Online Supplement

Association between antipsychotic polypharmacy and outcomes for people with serious mental illness in England.

Antipsychotic product codes

We downloaded the antipsychotic drug codes list from the ClinicalCodes database (https://clinicalcodes.rss.mhs.man.ac.uk/) - a web repository of clinical codes developed by the University of Manchester Institute of Population Health[1]. The repository holds a collection of peer-reviewed articles and the associated codes used irrespective of code type (e.g. Read, CPRD product/medical code, BNF code, ICD-10) and database (e.g. CPRD, THIN). We used the list of antipsychotic drug codes uploaded by Windfuhr et al[2]. The list includes three British National Formulary (http://www.bnf.org) chapter headings: first-generation antipsychotic drugs (FGAs) or typical antipsychotics, second-generation antipsychotics (SGAs) or atypical antipsychotics, and depot antipsychotics. From the list of 33 antipsychotic substances presented in Table S1, 27 were recorded at least once in our sample.

Table: Product codes used to identify antipsychotic substances

	Substance	Product codes									
1	**Amisupride***	80139020	68222020	81945020	35008020	35010020	85993020	69302020	68224020	00411021	89950020
		85994020	85992020	68217020	80154020	79348020	86000020	86001020	85999020		
2	**Aripiprazole**	91145020	87950020	91147020	87952020	91149020	87954020	88668020	10469020	94973020	91139020
		87944020	91141020	87946020	91143020	87948020	88666020	94971020			
3	**Asenapine**	00341021	337021								
4	**Benperidol**	64108020	98282020	64105020	84860020						
5	**Chlorpromazine**	61251020	61249020	61250020	72606020	61237020	58896020	55203020	72588020	55710020	72587020
		68531020	55217020	58894020	55204020	66353020	91404020	61244020	65188020	52087020	61238020
		72597020	55228020	68532020	60250020	55202020	66356020	91408020	61243020	61264020	56481020
		56450020	56444020	56445020	73791020	56446020	56468020	56456020			
6	Chlorprothixine	51832020									
7	**Clozapine**	72581020	97149020	72580020	97145020	97153020	72577020	72576020	88169020	97151020	88167020
		97147020	97155020	88806020	88804020						
8	**Droperidol**	58513020	72300020	58514020	62878020	62879020	72297020	94599020			
9	**Flupentixol**	48897020	62029020	48900020	91584020	53030020	53031020	89976020	89974020	57938020	89972020
		62034020	91582020	68096020	89970020	62033020	62032020				
10	**Fluphenazine**	62037020	62042020	50459020	50472020	92214020	62049020	92200020	92202020	61027020	62048020
		62954020	92212020	92204020	92206020	92208020	50445020	92210020	92218020	53053020	92216020
11	Fluspirilene	62066020	51357020								
12	**Haloperidol**	63137020	63136020	58501020	58505020	58502020	58500020	95205020	58506020	63104020	55437020
		53896020	54580020	75300020	63108020	99757020	60366020	63114020	511021	00443021	63115020
		55438020	53576020	63110020	78059020	63109020	88468020	20065020	20067020	75301020	53575020
		75302020	63113020	63118020	59312020	59028020	63105020	53898020	55351020	95203020	99755020
		72226020	55346020	91764020	56176020	56181020	56182020	56183020	56175020	56177020	56187020
		58510020	58509020	63124020							
13	Integrin	49952020	65318020								
14	**Levomepromazine**	87842020	38919020	64327020	64326020	32615020	97323020	87840020	52695020	3365020	52694020
15	Methotrimeprazine	64330020									

