eu53011	[X]Postnatal depression NOS	Depressive symptoms
15665	E292z00	Adjustment reaction with disturbance of other emotion NOS	Depressive symptoms
19054	Eu3y111	[X]Recurrent brief depressive episodes	Depressive symptoms
19439	212S.00	Depression resolved	Depressive symptoms
21753	Eu43y00	[X]Other reactions to severe stress	Depressive symptoms
23808	Eu4..00	[X]Neurotic, stress - related and somoform disorders	Depressive symptoms
23869	E284.00	Stress reaction causing mixed disturbance of emotion/conduct	Depressive symptoms
24212	E292.00	Adjustment reaction, predominant disturbance other emotions	Depressive symptoms
25435	1BQ..00	Loss of capacity for enjoyment	Depressive symptoms
26028	1BT..12	sad mood	Depressive symptoms
26138	E28z.00	Acute stress reaction NOS	Depressive symptoms
29527	R007z13	[D]Postoperative depression	Depressive symptoms
29707	E283z00	Other acute stress reaction NOS	Depressive symptoms
30405	9H92.00	Depression interim review	Depressive symptoms
30483	8CAa.00	Patient given advice about management of depression	Depressive symptoms
30583	9k4..00	Depression - enhanced services administration	Depressive symptoms
31515	Eu43z00	[X]Reaction to severe stress, unspecified	Depressive symptoms
32841	8HHq.00	Referral for guided self-help for depression	Depressive symptoms
32845	Eu92000	[X]Depressive conduct disorder	Depressive symptoms
36246	E290z00	Brief depressive reaction NOS	Depressive symptoms
38640	E283.00	Other acute stress reactions	Depressive symptoms
41599	E2C4.00	Mixed disturbance of conduct and emotion	Depressive symptoms
44848	8BK0.00	Depression management programme	Depressive symptoms
45603	E294.00	Adjustment reaction with disturbance emotion and conduct	Depressive symptoms
48349	1S40.00	Dysphoric mood	Depressive symptoms
48588	E292y00	Adjustment reaction with mixed disturbance of emotion	Depressive symptoms
53148	1BU..00	Loss of hope for the future	Depressive symptoms
56924	E292400	Adjustment reaction with anxious mood	Depressive symptoms
59869	1BP0.00	Loss of interest in previously enjoyable activity	Depressive symptoms

65435	9k40.00	Depression - enhanced service completed	symptoms
			Depressive symptoms
91580	Eu92.11	[X]Emotional behavioural problems	Depressive symptoms
96995	9kQ..00	On full dose long term treatment depression - enh serv admin	Depressive symptoms
100977	1JJ..00	Suspected depression	Depressive symptoms
103677	Eu32B00	[X]Antenatal depression	Depressive symptoms

eFigure1 – Selection of 40,770 patients with dementia and 283,933 controls from the Clinical Practice Research Datalink.



eTable 1. Frequency of prescriptions during the drug exposure period according to Anticholinergic Cognitive Burden (ACB) score and drug class. Drugs representing more than 1% of the prescriptions within each ACB level are shown, or the most prevalent drug within each subgroup where this represents fewer than 1% of prescriptions. Shaded areas indicate no drug within that group was prescribed during the course of the study.

Class	ACB1 (25,122,902 prescriptions)		ACB2 (132,731 prescriptions)		ACB3 (1,793,505 prescriptions)	
	Drug	%	Drug	%	Drug	%
Antidepressant	Citalopram	1%			Amitriptyline	29%
					Dosulepin	16%
					Paroxetine	8%
					Lofepamine	2%
					Clomipramine	2%
					Imipramine	2%
					Trimipramine	2%
					Nortriptyline	1%
Gastrointestinal	Ranitidine	2%			Hyoscine	1%
					Dicycloverine	1%
					Atropine	1%
Respiratory	Ipratropium	0.6%	Cyproheptadine	0.7%	Chlorphenamine	4%
					Hydroxyzine	2%
					Promethazine	1%
Antipsychotic	Prochlorperazine	1%	Zuclopenthixol	1%	Trifluoperazine	2%
					Olanzapine	2%
					Chlorpromazine	1%
					Thioridazine	1%
Parkinsonian			Amantadine	2%	Procyclidine	1%
Urological					Tolterodine	7%
					Oxybutynin	7%
					Solifenacin	1%
Analgesic	CODEINE	6%	Nefopam	6%		
	Dextropropoxyphene	4%	Pethidine	2%		
	Dihydrocodeine	3%				
	Tramadol	1%				
Cardiovascular	Bendroflumethiazide	13%				
	Atenolol	11%				
	Furosemide	6%				

	Ramipril	5%				
	Lisinopril	4%				
	Isosorbide	4%				
	Warfarin	4%				
	Nifedipine	3%				
	Doxazosin	3%				
	Digoxin	2%				
	Enalapril	2%				
	Perindopril	2%				
	Amiloride	2%				
	Glyceryl Trinitrate	2%				
Other	Prednisolone	2%	Carbamazepine	87%	Methocarbamol	0.4%
	Diazepam	1%				

eTable 2. Adjusted odds ratios of dementia by number of DDDs of anticholinergic medications by drug class and ACB score

