

ONLINE SUPPLEMENT

Title: The impact of changes to national hypertension guidelines on hypertension management and outcomes in the UK

Authors:

Sarah L Lay-Flurrie, BSc MSc DPhil, University of Oxford

James P Sheppard, BSc PGCert PhD, University of Oxford

Richard J Stevens, BA MSc PhD, University of Oxford

Christian Mallen, BMedSci BMBS MMedSci MPhil PhD FRCGP FFPH, Keele University

Carl Heneghan, BM BCH MA MRCGP, DPhil, University of Oxford

FD Richard Hobbs, FRCP(Lon) FESC FRCP(Ed) FRCGP FMedSci, University of Oxford

Bryan Williams, MD FRCP FAHA FESC, University College London

Jonathan Mant, MA MSc MBBS MD FFPH FRCP(Ed) FMedSci, University of Cambridge

Richard J McManus, MA PhD MBBS FRCGP FRCP, University of Oxford

Short title: Impact of hypertension guideline change in the UK

Corresponding author: Sarah L Lay-Flurrie, 01865 289449, sarah.lay-flurrie@phc.ox.ac.uk

Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, United Kingdom.

Extended methods

Study population

Eligible patients entered the study on the earliest of the following dates: study start date (1st April 2006), date of 18th birthday, current registration date with practice and practice up-to-standard date. Patients exited the study on the earliest date of the following dates: study end date (31st March 2017), date of death, date of de-registration with the practice, date of last data download from practice and end of follow-up in linked ONS/ HES data.

Sample size

We intended to estimate both changes in the level of hypertension incidence and changes in trend. Research regarding sample size calculations for interrupted time series has shown that models including 60 data points, with equal pre- and post-intervention time periods, have more than 95% power to detect both changes in level and trend when autocorrelation is low (0.2 to 0.3), even when effect sizes are small.¹ Based on our previous work examining the effect of policy changes on treatment for mild hypertension, where incidence rates were similar to those expected in this study,² we expected autocorrelations to be approximately 0.25. As we have 120 data points in our time series (120 months over 10 years), we therefore expected adequate power (>80%) to detect even small changes in incidence level and trend.

Outcomes

The medical/ Read code list for diagnosis of hypertension (primary outcome) is given in Table S1. The specific definition of each secondary outcome is given below. Due to their size, code lists are not given here but are available from the authors on request.

New antihypertensive treatment prescription: defined as new treatment prescriptions in any eligible patients in a given month (numerator) divided by person-years of follow-up in the month in all eligible patients who have not previously been prescribed antihypertensive treatment (denominator). Antihypertensive medication was defined as: any of or combination of: calcium channel blocker, ACE inhibitor, Angiotensin Receptor Blocker, thiazide or thiazide like diuretic, beta blocker, alpha blocker, spironolactone, centrally acting antihypertensive or other antihypertensive not previously mentioned but listed in the current BNF.

Blood pressure monitoring (office, home and ambulatory): defined as all instances of blood pressure monitoring in any eligible patient in a given month (numerator) divided by person-years of follow-up in the month in all eligible patients (denominator).

Cardiovascular disease morbidity: defined as all new cases of cardiovascular disease in any eligible patients in a given month (numerator) divided by person-years of follow-up in the month in all eligible patients who have not previously had a case of cardiovascular disease (denominator). Cardiovascular events were determined from the first clinical code recorded in the primary care record or linked hospital or mortality record. Major cardiovascular events were defined “hard” cardiovascular events comprising any of cardiovascular death, myocardial infarction, or stroke. Sensitivity analyses examined the impact of including unstable angina, coronary artery bypass graft and heart failure in the definition.

Cardiovascular mortality: defined as all cardiovascular deaths in any eligible patients in a given month (numerator) divided by person-years of follow-up in the month in all eligible patients (still alive) (denominator). Date and cause of death were determined from linked mortality data.

All-cause mortality: defined as all deaths in any eligible patients in a given month (numerator) divided by person-years of follow-up in the month in all eligible patients (still alive) (denominator). Date of death was determined from linked mortality data.

Data cleaning and analysis

SLF had access to the full CPRD database and conducted all data cleaning and analysis. Linked data for eligible patients only was provided directly by CPRD. Code lists and programming code is available from the authors on request.

Data cleaning

All data was drawn from the coded primary care data, with the following exceptions. Date and cause of death was drawn from linked mortality data only. Cardiovascular outcomes were defined according to the earliest record of a cardiovascular event in the primary care record, linked inpatient hospital data or any cardiovascular cause in linked mortality data. Ethnicity data was derived from primary care records and from hospital episode statistics data where missing in the primary care record. The most recent record of ethnic group was used. Deprivation data was drawn from linked index of multiple deprivation data only.