16	**Olanzapine**	00719021	81016020	00717021	00715021	87556020	83405020	00727021	55972020	00725021	00723021
		59434020	81014020	03580020	00733021	90165020	00731021	00729021	92053020	00713021	81015020
		00711021	00709021	83403020	83404020	00589021	87558020	83399020	78913020	58203020	79499020
		81008020	92055020	90167020	83397020	78912020	83398020	98278020	98329020		
17	**Paliperidone**	93747020	93739020	93741020	93743020	99845020	99847020	99841020	99843020	99853020	99855020
		99849020	99851020								
18	**Pericyazine**	50678020	96724020	50677020	96722020	50679020	52648020	65580020	65584020	65579020	65581020
19	**Perphenazine**	49428020	49429020	53721020	65588020	65592020	65593020	56832020	65589020	56833020	65587020
		52047020									
20	**Pimozide**	58519020	58518020	65799020	65798020						
21	**Pipotizine**	53586020	91989020	91987020	91985020	91981020	65842020				
22	**Prochlorperazine**	68249020	91364020	54878020	66241020	66242020	66237020	54234020	57101020	69868020	60605020
		55530020	56337020	66245020	69516020	69517020	72187020	56506020	91368020	58525020	52717020
		52716020	51690020	04131020	4128020	04129020	96911020	04123020	51692020	96913020	52248020
		52249020									
23	**Promazine**	72991020	66279020	51749020	72987020	66278020	55705020	72988020	51751020	66277020	66283020
		66282020	55706020	72183020	72184020	58296020	52959020	52957020	52958020	52968020	51649020
24	**Quetiapine**	85204020	97203020	97205020	00209021	00447021	98873020	85207020	94789020	85206020	85203020
		42176020	33610020	99745020	94791020	87045020	94793020	94787020	36328020	85202020	85213020
		85216020	85215020	85212020	87047020	98875020	95789020	95791020	95793020	95787020	
25	Remoxipride	73439020	73440020	73441020	73474020	73475020	84528020				
26	**Risperidone**	49437020	73799020	49438020	49439020	73798020	77749020	73800020	78753020	77550020	82616020
		13768020	81545020	77501020	92723020	92725020	88877020	36905020	79476020	53727020	74841020
		49490020	86494020	81543020	53728020	86496020	92717020	53729020	92721020	49489020	88875020
		77912020	74927020	74786020	65788020	49491020					
27	**Sertindole**	82836020	82837020	82835020	82828020	82829020	82831020	82827020			
28	**Sulpiride**	52921020	52922020	80696020	66836020	60498020	56102020	56529020	59205020	66837020	66838020
		59150020	82057020								
29	**Thioridazine**	54413020	67032020	75277020	67027020	67037020	54418020	54411020	67028020	67036020	67038020
		54412020	67029020	75276020	55600020						
30	**Trifluoperazine**	51013020	51663020	51681020	51676020	51678020	51687020	51677020	87980020	67148020	67234020

		75976020	55747020	75977020	67240020	67235020	55746020	67241020	69003020		
31	Trifluperidol	67244020	67245020	67248020	67249020						
32	**Zotepine**	55209020	55210020	50782020	50780020	50781020					
33	**Zuclopenthixol**	48713020	48714020	48712020	90151020	90149020	72839020	61507020	61508020	61506020	90147020
		90145020	72836020	91596020	53027020	67405020	91592020	61511020	61512020		

*in bold the 27 substances that were recorded at least once in our sample

Calculation of treatment duration

To mark the beginning and end of an APP episode we need information about the prescription date and the number of days the antipsychotic drug was prescribed. The CPRD therapy file provides the prescription date but the treatment duration is poorly populated with 99% missing values for antipsychotic drugs. The reason is that in most cases, GPs prescribe the quantity a patient should use until it runs out and therefore they are not interested in recording the duration of the prescription.

To overcome this problem we calculated the treatment duration as the ratio of the total quantity entered by the GP for the prescribed product (qty) over the numeric daily dose (ndd) prescribed for the event (drug). Because information on ndd is missing for over 23% of the therapy events we employ the following imputation strategy: to events with missing ndd we assigned the most frequent ndd across all events with the specific product code. About 1% of the therapy events involve a product for which all events have missing ndd. For these events, we imputed the ndd by assigning the most frequent ndd across all events with the specific substance.

Estimating the treatment duration as the ratio qty/ndd was further complicated by another two issues. First, while pack size or type of the prescribed product is provided (e.g. 560 ML, 21 tablets) the unit in which ndd is recorded is not and in some cases it is obvious that qty and ndd are recorded in different units (e.g. qty=21 tablets, ndd=300). In these cases we divided ndd by the strength of the prescribed substance to impute the true ndd (e.g. ndd=300/100mg=3 tablets). Second, less than 0.02% of prescription records (245 of 1,035,856) had an implausibly large calculated duration and were dropped from the analysis.