Drug class	Cases (n=40,770) n (%)	Controls (283,933) n (%)	Adjusted for covariates measured at start of DEP aOR (95% CI)	Adjusted for covariates measured at end of DEP aOR (95% CI)
Analgesic				
0	16,899 (41.4%)	125,771 (44.3%)	1	1
>0-13	6,581 (16.1%)	45,258 (15.9%)	1.03 (1.00 to 1.07)	1.02 (0.99 to 1.05)
14-89	8,166 (20.0%)	55,924 (19.7%)	1.00 (0.97 to 1.03)	1.00 (0.97 to 1.03)
90-364	5,216 (12.8%)	33,483 (11.8%)	1.03 (0.99 to 1.07)	1.04 (1.00 to 1.08)
365-1459	3,293 (8.1%)	20,172 (7.1%)	1.04 (1.00 to 1.09)	1.06 (1.01 to 1.11)
1460+	615 (1.5%)	3,325 (1.2%)	1.12 (1.02 to 1.23)	1.16* (1.05 to 1.27)
Antidepressant				
0	34,812 (85.4%)	255,166 (89.9%)	1	1
>0-13	114 (0.3%)	0,713 (0.3%)	1.05 (0.86 to 1.28)	0.99 (0.81 to 1.21)
14-89	2,103 (5.2%)	10,967 (3.9%)	1.29* (1.23 to 1.36)	1.19* (1.13 to 1.25)
90-364	1,481 (3.6%)	7,222 (2.5%)	1.36* (1.28 to 1.44)	1.23* (1.16 to 1.31)
365-1459	1,552 (3.8%)	6,883 (2.4%)	1.47* (1.39 to 1.57)	1.34* (1.26 to 1.43)
1460+	708 (1.7%)	2,982 (1.1%)	1.55* (1.42 to 1.69)	1.47* (1.34 to 1.60)
Antipsychotic				
0	32,719 (80.3%)	233,854 (82.4%)	1	1
>0-13	6,453 (15.8%)	41,234 (14.5%)	1.04 (1.01 to 1.07)	1.03 (1.00 to 1.06)
14-89	1,102 (2.7%)	6,195 (2.2%)	1.10* (1.02 to 1.17)	1.09 (1.01 to 1.16)
90-364	359 (0.9%)	1,977 (0.7%)	1.09 (0.97 to 1.23)	1.07 (0.95 to 1.20)
365-1459	108 (0.3%)	0,542 (0.2%)	1.11 (0.90 to 1.38)	1.09 (0.88 to 1.36)
1460+	29 (0.1%)	0,131 (0.0%)	1.04 (0.68 to 1.59)	1.03 (0.67 to 1.57)
Cardiovascular				
0	12,844 (31.5%)	92,038 (32.4%)	1	1
>0-13	713 (1.7%)	4,550 (1.6%)	1.00 (0.92 to 1.09)	0.99 (0.91 to 1.07)
14-89	1,863 (4.6%)	11,912 (4.2%)	1.03 (0.98 to 1.09)	1.03 (0.97 to 1.09)
90-364	2,625 (6.4%)	17,242 (6.1%)	1.01 (0.96 to 1.06)	1.01 (0.96 to 1.06)
365-1459	6,802 (16.7%)	46,285 (16.3%)	0.98 (0.94 to 1.01)	0.98 (0.95 to 1.02)
1460+	15,923 (39.1%)	111,906 (39.4%)	0.93* (0.90 to 0.96)	0.95* (0.91 to 0.99)

Gastro-intestinal				
0	29,925 (73.4%)	212,119 (74.7%)	1	1
>0-13	2,995 (7.3%)	19,201 (6.8%)	1.03 (0.98 to 1.07)	1.01 (0.97 to 1.06)
14-89	3,592 (8.8%)	24,251 (8.5%)	0.95* (0.91 to 0.99)	0.94* (0.90 to 0.98)
90-364	2,216 (5.4%)	15,138 (5.3%)	0.92* (0.88 to 0.97)	0.92* (0.87 to 0.96)
365-1459	1,607 (3.9%)	10,409 (3.7%)	0.96 (0.91 to 1.01)	0.96 (0.90 to 1.01)
1460+	435 (1.1%)	2,815 (1.0%)	0.94 (0.85 to 1.05)	0.95 (0.86 to 1.06)
Respiratory				
0	31,385 (77.0%)	221,146 (77.9%)	1	1
>0-13	1,507 (3.7%)	10,163 (3.6%)	1.01 (0.95 to 1.07)	1.02 (0.96 to 1.08)
14-89	4,702 (11.5%)	31,037 (10.9%)	1.01 (0.98 to 1.05)	1.00 (0.97 to 1.04)
90-364	1,515 (3.7%)	10,357 (3.6%)	0.95 (0.89 to 1.00)	0.95 (0.89 to 1.00)
365-1459	1,095 (2.7%)	7,363 (2.6%)	0.97 (0.91 to 1.04)	0.98 (0.92 to 1.05)
1460+	566 (1.4%)	3,867 (1.4%)	0.94 (0.86 to 1.04)	0.96 (0.87 to 1.05)
Other				
0	29,249 (71.7%)	206,588 (72.8%)	1	1
>0-13	2,653 (6.5%)	17,447 (6.1%)	0.98 (0.93 to 1.03)	0.97 (0.93 to 1.02)
14-89	5,013 (12.3%)	33,590 (11.8%)	0.95* (0.92 to 0.99)	0.95 (0.92 to 0.99)
90-364	2,182 (5.4%)	14,688 (5.2%)	0.93* (0.88 to 0.98)	0.94 (0.89 to 0.99)
365-1459	1,362 (3.3%)	9,441 (3.3%)	0.92* (0.86 to 0.97)	0.91* (0.86 to 0.97)
1460+	311 (0.8%)	2,179 (0.8%)	0.86 (0.76 to 0.97)	0.86 (0.76 to 0.98)
ACB2				
Analgesic				
0	40,385 (99.1%)	281,596 (99.2%)	1	1
>0-13	116 (0.3%)	0,832 (0.3%)	0.89 (0.73 to 1.08)	0.89 (0.73 to 1.09)
14-89	208 (0.5%)	1,189 (0.4%)	1.10 (0.94 to 1.27)	1.10 (0.95 to 1.28)
90-364	39 (0.1%)	0,208 (0.1%)	1.13 (0.79 to 1.59)	1.12 (0.79 to 1.59)
365+	22 (0.1%)	0,108 (0.0%)	1.21 (0.76 to 1.93)	1.21 (0.76 to 1.93)
Antipsychotic				
0	40,748 (99.9%)	283,864 (100.0%)	1	1
>0-89	6 (0.0%)	0,024 (0.0%)	1.11 (0.45 to 2.75)	0.92 (0.36 to 2.33)
90+	16 (0.0%)	0,045 (0.0%)	1.62 (0.90 to 2.92)	1.61 (0.89 to 2.91)
Parkinsonian				
0	40,713 (99.9%)	283,792 (100.0%)	1	1