Table: Read codes used to identify SMI diagnostic categories

Category	Read codes									
Schizophrenia and other psychoses	E100.00	E100.11	E100000	E100100	E100200	E100300	E100400	E100500	E100z00	E101.00
	E101000	E101400	E101500	E101z00	E102.00	E102000	E102100	E102500	E102z00	E103.00
	E103000	E103200	E103300	E103400	E103500	E103z00	E104.00	E105.00	E105000	E105200
	E105500	E105z00	E106.00	E107.00	E107.11	E107000	E107100	E107200	E107300	E107400
	E107500	E107z00	E10y.00	E10y.11	E10y000	E10y100	E10yz00	E10z.00	E120.00	E121.00
	E122.00	E123.00	E123.11	E12y.00	E12y000	E12yz00	E12z.00	E13..00	E13..11	E131.00
	E132.00	E133.00	E133.11	E134.00	E13y.00	E13y100	E13yz00	E13z.00	E13z.11	E1z..00
	E212200	Eu20.00	Eu20000	Eu20011	Eu20100	Eu20111	Eu20200	Eu20211	Eu20212	Eu20213
	Eu20214	Eu20300	Eu20311	Eu20400	Eu20500	Eu20511	Eu20600	Eu20y00	Eu20y12	Eu20y13
	Eu20z00	Eu21.00	Eu21.11	Eu21.12	Eu21.13	Eu21.14	Eu21.15	Eu21.16	Eu21.17	Eu21.18
	Eu22.00	Eu22000	Eu22011	Eu22012	Eu22013	Eu22014	Eu22015	Eu22100	Eu22111	Eu22200
	Eu22300	Eu22y00	Eu22y11	Eu22y12	Eu22y13	Eu22z00	Eu23.00	Eu23000	Eu23011	Eu23012
	Eu23100	Eu23112	Eu23200	Eu23211	Eu23212	Eu23214	Eu23300	Eu23312	Eu23y00	Eu23z00
	Eu23z11	Eu23z12	Eu24.00	Eu24.12	Eu24.13	Eu25.00	Eu25000	Eu25011	Eu25012	Eu25100
	Eu25111	Eu25112	Eu25200	Eu25212	Eu25y00	Eu25z00	Eu25z11	Eu26.00	Eu2y.00	Eu2y.11
	Eu2z.00	Eu2z.11	Eu44.14							
Bipolar disorder and affective psychoses	E11..00	E11..12	E110.00	E110.11	E110000	E110100	E110200	E110300	E110400	E110600
	E110z00	E111.00	E111000	E111100	E111200	E111300	E111400	E111500	E111600	E111z00
	E112400	E113400	E114.00	E114.11	E114000	E114100	E114200	E114300	E114400	E114500
	E114600	E114z00	E115.00	E115.11	E115000	E115100	E115200	E115300	E115400	E115500
	E115600	E115z00	E116.00	E116000	E116100	E116200	E116300	E116400	E116500	E116600
	E116z00	E117.00	E117000	E117100	E117200	E117300	E117400	E117500	E117600	E117z00
	E11y.00	E11y000	E11y100	E11y300	E11yz00	E11z.00	E11z000	E11zz00	E130.00	E130.11
	E13y000	Eu30.00	Eu30.11	Eu30000	Eu30100	Eu30200	Eu30211	Eu30212	Eu30y00	Eu30z00
	Eu30z11	Eu31.00	Eu31.11	Eu31.12	Eu31.13	Eu31000	Eu31100	Eu31200	Eu31300	Eu31400
	Eu31500	Eu31600	Eu31700	Eu31800	Eu31900	Eu31911	Eu31y00	Eu31y11	Eu31y12	Eu31z00
	Eu32300	Eu32311	Eu32312	Eu32313	Eu32314	Eu32800	Eu33213	Eu33300	Eu33311	Eu33312

	Eu33313	Eu33314	Eu33315	Eu33316	Eu3z.11					

Table: Covariates

Measured at the date of entry to the study sample		
Variable	Type	Details
Age	Categorical (19-35,36-45, 46-55, 56-65, >65)	CPRD Read codes
Male	Binary	CPRD Read codes
IMD (Deprivation level associated with patient's residence area)	Categorical (Quintiles)	For practices that have consented to participate in the linkage scheme, the patient postcode of residence is mapped to LSOA using a postcode lookup file. The LSOA of residence then allows linkage to the 2010 English Index of Multiple Deprivation.
Number of Charlson Index comorbidities	Categorical 0, 1, 2, >=3	CPRD Read codes recorded any time before the date of entry to the study sample.
Depression diagnosis	Binary	CPRD Read codes
Alcohol status Smoking status	Binary	Diagnostic or management codes recorded in CPRD.
Number of GP contacts in the preceding 12 months (face-to-face visits and telephone calls)	Categorical 0-4, 5-9, 10-14, 15-19, >=20	From CPRD consultation file.
Distance from GP to nearest acute provider Distance from GP to nearest MH provider	Categorical 0-3km, 3-6km, 6-9km, >9km	We provided CPRD with a look-up table of all postcodes in England, the estimated straight line distance from the postcode to the nearest mental health and acute hospital provider. CPRD carried out the linkage using contributing practices' post-code information. Once linked, distances were categorised into distance bands by CPRD e.g. 0-3km, 3-6km etc.
GP practice in rural area	Binary	To construct a practice level rurality flag we provided CPRD with a look-up table of all lower layer super output area (LSOA) levels (small areas) in England

		and rurality information derived based on the 2011 Rural-Urban Classification for Small Area Geographies (RUC2011). This information was used to link contributing practices to their corresponding rurality flag using the practice LSOA.
Calendar year	Binary	
Time since first diagnosis	Categorical 1 year, 1-5 years, >5 years	
Defined using the entire patient's history		
Variable	Type	Details
Schizophrenia diagnosis Bipolar diagnosis Both schizophrenia and bipolar diagnosis	Binary	CPRD Read codes (provided in Table 2)

Measures of polypharmacy prevalence

We calculated two measures of polypharmacy prevalence. First, the annual prevalence of polypharmacy as the number of patients with at least one polypharmacy episode in a year divided by the total number of patients observed during that year. Second, the rate of polypharmacy defined as the sum of all patients' polypharmacy days in a year over the sum of all patients' days at risk of polypharmacy in that year.

Our second measure – the rate of polypharmacy – is an improvement over the point estimates of polypharmacy prevalence often reported in the literature. Point estimates of prevalence show what fraction of eligible individuals are prescribed polypharmacy on a given day. Average point estimates of prevalence can be calculated by averaging daily point estimates.

In the following, we prove that the rate of polypharmacy is a weighted average of the point estimates of polypharmacy on each of the 365 days of the year. Instead of assigning an equal weight to each day of the year, our measure puts a different weight according to the ratio of patients at risk on that day over the patients at risk in the entire year.

Let POL_{nt} and POP_{nt} be defined as:

$$POL_{nt} = \begin{cases} 1, & \text{if individual n is on polypharmacy on day t} \\ 0, & \text{otherwise} \end{cases}$$

$$POP_{nt} = \begin{cases} 1, & \text{if individual n is present (at risk) on day t} \\ 0, & \text{otherwise} \end{cases}$$

The average point estimate of polypharmacy prevalence is:

$$\text{average point estimate} = \frac{1}{365}\sum_{t=1}^{365}\frac{\text{number of patients on polypharamcy on day t}}{\text{number of patients present (at risk) on day t}}$$

$$= \frac{1}{365}\left(\frac{\sum_{n=1}^{N} P_{n1}}{\sum_{n=1}^{N} POP_{n1}} + \ldots + \frac{\sum_{n=1}^{N} P_{n,365}}{\sum_{n=1}^{N} POP_{n,365}}\right) \quad (1)$$

$$= \frac{\sum_{n=1}^{N} P_{n1}}{\sum_{n=1}^{N} POP_{n1}}\left(\frac{1}{365}\right) + \ldots + \frac{\sum_{n=1}^{N} P_{n,365}}{\sum_{n=1}^{N} POP_{n,365}}\left(\frac{1}{365}\right)$$

The rate of polypharmacy is:

$$\text{rate} = \frac{\text{number of polypharmacy days in a year}}{\text{number of days at risk in a year}}$$

$$= \frac{\sum_{n=1}^{N}\sum_{t=1}^{365} POL_{nt}}{\sum_{n=1}^{N}\sum_{t=1}^{365} POP_{nt}}$$

$$= \frac{\sum_{n=1}^{N} P_{n1}}{\sum_{n=1}^{N}\sum_{t=1}^{365} POP_{nt}} + \ldots + \frac{\sum_{n=1}^{N} P_{n,365}}{\sum_{n=1}^{N}\sum_{t=1}^{365} POP_{nt}} \quad (2)$$

$$= \frac{\sum_{n=1}^{N} P_{n1}}{\sum_{n=1}^{N} POP_{n1}}\left(\frac{\sum_{n=1}^{N} POP_{n1}}{\sum_{n=1}^{N}\sum_{t=1}^{365} POP_{nt}}\right) + \ldots + \frac{\sum_{n=1}^{N} P_{n,365}}{\sum_{n=1}^{N} POP_{n,365}}\left(\frac{\sum_{n=1}^{N} POP_{n,365}}{\sum_{n=1}^{N}\sum_{t=1}^{365} POP_{nt}}\right)$$

From (1) and (2) follows that the two measures differ only in the weights used.

The figure below is the same as the figure in the paper with the addition of the polypharmacy prevalence calculated on 1st of January of each calendar year. The trends of the rate of polypharmacy and the point estimate of polypharmacy prevalence are very similar.