>0-89	20 (0.0%)	0,063 (0.0%)	1.43 (0.85 to 2.40)	1.33 (0.79 to 2.23)
90-364	19 (0.0%)	0,037 (0.0%)	1.80 (1.02 to 3.17)	1.47 (0.84 to 2.59)
365+	18 (0.0%)	0,041 (0.0%)	1.48 (0.84 to 2.62)	1.18 (0.67 to 2.08)
Respiratory				
0	40,751 (100.0%)	283,810 (100.0%)	1	1
>0-13	6 (0.0%)	0,041 (0.0%)	0.89 (0.37 to 2.11)	0.80 (0.34 to 1.93)
14+	13 (0.0%)	0,082 (0.0%)	0.89 (0.49 to 1.61)	0.85 (0.47 to 1.53)
Other				
0	39,785 (97.6%)	278,479 (98.1%)	1	1
>0-13	424 (1.0%)	2,499 (0.9%)	1.02 (0.92 to 1.14)	1.05 (0.94 to 1.17)
14-89	218 (0.5%)	1,338 (0.5%)	0.97 (0.84 to 1.12)	0.99 (0.85 to 1.15)
90-364	152 (0.4%)	0,773 (0.3%)	1.17 (0.98 to 1.39)	1.17 (0.97 to 1.40)
365-1459	143 (0.4%)	0,674 (0.2%)	1.26 (1.05 to 1.52)	1.23 (1.01 to 1.48)
1460+	48 (0.1%)	0,170 (0.1%)	1.58* (1.14 to 2.20)	1.56* (1.12 to 2.17)
ACB3				
Antidepressant				
0	31,947 (78.4%)	233,116 (82.1%)	1	1
>0-13	3,389 (8.3%)	21,235 (7.5%)	1.08* (1.04 to 1.13)	1.07* (1.02 to 1.11)
14-89	1,505 (3.7%)	8,976 (3.2%)	1.07 (1.01 to 1.14)	1.05 (0.99 to 1.12)
90-364	1,775 (4.4%)	9,682 (3.4%)	1.16* (1.10 to 1.23)	1.14* (1.08 to 1.21)
365-1459	1,498 (3.7%)	7,732 (2.7%)	1.24* (1.17 to 1.31)	1.22* (1.14 to 1.29)
1460+	656 (1.6%)	3,192 (1.1%)	1.30* (1.18 to 1.42)	1.29* (1.18 to 1.41)
Antipsychotic				
0	39,734 (97.5%)	278,793 (98.2%)	1	1
>0-13	413 (1.0%)	2,356 (0.8%)	0.98 (0.88 to 1.09)	0.96 (0.86 to 1.07)
14-89	243 (0.6%)	1,175 (0.4%)	1.11 (0.96 to 1.28)	1.10 (0.95 to 1.27)
90-364	194 (0.5%)	800 (0.3%)	1.31* (1.12 to 1.54)	1.29* (1.09 to 1.52)
365-1459	134 (0.3%)	601 (0.2%)	1.20 (0.99 to 1.46)	1.16 (0.95 to 1.42)
1460+	52 (0.1%)	208 (0.1%)	1.31 (0.96 to 1.80)	1.32 (0.96 to 1.82)
Gastro-intestinal				
0	38,953 (95.5%)	271,876 (95.8%)	1	1
>0-13	1,205 (3.0%)	8,052 (2.8%)	0.95 (0.90 to 1.02)	0.95 (0.89 to 1.01)
14-89	454 (1.1%)	2,977 (1.0%)	0.91 (0.82 to 1.00)	0.91 (0.82 to 1.01)
90-364	101 (0.2%)	717 (0.3%)	0.80 (0.65 to 0.99)	0.82 (0.66 to 1.02)