Figure: Measures of polypharmacy prevalence

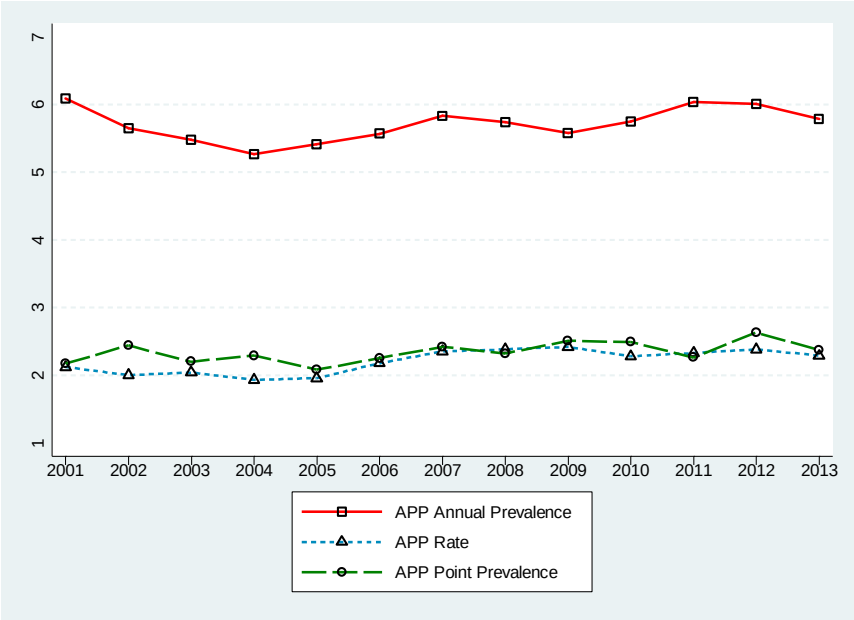


Figure: APP annual prevalence

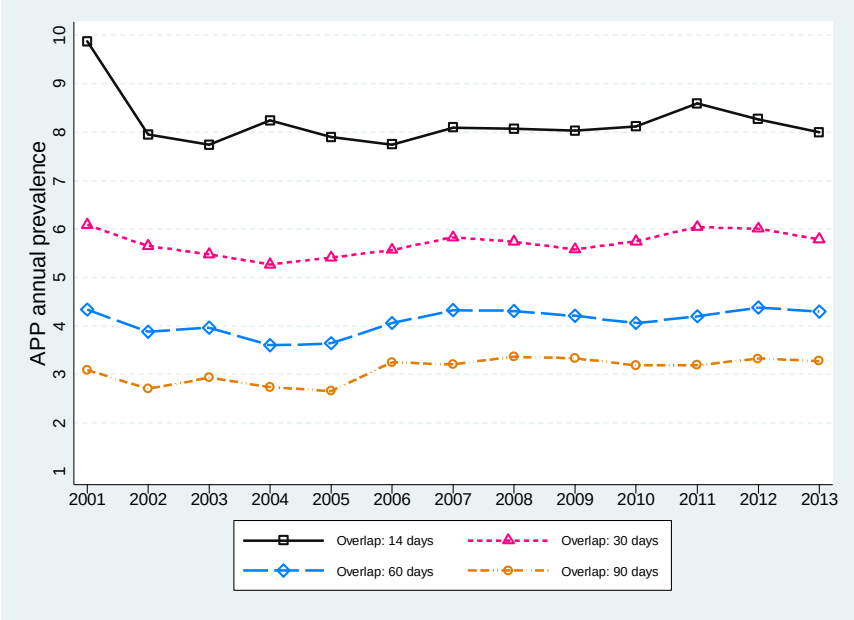
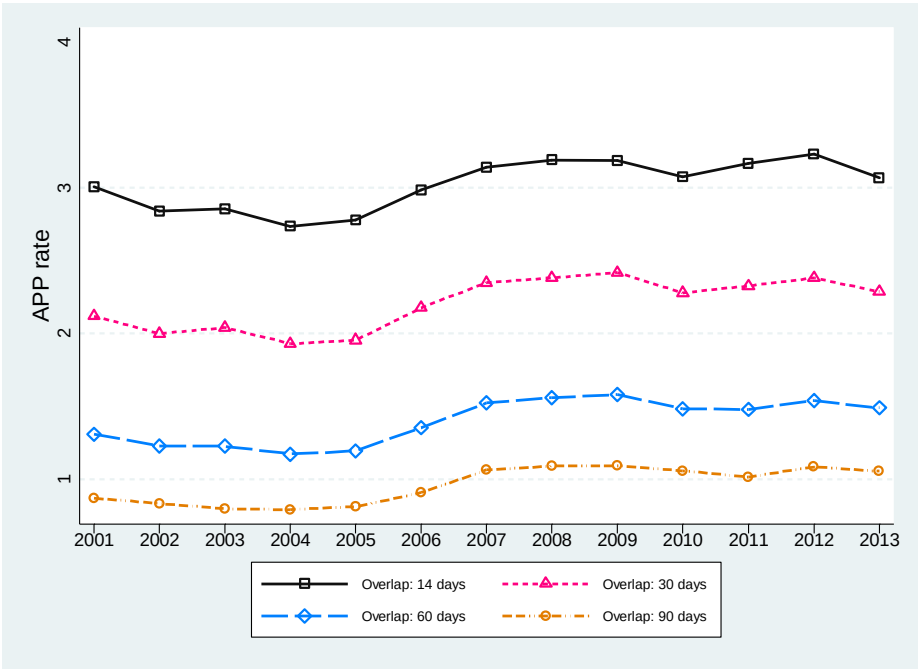