365+	57 (0.1%)	311 (0.1%)	1.09 (0.82 to 1.46)	1.12 (0.84 to 1.49)
Parkinsonian				
0	40,500 (99.3%)	282,982 (99.7%)	1	1
>0-13	30 (0.1%)	125 (0.0%)	1.29 (0.95 to 1.74)	1.19 (0.88 to 1.61)
14-89	60 (0.1%)	207 (0.1%)	1.40 (0.94 to 2.07)	1.27 (0.86 to 1.89)
90-364	65 (0.2%)	220 (0.1%)	1.44 (1.08 to 1.92)	1.27 (0.95 to 1.70)
365-1459	88 (0.2%)	301 (0.1%)	1.56* (1.22 to 2.01)	1.35 (1.05 to 1.74)
1460+	27 (0.1%)	98 (0.0%)	1.61 (1.04 to 2.50)	1.39 (0.89 to 2.18)
Respiratory				
0	36,768 (90.2%)	258,738 (91.1%)	1	1
>0-13	1,997 (4.9%)	12,966 (4.6%)	1.02 (0.97 to 1.08)	1.02 (0.97 to 1.07)
14-89	1,511 (3.7%)	9,321 (3.3%)	1.05 (1.00 to 1.12)	1.05 (0.99 to 1.11)
90-364	293 (0.7%)	1,809 (0.6%)	1.02 (0.90 to 1.15)	1.01 (0.89 to 1.15)
365-1459	169 (0.4%)	893 (0.3%)	1.18 (1.00 to 1.40)	1.18 (1.00 to 1.40)
1460+	32 (0.1%)	206 (0.1%)	1.01 (0.69 to 1.47)	1.01 (0.70 to 1.48)
Urological				
0	37,509 (92.0%)	267,060 (94.1%)	1	1
>0-13	295 (0.7%)	1,810 (0.6%)	1.06 (0.94 to 1.20)	1.02 (0.90 to 1.15)
14-89	1,167 (2.9%)	6,514 (2.3%)	1.15* (1.08 to 1.23)	1.10* (1.03 to 1.17)
90-364	773 (1.9%)	3,891 (1.4%)	1.27* (1.18 to 1.38)	1.21* (1.12 to 1.31)
365-1459	800 (2.0%)	3,550 (1.3%)	1.41* (1.30 to 1.53)	1.35* (1.24 to 1.46)
1460+	226 (0.6%)	1,108 (0.4%)	1.28* (1.11 to 1.48)	1.24* (1.07 to 1.44)
Other				
0	40,483 (99.3%)	282,179 (99.4%)	1	1
>0-13	83 (0.2%)	488 (0.2%)	1.06 (0.84 to 1.35)	1.04 (0.82 to 1.32)
14-89	165 (0.4%)	1,109 (0.4%)	0.89 (0.75 to 1.05)	0.89 (0.76 to 1.06)
90-364	36 (0.1%)	144 (0.1%)	1.52 (1.05 to 2.20)	1.55 (1.07 to 2.24)

DEP, drug exposure period; DDD, defined daily dose; OR, odds ratio, aOR, adjusted odds ratio; CI confidence interval; ACB Anticholinergic cognitive burden

* p<0.01

eTable 3. Adjusted odds ratios of dementia by any new prescription of a probably or potentially anticholinergic medication and by drug class

	Cases (n=35,555)	Controls (n=221,772)	Measured at start of DEP	Measured at end of DEP
Any use during DEP	n (%)	n (%)	aOR (95% CI)	aOR (95% CI)
Any use by ACB score				
No prescription	3,791 (10.7%)	28,866 (13.0%)	1	1
Any ACB 1	31,463 (88.5%)	191,183 (86.2%)	1.12* (1.08 to 1.16)	1.11* (1.07 to 1.16)
New ACB 2	912 (2.6%)	4,594 (2.1%)	1.11* (1.03 to 1.20)	1.12* (1.04 to 1.21)
New ACB 3	10,163 (28.6%)	55,534 (25.0%)	1.13* (1.09 to 1.16)	1.07* (1.04 to 1.10)
Any use by ACB score and class				
No prescription	3,791 (10.7%)	28,866 (13.0%)	1	1
Any ACB1				
Analgesic	20,056 (56.4%)	119,509 (53.9%)	1.02 (1.00 to 1.05)	1.02 (0.99 to 1.05)
Antidepressant	4,468 (12.6%)	19,010 (8.6%)	1.39* (1.34 to 1.45)	1.26* (1.20 to 1.32)
Antipsychotic	6,534 (18.4%)	36,702 (16.5%)	1.05* (1.02 to 1.09)	1.04 (1.01 to 1.07)
Cardiovascular	24,092 (67.8%)	148,297 (66.9%)	0.97 (0.94 to 1.00)	0.98 (0.95 to 1.02)
Gastro-intestinal	8,870 (24.9%)	53,297 (24.0%)	0.96* (0.93 to 0.99)	0.95* (0.93 to 0.98)
Respiratory	7,853 (22.1%)	47,517 (21.4%)	0.99 (0.96 to 1.02)	0.95* (0.92 to 0.98)
Other	9,470 (26.6%)	57,341 (25.9%)	0.95* (0.92 to 0.98)	0.99 (0.96 to 1.02)
New ACB2				
Analgesic	286 (0.8%)	1,510 (0.7%)	1.08 (0.95 to 1.23)	1.09 (0.96 to 1.24)
Antipsychotic	6 (0.0%)	12 (0.0%)	NA	NA
Parkinsonian	39 (0.1%)	83 (0.0%)	1.55 (1.04 to 2.30)	1.32 (0.88 to 1.96)
Respiratory	13 (0.0%)	77 (0.0%)	0.89 (0.49 to 1.61)	0.85 (0.47 to 1.54)
Other	591 (1.7%)	3,019 (1.4%)	1.07 (0.98 to 1.18)	1.10 (1.00 to 1.21)
New ACB3				
Antidepressant	5,708 (16.1%)	30,035 (13.5%)	1.10* (1.06 to 1.14)	1.08* (1.04 to 1.11)
Antipsychotic	503 (1.4%)	2,230 (1.0%)	1.14 (1.03 to 1.27)	1.12 (1.01 to 1.25)
Gastro-intestinal	1,296 (3.6%)	7,854 (3.5%)	0.93 (0.88 to 0.99)	0.93 (0.87 to 0.99)
Parkinsonian	91 (0.3%)	283 (0.1%)	1.32 (1.03 to 1.69)	1.16 (0.90 to 1.49)
Respiratory	3,114 (8.8%)	17,752 (8.0%)	1.04 (1.00 to 1.09)	1.04 (0.99 to 1.08)
Urological	2,239 (6.3%)	10,630 (4.8%)	1.22* (1.16 to 1.28)	1.17* (1.11 to 1.23)
Other	220 (0.6%)	1,169 (0.5%)	1.03 (0.89 to 1.19)	1.03 (0.89 to 1.20)

DEP, drug exposure period; aOR, adjusted odds ratio; CI confidence interval; ACB Anticholinergic cognitive burden

* p<0.01

eTable 4. Adjusted odds ratios of dementia by prescription of an anticholinergic medication as measured by the Anticholinergic Drug Scale and by drug class

Drug class	Cases (n=40,770) n (%)	Controls (n=283,933) n (%)	Measured at start of DEP aOR (95% CI)	Measured at end of DEP aOR (95% CI)
Any use by ADS score				
No prescription	14,585 (35.8%)	114,814 (40.4%)	1	1
ADS1	21,074 (51.7%)	135,248 (47.6%)	1.07* (1.04 to 1.09)	1.03 (1.01 to 1.06)
ADS2	7,038 (17.3%)	45,301 (16.0%)	0.98 (0.95 to 1.01)	0.96 (0.93 to 0.99)
ADS3	13,203 (32.4%)	79,114 (27.9%)	1.13* (1.10 to 1.16)	1.08* (1.06 to 1.11)
Any use by ADS score and class				
No prescription	14,585 (35.8%)	114,814 (40.4%)	1	1
ADS1				
Analgesic	5,275 (12.9%)	33,364 (11.8%)	0.96 (0.93 to 1.00)	0.97 (0.93 to 1.00)
Antidepressant	6,061 (14.9%)	29,393 (10.4%)	1.34* (1.30 to 1.39)	1.22* (1.18 to 1.27)
Antipsychotic	7,602 (18.6%)	47,934 (16.9%)	1.03 (1.00 to 1.06)	1.02 (0.99 to 1.05)
Cardiovascular	4,320 (10.6%)	27,358 (9.6%)	1.02 (0.98 to 1.06)	1.02 (0.98 to 1.06)
Gastro-intestinal	832 (2.0%)	5,513 (1.9%)	0.96 (0.89 to 1.04)	0.96 (0.89 to 1.04)
Respiratory	3,206 (7.9%)	21,246 (7.5%)	1.01 (0.97 to 1.05)	1.00 (0.96 to 1.04)
Other	7,240 (17.8%)	49,734 (17.5%)	0.94* (0.91 to 0.97)	0.94* (0.92 to 0.97)
ADS2				
Antipsychotic	367 (0.9%)	1,707 (0.6%)	1.12 (1.00 to 1.26)	1.10 (0.97 to 1.24)
Gastro-intestinal	5,820 (14.3%)	39,251 (13.8%)	0.94* (0.91 to 0.97)	0.93* (0.90 to 0.96)
Other	1,314 (3.2%)	6,688 (2.4%)	1.10* (1.04 to 1.18)	1.07 (1.00 to 1.14)
ADS3				
Antidepressant	7,778 (19.1%)	45,295 (16.0%)	1.10* (1.07 to 1.14)	1.09* (1.06 to 1.12)
Antipsychotic	649 (1.6%)	3,247 (1.1%)	1.02 (0.93 to 1.12)	1.01 (0.92 to 1.10)
Gastro-intestinal	921 (2.3%)	6,176 (2.2%)	0.90* (0.84 to 0.97)	0.91 (0.85 to 0.98)
Parkinsonian	270 (0.7%)	951 (0.3%)	1.48* (1.28 to 1.72)	1.28* (1.10 to 1.49)
Respiratory	4,281 (10.5%)	26,921 (9.5%)	1.02 (0.98 to 1.06)	1.01 (0.98 to 1.05)
Urological	3,236 (7.9%)	16,750 (5.9%)	1.24* (1.19 to 1.29)	1.17* (1.12 to 1.23)

DEP, drug exposure period; OR, odds ratio, aOR, adjusted odds ratio; CI confidence interval; ADS Anticholinergic drug scale

* p<0.01

etable 5a. Adjusted odds ratios of dementia by prescription of a potent anticholinergic by drug class, by adjustment for BMI, smoking and alcohol abuse and by patients with complete data. Adjustments made for covariates as measured at the start of the drug exposure period.