Figure: Rate of APP



Survival analysis

Complete linkage of primary, secondary and mortality data provides important information about the timing of APP episodes and the three outcomes. To exploit this rich information, we employ a time-to-event design. Our modelling choice is also supported by the following three features of the data: patients enter the study at different times, they may exit the study before the outcome occurs (right censoring), and APP is a time-varying variable which does not occur at consistent intervals for all patients.

We follow each individual from entry date until the outcome of interest or until censoring. Censoring may occur because i) a patient dies, ii) registration with the practice ends, or iii) the study period ends (i.e. the patient is still registered on 31 March 2014). We treat death as censoring rather than a competing risk because our focus is on the relationship between quality indicators and outcomes, rather than on the prediction of the probability of an event at a given point in time [3]. While some patients experience multiple events, we consider only the time to first event.

The hazard function for each outcome is specified as:

$$h_i(t) = \lambda_0(t)\exp\{X_{i1}\beta_1 + \ldots + X_{ik}\beta_k + \alpha_1 APP_i(t) + \alpha_2 NS_i(t)\} \qquad (3)$$

It is the product of the baseline hazard, $\lambda_0(t)$, and an exponentiated linear function of time-invariant covariates, $X_{i1}, \ldots, X_{ik}$, and the two time-varying variables APP(t) and NS(t) indicating whether the patient is on APP at time t and whether the patient is not on an antipsychotic medication at time t.

In survival analysis model without time dependent variables the baseline hazard cancels out and the hazard ratio between two individuals is constant over time. However, the proportionality of hazards does not hold in our case because the time-dependent APP and ALOS change at

different times for different individuals. Estimation of the Cox model via partial likelihood is still feasible.

A hazard ratio (HR) greater than 1 indicates an increase in the hazard of the outcome associated with a unit change in the explanatory variable, and vice versa for a HR below 1.

Table: Hazard Ratios – Unplanned all and unplanned SMI admissions

	Unplanned admissions		**Unplanned SMI admissions**	
	HR	**95% CI**	**HR**	**95% CI**
APP (time varying)	1.14	(.99 – 1.32)	1.19	(.92 – 1.53)
No substance (time varying)	1.08**	(1.03 – 1.14)	1.23***	(1.13 – 1.35)
Age at FSDT				
19-35 (base)				
36-45	.95	(.86 – 1.04)	.88	(.76 – 1.02)
46-55	.86**	(.79 – .94)	.69***	(.60 – .79)
56-65	0.98	(.89 – 1.09)	.56***	(.47 – .67)
>=66	1.51***	(1.37 – 1.67)	.42***	(.35 – .51)
Male	.99	(.90 – 1.10)	1.01	(.87 – 1.16)
Age at diagnosis*Male				
19-35*Male (base)				
36-45*Male	.94	(.82 – 1.07)	.96	(.81 – 1.16)
46-55*Male	1.01	(.88 – 1.17)	.96	(.78 – 1.18)
56-65*Male	1.01	(.88 – 1.15)	.92	(.71 – 1.20)
>=66* Male	1.09	(.96 – 1.25)	.95	(.72 – 1.26)
Year of FSDT				
2000	(base)			
2001	1.09*	(1.01 – 1.17)	1.03	(.90 – 1.18)
2002	1.10*	(1.00 – 1.21)	.98	(.84 – 1.14)
2003	1.13*	(1.02 – 1.24)	.88	(.73 – 1.07)
2004	1.17**	(1.06 – 1.29)	.92	(.77 – 1.10)
2005	1.17**	(1.06 – 1.28)	.97	(.81 – 1.16)
2006	1.19***	(1.08 – 1.31)	.92	(.77 – 1.11)
2007	1.11	(1.00 – 1.24)	.83	(.69 – 1.01)
2008	1.14**	(1.04 – 1.25)	.82*	(.68 – .98)
2009	1.10	(.99 – 1.23)	.82*	(.68 – .99)
2010	1.10	(.99 – 1.26)	.81*	(.67 – .98)
2011	1.16**	(1.04 – 1.29)	.85	(.70 – 1.02)
2012	1.21**	(1.08 – 1.37)	.86	(.67 – 1.10)
2013	.94	(.79 – 1.13)	.70	(.49 – 1.01)