ACB score and drug class	Adjusted for covariates measured at the start of the drug exposure period			
	All patients (40,770 cases, 283,933 controls)		Patients without missing data at start of DEP (15,214 cases, 48,486 controls)	
	Fully adjusted model aOR (95% CI)	Unadjusted for alcohol abuse, smoking, BMI aOR (95% CI)	Fully adjusted model aOR (95% CI)	Unadjusted for alcohol abuse, smoking, BMI aOR (95% CI)
Any use by ACB score				
No prescriptions	1	1	1	1
ACB 1 prescription	1.11* (1.07 to 1.15)	1.11* (1.07 to 1.15)	1.08 (1.01 to 1.16)	1.07 (1.00 to 1.15)
ACB 2 prescription	1.10* (1.03 to 1.17)	1.10* (1.03 to 1.16)	1.13 (1.01 to 1.26)	1.13 (1.01 to 1.26)
ACB 3 prescription	1.16* (1.13 to 1.19)	1.16* (1.13 to 1.19)	1.16* (1.11 to 1.21)	1.16* (1.11 to 1.21)
No prescription				
ACB1	1	1	1	1
Analgesic	1.02 (1.00 to 1.05)	1.02 (0.99 to 1.04)	1.02 (0.97 to 1.06)	1.01 (0.96 to 1.05)
Antidepressant	1.37* (1.32 to 1.42)	1.37* (1.32 to 1.42)	1.43* (1.34 to 1.52)	1.42* (1.34 to 1.51)
Antipsychotic	1.05* (1.02 to 1.08)	1.05* (1.02 to 1.08)	1.08* (1.02 to 1.14)	1.08* (1.02 to 1.13)
Cardiovascular	0.97 (0.94 to 0.99)	0.96 (0.94 to 0.99)	0.94 (0.90 to 0.99)	0.93* (0.88 to 0.97)
Gastro-intestinal	0.97 (0.94 to 0.99)	0.97 (0.94 to 0.99)	0.98 (0.94 to 1.03)	0.98 (0.94 to 1.03)
Respiratory	0.99 (0.97 to 1.02)	1.00 (0.97 to 1.02)	0.97 (0.93 to 1.02)	0.98 (0.93 to 1.03)
Other	0.95* (0.92 to 0.97)	0.95* (0.92 to 0.97)	0.94 (0.90 to 0.99)	0.94 (0.90 to 0.99)
ACB2				
Analgesic	1.03 (0.92 to 1.15)	1.03 (0.92 to 1.15)	1.02 (0.82 to 1.26)	1.01 (0.82 to 1.25)
Antipsychotic	1.44 (0.87 to 2.36)	1.43 (0.87 to 2.35)	1.13 (0.40 to 3.17)	1.12 (0.40 to 3.15)
Parkinsonian	1.55* (1.12 to 2.14)	1.56* (1.13 to 2.15)	1.23 (0.68 to 2.25)	1.26 (0.69 to 2.29)
Respiratory	0.89 (0.55 to 1.45)	0.90 (0.55 to 1.46)	0.74 (0.30 to 1.82)	0.76 (0.31 to 1.86)
Other	1.07 (1.00 to 1.15)	1.07 (1.00 to 1.15)	1.13 (0.99 to 1.28)	1.13 (0.99 to 1.28)
ACB3				
Antidepressant	1.13* (1.10 to 1.16)	1.13* (1.10 to 1.16)	1.18* (1.12 to 1.24)	1.18* (1.12 to 1.24)
Antipsychotic	1.09 (1.02 to 1.18)	1.09 (1.02 to 1.18)	1.01 (0.88 to 1.17)	1.01 (0.88 to 1.17)
Gastro-intestinal	0.94 (0.89 to 0.99)	0.94 (0.89 to 0.99)	0.94 (0.86 to 1.03)	0.94 (0.86 to 1.04)
Parkinsonian	1.45* (1.25 to 1.68)	1.44* (1.24 to 1.68)	1.47* (1.10 to 1.97)	1.46* (1.09 to 1.95)
Respiratory	1.04 (1.00 to 1.08)	1.04 (1.00 to 1.08)	1.03 (0.97 to 1.11)	1.03 (0.96 to 1.10)
Urological	1.23* (1.18 to 1.28)	1.23* (1.18 to 1.28)	1.26* (1.17 to 1.36)	1.26* (1.17 to 1.35)
Other	0.99 (0.87 to 1.13)	0.99 (0.87 to 1.12)	0.96 (0.77 to 1.19)	0.96 (0.77 to 1.19)

DEP, drug exposure period; OR, odds ratio, aOR, adjusted odds ratio; CI, confidence interval; ACB, Anticholinergic Cognitive Burden score; BMI, body mass index

* p<0.01

etable 5b. Adjusted odds ratios of dementia by prescription of a potent anticholinergic by drug class, by adjustment for BMI, smoking and alcohol abuse and by patients with complete data. Adjustments made for covariates as measured at the end of the drug exposure period.

ACB score and drug class	Adjusted for covariates measured at the start of the drug exposure period			
	All patients (40,770 cases, 283,933 controls)		Patients without missing data at start of DEP (15,214 cases, 48,486 controls)	
	Fully adjusted model aOR (95% CI)	Unadjusted for alcohol abuse, smoking, BMI aOR (95% CI)	Fully adjusted model aOR (95% CI)	Unadjusted for alcohol abuse, smoking, BMI aOR (95% CI)
Any use by ACB score				
No prescriptions	1	1	1	1
ACB 1 prescription	1.10* (1.06 to 1.15)	1.12* (1.07 to 1.16)	1.07 (1.01 to 1.13)	1.05 (1.00 to 1.11)
ACB 2 prescription	1.10* (1.03 to 1.16)	1.09* (1.02 to 1.16)	1.09 (1.01 to 1.18)	1.09 (1.01 to 1.17)
ACB 3 prescription	1.11* (1.08 to 1.14)	1.10* (1.08 to 1.13)	1.09* (1.06 to 1.13)	1.09* (1.05 to 1.12)
Any use by ACB score and class				
No prescription	1	1	1	1
ACB1				
Analgesic	1.02 (0.99 to 1.04)	1.00 (0.98 to 1.03)	1.01 (0.98 to 1.04)	0.99 (0.96 to 1.02)
Antidepressant	1.25* (1.20 to 1.30)	1.25* (1.20 to 1.30)	1.22* (1.16 to 1.28)	1.22* (1.16 to 1.28)
Antipsychotic	1.04 (1.01 to 1.07)	1.04 (1.01 to 1.07)	1.05* (1.02 to 1.09)	1.05* (1.02 to 1.09)
Cardiovascular	0.98 (0.95 to 1.01)	0.97 (0.94 to 1.00)	0.97 (0.93 to 1.01)	0.94 (0.91 to 0.98)
Gastro-intestinal	0.96* (0.93 to 0.99)	0.96 (0.94 to 0.99)	0.97 (0.94 to 1.01)	0.97 (0.94 to 1.01)
Respiratory	0.99 (0.97 to 1.02)	1.00 (0.97 to 1.02)	1.00 (0.97 to 1.04)	1.00 (0.97 to 1.04)
Other	0.95* (0.92 to 0.98)	0.95* (0.92 to 0.97)	0.95* (0.91 to 0.98)	0.94* (0.91 to 0.98)
ACB2				
Analgesic	1.03 (0.92 to 1.16)	1.02 (0.91 to 1.14)	1.04 (0.91 to 1.19)	1.02 (0.89 to 1.17)
Antipsychotic	1.35 (0.82 to 2.23)	1.32 (0.80 to 2.18)	1.65 (0.84 to 3.27)	1.58 (0.80 to 3.12)
Parkinsonian	1.32 (0.96 to 1.82)	1.37 (1.00 to 1.89)	1.40 (0.93 to 2.10)	1.47 (0.97 to 2.21)
Respiratory	0.83 (0.51 to 1.36)	0.88 (0.54 to 1.44)	0.75 (0.42 to 1.33)	0.82 (0.46 to 1.45)
Other	1.09 (1.01 to 1.17)	1.09 (1.01 to 1.17)	1.07 (0.98 to 1.18)	1.07 (0.97 to 1.17)
ACB3				
Antidepressant	1.11* (1.08 to 1.14)	1.11* (1.07 to 1.14)	1.11* (1.07 to 1.16)	1.11* (1.07 to 1.15)
Antipsychotic	1.07 (1.00 to 1.16)	1.07 (0.99 to 1.15)	1.01 (0.91 to 1.11)	1.00 (0.91 to 1.10)
Gastro-intestinal	0.94 (0.89 to 0.99)	0.94 (0.89 to 0.99)	0.95 (0.89 to 1.01)	0.95 (0.89 to 1.02)
Parkinsonian	1.29* (1.11 to 1.50)	1.29* (1.11 to 1.50)	1.31* (1.07 to 1.59)	1.31* (1.08 to 1.59)
Respiratory	1.03 (1.00 to 1.07)	1.03 (0.99 to 1.07)	1.04 (0.99 to 1.08)	1.03 (0.99 to 1.08)
Urological	1.18* (1.13 to 1.23)	1.17* (1.12 to 1.22)	1.16* (1.10 to 1.22)	1.16* (1.09 to 1.22)
Other	0.99 (0.87 to 1.13)	0.98 (0.86 to 1.12)	1.01 (0.87 to 1.17)	1.00 (0.86 to 1.16)

DEP, drug exposure period; OR, odds ratio, aOR, adjusted odds ratio; CI, confidence interval; ACB, Anticholinergic Cognitive Burden score; BMI, body mass index

* p<0.01

Appendix 4. Extended analysis of the association between antidepressants, depression and dementia

Aim

To further document the association between antidepressants, depression and dementia shown in tables 3 and 4, in particular to test the possibility that the apparent link between dementia and antidepressant use is induced by residual confounding by depression.

Method

Depression was recoded into a five-level variable corresponding to the maximum recorded depression severity in a participants' available history up to the end of the drug exposure period as "No record", "Depressive symptoms", "Mild Depression", "Moderate Depression" and "Severe Depression".

The relationship between depression and anticholinergic antidepressant use during the DEP was tabulated. Several conditional logistic regression models were then estimated with incident dementia as the outcome variable and the following predictors:

1. Depression only
2. Depression and all other covariates.
3. All anti-depressants only
4. Depression and all anti-depressants.
5. Depression, all anti-depressants, and all other covariates

Anti-depressants are coded in categories corresponding to levels of exposure during the DEP. ACB1 and ACB3 are coded by DDDs, ACB0 antidepressants are coded by number of prescriptions.

Finally, models were estimated including the main effects of antidepressants, depression and all covariates as well as the interaction between antidepressants and depression. The effect of ACB3 antidepressants was derived at each level of depression by combining the relevant main effect and interaction term and was tabulated.

This analysis was then repeated restricted to the exposures 15-20 years before index date and confounders measured up to 15 years before index date. Here the antidepressant variables are coded as binary (present or absent).

Results

There is a strong relationship between ACB3 antidepressants and recorded depression. 11% of the population with no depression have been prescribed an ACB3 antidepressant compared to 61% of those with a record of severe depression (table e6).

In univariable analysis depression is associated with dementia incidence, with that association attenuated by 50% after adjusting for covariates (not including the use of antidepressants). Each antidepressant class is associated with dementia with this association not being substantially affected by including covariates. When depression and antidepressants are both included in the model, there is no longer an independent effect of depression, but the effect of antidepressants remains essentially unaffected. Each antidepressant group (ACB0, ACB1 and ACB3) is independently associated with dementia incidence (table e7). This pattern is repeated when exposures and covariates are only measured up to 15 years before index date, except here only ACB3 antidepressants are independently associated with dementia, while ACB0 and ACB1 antidepressants are not (table e8).

The association between ACB3 antidepressants and dementia incidence is not systematically affected by recorded depression severity (table e9).