2014	.99	(.54 – 1.85)	.76	(.25 – 2.32)
Time since diagnosis				
< 1 year				
1-5 years	.97	(.91 – 1.03)	1.22***	(1.11 – 1.34)
>5 years	.86***	(.81 – .90)	1.15**	(1.04 – 1.27)
IMD				
1st quintile (base)				
2nd quintile	1.00	(.93 – 1.08)	.98	(.86 – 1.12)
3rd quintile	1.08	(.99 – 1.17)	1.01	(.87 – 1.19)
4th quintile	1.11*	(1.02 – 1.20)	1.03	(.90 – 1.18)
5th quintile	1.21***	(1.11 – 1.31)	1.16*	(1.01 – 1.33)
Ethnicity white	2.26***	(2.11 – 2.41)	2.11***	(1.86 – 2.34)
Practice is in rural area	.96	(.89 – 1.04)	.97	(.82 – 1.15)
Minimum distance to acute health services				
<3km (base)				
3-6km	1.03	(.97 – 1.09)	1.04	(.91 – 1.18)
6-9km	.92	(.84 – 1.01)	.97	(.82 – 1.16)
>9km	1.02	(.94 – 1.11)	.98	(.82 – 1.18)
Minimum distance to mental health services				
<3km (base)				
3-6km	.99	(.92 – 1.07)	.96	(.82 – 1.14)
6-9km	1.03	(.95 – 1.12)	1.00	(.84 – 1.20)
>9km	.98	(.90 – 1.06)	.97	(.81 – 1.16)
Number of primary care contacts within 12 months prior to diagnosis				
<5 (base)				
5-9	1.05	(.99 – 1.12)	.88*	(.80 – .97)
10-14	1.08*	(1.01 – 1.16)	.84***	(.76 – .93)
15-19	1.18***	(1.10 – 1.27)	.85*	(.75 – .96)
>=20	1.30***	(1.22 – 1.39)	.85**	(.75 – .96)
Current or ex-smoker	1.08**	(1.02 – 1.14)	1.04	(.94 – 1.15)
Current or ex-alcohol user	.97	(.93 – 1.02)	1.03	(.95 – 1.11)
Number of Charlson Index comorbidities	1.22***	(1.18 – 1.25)	.94	(.88 – 1.00)
Diagnosis of depression	1.02	(.97 – 1.06)	.84***	(.77 – .90)
SMI diagnosis group				
Bipolar disorder or affective psychosis (base)				
Schizophrenia or other psychosis	1.02	(.97 – 1.07)	1.10*	(1.01 – 1.20)
Both	1.20***	(1.12 – 1.29)	1.77***	(1.58 – 1.98)