	Maximum recorded depression N(%)					
	No record	Symptoms only	Mild	Moderate	Severe	All
Total	259,406 (100%)	13,003 (100%)	17,181 (100%)	30,253 (100%)	4,860 (100%)	324,703 (100%)
ACB3 Anticholinergics (DDD)						
0	229,617 (89%)	8,566 (66%)	10,169 (59%)	14,829 (49%)	1,882 (39%)	265,063 (82%)
1-29	16,270 (6%)	1,885 (15%)	2,249 (13%)	3,746 (12%)	474 (10%)	24,624 (8%)
30-89	4,861 (2%)	912 (7%)	1,360 (8%)	2,898 (10%)	450 (9%)	10,481 (3%)
90-364	4,854 (2%)	841 (6%)	1,469 (9%)	3,612 (12%)	681 (14%)	11,457 (4%)
365-1459	3,072 (1%)	619 (5%)	1,373 (8%)	3,369 (11%)	797 (16%)	9,230 (3%)
1460+	732 (0%)	180 (1%)	561 (3%)	1,799 (6%)	576 (12%)	3,848 (1%)

Table e6. Relationship between maximum recorded depression severity and DDDs of ACB3 antidepressants during the DEP.

	Terms included in model				
	Depression only	Depression + covariates	Antidepressants only	Depression + Antidepressants	Full model
	aOR (se)	aOR (se)	aOR (se)	aOR (se)	aOR (se)
Depression severity					
None	1	1		1	1
Symptoms	1.26* (0.03)	1.15* (0.03)		1.11* (0.03)	1.06 (0.03)
Mild	1.34* (0.03)	1.20* (0.03)		1.12* (0.03)	1.08* (0.03)
Moderate	1.35* (0.02)	1.18* (0.02)		1.09* (0.02)	1.03 (0.02)
Severe	1.48* (0.06)	1.24* (0.05)		1.09 (0.05)	1.02 (0.04)
ACB3 antidepressants (DDD)					
0			1	1	1
1-29			1.12* (0.02)	1.11* (0.02)	1.07* (0.02)
30-89			1.12* (0.03)	1.09* (0.03)	1.06 (0.03)
90-364			1.21* (0.03)	1.18* (0.03)	1.15* (0.03)
365-1459			1.29* (0.04)	1.25* (0.04)	1.21* (0.04)
1460+			1.37* (0.06)	1.31* (0.06)	1.28* (0.06)
ACB0 antidepressants (number of prescriptions)					
0			1	1	1
1			1.03 (0.06)	1.01 (0.06)	0.98 (0.06)
2			1.19* (0.06)	1.17* (0.06)	1.13 (0.06)
3-10			1.26* (0.08)	1.22* (0.08)	1.18* (0.07)
10-50			1.36* (0.16)	1.31 (0.15)	1.26 (0.15)
ACB1 antidepressants (DDD)					
0			1	1	1
1-29			1.11 (0.11)	1.07 (0.11)	1.01 (0.10)
30-89			1.33* (0.03)	1.27* (0.03)	1.23* (0.03)
90-364			1.42* (0.04)	1.35* (0.04)	1.28* (0.04)
365-1459			1.55* (0.05)	1.47* (0.05)	1.39* (0.04)
1460+			1.62* (0.07)	1.54* (0.07)	1.49* (0.07)

DDD – defined daily dose; aOR – adjusted odds ratio; se – standard error; * p<0.01

Table e7. Association between DDDs/number of prescriptions of antidepressant use and maximum recorded depression before index date and dementia incidence estimated in different conditional logistic regression models.

		Terms included in model				
		Depression only	Depression and covariates	Antidepr. only	Antidepr. and covariates	Full model
		aOR (se)	aOR (se)	aOR (se)	aOR (se)	aOR (se)
Depression severity						
	Symptoms	1.19 (0.14)	1.09 (0.13)			1.08 (0.13)
	Mild	1.12 (0.07)	1.05 (0.07)			1.01 (0.07)
	Moderate	1.19* (0.04)	1.10* (0.04)			1.03 (0.04)
	Severe	1.35* (0.15)	1.23 (0.14)			1.13 (0.13)
Use of any antidepressant						
	ACB3 antidepressants			1.29* (0.05)	1.21* (0.05)	1.19* (0.05)
	ACB1 antidepressants			1.15 (0.08)	1.08 (0.08)	1.07 (0.08)
	ACB0 antidepressants			1.04 (0.11)	0.93 (0.10)	0.92 (0.10)

DDD – defined daily dose; aOR – adjusted odds ratio; se – standard error; * p<0.01

Table e8. Association between antidepressants and maximum recorded depression severity 15-20 years before index date and dementia incidence estimated using different conditional logistic regression models.

	Complete data	Exposures 15-20 years before index date
	aOR (95% CI)	aOR (95% CI)
Overall	1.11 (1.08-1.14)	1.19 (1.10-1.30)
Depression		
None	1.13 (1.09-1.18)	1.23 (1.10-1.37)
Symptoms		
Mild	1.10 (1.01-1.20)	0.99 (0.75-1.30)
Moderate	1.11 (1.04-1.19)	1.15 (1.01-1.31)
Severe	1.11 (0.95-1.31)	1.50 (0.96-2.36)

aOR – adjusted odds ratio; se – standard error

Table e9. Effect of ACB3 Antidepressants on dementia incidence by highest level of recorded depressive disorder, estimated using an interaction term between depression and ACB3 antidepressant use, both for the complete data and restricted to exposures occurring 15-20 years before index date.