*p<0.05, **p<0.01, ***p<0.001

Table: Hazard Ratios – Death and ED presentations

	Death		ED presentations	
	HR	**95% CI**	**HR**	**95% CI**
APP (time varying)	1.02	(.76 – 1.37)	0.95	(.80 – 1.14)
No substance (time varying)	1.02	(.94 – 1.10)	1.19***	(1.14 – 1.24)
Age at FSDT				
19-35 (base)				
36-45	2.53***	(1.57 – 4.09)	.86**	(.78 – .95)
46-55	4.34***	(2.82 – 6.66)	.75***	(.68 – .82)
56-65	9.22***	(6.09 – 13.97)	.71***	(.64 – .79)
>=66	31.72***	(21.38 – 47.05)	1.02	(.93 – 1.12)
Male	1.98**	(1.27 – 3.09)	.97	(.88 – 1.07)
Age at diagnosis*Male				
19-35*Male (base)				
36-45*Male	.77	(.45 – 1.32)	.97	(0.84 – 1.13)
46-55*Male	.74	(.45 – 1.21)	1.05	(.91 – 1.20)
56-65*Male	.63	(.39 – 1.02)	1.10	(.95 – 1.28)
>=66* Male	.60*	(.39 – .94)	1.03	(.89 – 1.18)
Year of FSDT				
2000				
2001	.95	(.82, – 1.09)		
2002	1.16	(1.00, – 1.34)		
2003	1.04	(.88, – 1.23)		
2004	1.19*	(1.00, – 1.42)		
2005	1.07	(.89, – 1.27)		
2006	1.09	(.88 – 1.34)		
2007	1.10	(.89 – 1.35)		
2008	1.14	(.93 – 1.40)	1.21***	(1.11 – 1.31)
2009	1.08	(.88 – 1.32)	1.27***	(1.14 – 1.40)
2010	.89	(.67 – 1.17)	1.56***	(1.39 – 1.76)
2011	1.42*	(1.07 – 1.88)	1.59***	(1.43 – 1.76)
2012	1.29	(.91 – 1.83)	1.64***	(1.47 – 1.84)
2013	.80	(.45 – 1.42)	1.57***	(1.36 – 1.82)
2014	.00	(.00 – .00)	1.64	(.98 – 2.74)
Time since diagnosis				
< 1 year				
1-5 years	1.01	(.91 – 1.13)	.97	(.90 – 1.05)
>5 years	.76***	(.68 – .85)	.90**	(.84 – .96)
IMD				
1st quintile (base)				
2nd quintile	.92	(.80 – 1.06)	1.07	(.97 – 1.18)
3rd quintile	1.06	(.93 – 1.20)	1.11*	(1.00 – 1.23)

4th quintile	.99	(.86 – 1.14)	1.18**	(1.06 – 1.31)
5th quintile	1.05	(.91 – 1.22)	1.31***	(1.17 – 1.47)
Ethnicity white	.92	(.83 – 1.02)	1.49***	(1.40 – 1.58)
Practice is in rural area	1.03	(.88 – 1.20)	.85*	(.75 – .97)
Minimum distance to acute health services				
<3km (base)				
3-6km	1.07	(.95 – 1.20)	.92	(.83 – 1.02)
6-9km	1.11	(.96 – 1.29)	.90	(.78 – 1.05)
>9km	1.17	(.99 – 1.34)	.99	(.85 – 1.17)
Minimum distance to mental health services				
<3km (base)				
3-6km	.95	(.82 – 1.10)	1.02	(.90 – 1.16)
6-9km	.96	(.82 – 1.12)	.97	(.85 – 1.10)
>9km	.97	(.83 – 1.14)	.88	(.77 – 1.00)
Number of primary care contacts within 12 months prior to diagnosis				
<5 (base)				
5-9	1.04	(.91 – 1.18)	1.12**	(1.04 – 1.20)
10-14	1.06	(.93 – 1.21)	1.22***	(1.13 – 1.33)
15-19	1.28**	(1.10 – 1.48)	1.37***	(1.25 – 1.50)
>=20	1.28***	(1.11 – 1.48)	1.59***	(1.46 – 1.73)
Current or ex-smoker	.93	(.85 – 1.03)	1.07*	(1.01 – 1.14)
Current or ex-alcohol user	.83***	(.76 – .92)	.98	(.92 – 1.04)
Number of Charlson Index comorbidities	1.43***	(1.37 – 1.49)	1.14***	(1.11 – 1.18)
Diagnosis of depression	.89**	(.81 – .96)	1.07**	(1.02 – 1.13)
SMI diagnosis group				
Bipolar disorder or affective psychosis (base)				
Schizophrenia or other psychosis	1.42***	(1.29 – 1.56)	.94*	(.89 – 1.00)
Both	1.07	(.93 – 1.25)	1.02	(.94 – 1.09)

*p<0.05, **p<0.01, ***p<0.001

Online-Only References

1. Springate D, Kontopantelis E, Ashcroft D, et al. ClinicalCodes: An online clinical codes repository to improve the validity and reproducibility of research using electronic medical recors. *PloS ONE* 2014;9(6) doi: 10.1371/journal.pone.0099825
2. Windfuhr K, While D, Kapur N, et al. Suicide risk linked with clinical consultation frequency, psychiatric diagnoses and psychotropic medication prescribing in a national study of primary-care patients. *Psychological Medicine* 2016;46:3407-17.
3. Noordzij M, Leffondré K, van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? *Nephrology Dialysis Transplantation* 2013;28(11):2670-77.