In all analyses, blood pressure readings not explicitly defined as readings taken at home or through ambulatory BP monitoring were classified as clinic measurements. In analyses of the rate of BP monitoring, repeat clinic measurements on the same day were counted as a single measurement. Repeat home/ ambulatory measurements within a week were also only counted as a single instance of home/ ambulatory monitoring, allowing for the fitting and return of devices. For the sensitivity analysis defining hypertension based on blood pressure readings, BP readings below 70/30 mm Hg and above 260/140 mm Hg were deemed implausible and removed. For multiple measurements on the same day, the lowest BP measurement was used.

References

1. Zhang F, Wagner AK, Ross-Degnan D. Simulation-based power calculation for designing interrupted time series analyses of health policy interventions. *J Clin Epidemiol.* 2011;64(11):1252-1261. doi:10.1016/J.JCLINEPI.2011.02.007
2. Sheppard JP, Stevens S, Stevens RJ, et al. Association of guideline and policy changes with incidence of lifestyle advice and treatment for uncomplicated mild hypertension in primary care: a longitudinal cohort study in the Clinical Practice Research Datalink. *BMJ Open.* 2018;8(9):e021827. doi:10.1136/bmjopen-2018-021827

Table S1: Hypertension diagnostic codes used to define primary outcome

Medical code	Read code	Read Term
16565	6627	Good hypertension control
27511	6628	Poor hypertension control
30776	6629	Hypertension:follow-up default
32976	6146200	Hypertension induced by oral contraceptive pill
2666	14A2.00	H/O: hypertension
109611	661M600	Hypertension self-management plan agreed
110631	661N600	Hypertension self-management plan review
4444	662..12	Hypertension monitoring
18590	662b.00	Moderate hypertension control
18482	662c.00	Hypertension six month review
19070	662d.00	Hypertension annual review
21826	662F.00	Hypertension treatm. started
13188	662G.00	Hypertensive treatm.changed
12948	662H.00	Hypertension treatm.stopped
3425	662O.00	On treatment for hypertension
13186	662P.00	Hypertension monitoring
102406	662P000	Hypertension 9 month review
109771	662P100	Telehealth hypertension monitoring
71433	66b2.00	Hypertension monitoring not required
204	G2...00	Hypertensive disease
8732	G2...11	BP - hypertensive disease
799	G20..00	Essential hypertension
351	G20..11	High blood pressure
107704	G20..12	Primary hypertension
15377	G200.00	Malignant essential hypertension
1894	G201.00	Benign essential hypertension
4372	G202.00	Systolic hypertension
83473	G203.00	Diastolic hypertension
10818	G20z.00	Essential hypertension NOS
3712	G20z.11	Hypertension NOS
7329	G24..00	Secondary hypertension
31755	G240.00	Secondary malignant hypertension
59383	G240000	Secondary benign renovascular hypertension

73293	G240z00	Secondary malignant hypertension NOS
57288	G241.00	Secondary benign hypertension
25371	G241000	Secondary benign renovascular hypertension
51635	G241z00	Secondary benign hypertension NOS
34744	G244.00	Hypertension secondary to endocrine disorders
16059	G24z.00	Secondary hypertension NOS
31387	G24z000	Secondary renovascular hypertension NOS
31341	G24z100	Hypertension secondary to drug
42229	G24zz00	Secondary hypertension NOS
105371	G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
105316	G25..11	Stage 1 hypertension
108136	G250.00	Stage 1 hyperten (NICE 2011) without evidnce end organ damage
109797	G251.00	Stage 1 hyperten (NICE 2011) with evidnce end organ damage
105989	G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
105487	G26..11	Severe hypertension
105480	G27..00	Hypertension resistant to drug therapy
105274	G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
18765	G2y..00	Other specified hypertensive disease
7057	G2z..00	Hypertensive disease NOS
69753	Gyu2.00	[X]Hypertensive diseases
102458	Gyu2000	[X]Other secondary hypertension
97533	Gyu2100	[X]Hypertension secondary to other renal disorders

Table S2: Crude incidence rates of hypertension (per 100 person years (%)) in each age-sex strata by year:

Gender	Age group	2006/7	2007/8	2008/9	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17
Men	18-24	0.07	0.05	0.04	0.04	0.04	0.04	0.04	0.04	0.05	0.05	0.05
Men	25-44	0.51	0.49	0.51	0.46	0.43	0.41	0.43	0.46	0.38	0.41	0.41
Men	45-54	1.93	1.85	1.81	1.64	1.57	1.55	1.57	1.54	1.45	1.48	1.57
Men	55-64	3.50	3.26	3.28	2.97	2.80	2.62	2.73	2.63	2.38	2.33	2.51
Men	65-74	5.06	4.44	4.34	4.11	3.85	3.47	3.55	3.41	2.97	3.10	3.15
Men	75-84	5.07	4.45	4.21	3.86	3.69	3.08	3.35	3.25	3.14	3.09	3.30
Men	85+	3.39	3.15	3.10	2.70	2.55	2.32	2.61	2.53	2.40	2.45	2.33
Women	18-24	0.08	0.07	0.08	0.06	0.07	0.07	0.06	0.05	0.07	0.08	0.06
Women	25-44	0.43	0.41	0.44	0.40	0.36	0.34	0.37	0.37	0.36	0.34	0.34
Women	45-54	1.60	1.54	1.46	1.36	1.22	1.14	1.22	1.24	1.11	1.24	1.32
Women	55-64	2.83	2.57	2.56	2.27	2.12	2.02	1.94	1.95	1.75	1.84	1.92
Women	65-74	5.11	4.57	4.17	3.72	3.45	3.14	3.06	3.20	2.74	2.69	2.81
Women	75-84	6.33	5.91	5.58	4.61	4.52	4.11	3.88	4.04	3.71	4.03	3.86
Women	85+	4.36	3.77	3.96	3.30	3.12	3.02	3.17	3.12	2.61	3.03	3.49

Table S3: Results from interrupted time series analysis of age and sex standardized rates of treated and untreated incident hypertension between April 2006 and March 2017, with interruption between April 2011 and March 2012

Model parameter	Treated hypertension			Untreated hypertension		
	Estimate (per 100 person-years)	95% confidence interval		Estimate (per 100 person-years)	95% confidence interval	
Initial rate (April 2006)	1.666	1.556	1.776	0.438	0.395	0.480
Initial trend per year (April 2006 - March 2011)	-0.081	-0.117	-0.045	-0.027	-0.039	-0.015
Predicted rate (April 2012)	1.174	1.042	1.306	0.275	0.238	0.312
Post-intervention rate (April 2012)	1.141	1.061	1.221	0.318	0.297	0.339
Post-intervention trend per year (April 2012 - March 2017)	-0.018	-0.048	0.012	0.003	-0.004	0.011
Change in rate	-0.033	-0.187	0.121	0.043	0.000	0.086
Change in trend	0.063	0.016	0.110	0.030	0.016	0.044
End rate (March 2017)	1.053	0.965	1.142	0.334	0.310	0.359

Table S4: Results from interrupted time series analysis of age and sex standardized rates incident hypertension between April 2006 and March 2017, with interruption between April 2011 and March 2012 (sensitivity analysis with more sensitive definition of hypertension)

Model parameter	Estimate (per 100 person-years)	95% confidence interval	
Initial rate (April 2006)	3.205	3.014	3.396
Initial trend per year (April 2006 - March 2011)	-0.124	-0.187	-0.061
Predicted rate (April 2012)	2.452	2.223	2.681
Post-intervention rate (April 2012)	2.433	2.289	2.577
Post-intervention trend per year (April 2012 - March 2017)	-0.027	-0.077	0.024
Change in rate	-0.019	-0.289	0.252
Change in trend	0.097	0.016	0.178
End rate (March 2017)	2.301	2.157	2.444

Table S5: Results from interrupted time series analysis of age and sex standardized rates of blood pressure monitoring between April 2006 and March 2017, with interruption between April 2011 and March 2012

	Home			ABPM			Office		
Model parameter	Estimate	95% confidence interval		Estimate	95% confidence interval		Estimate	95% confidence interval	
Initial rate (April 2006)	0.041	0.032	0.050	0.308	0.282	0.334	82.789	78.888	86.689
Initial trend per year (April 2006 - March 2011)	0.017	0.013	0.020	0.014	0.004	0.024	1.111	-0.269	2.491
Predicted rate (April 2012)	0.142	0.129	0.154	0.393	0.355	0.431	89.548	84.178	94.918
Post-intervention rate (April 2012)	0.278	0.237	0.318	0.908	0.835	0.982	86.420	82.589	90.251
Post-intervention trend per year (April 2012 - March 2017)	0.101	0.084	0.119	-0.013	-0.037	0.011	-2.785	-4.069	-1.501
Change in rate	0.136	0.093	0.178	0.515	0.433	0.598	-3.128	-9.724	3.469
Change in trend	0.085	0.067	0.102	-0.027	-0.053	-0.001	-3.896	-5.781	-2.011
End rate (March 2017)	0.775	0.717	0.834	0.847	0.787	0.907	72.727	69.367	76.088

Table S6: Results from interrupted time series analysis of age and sex standardized rates of incident cardiovascular disease, cardiovascular mortality and all-cause mortality (per 100 person-years) between April 2006 and March 2017, with interruption between April 2011 and March 2012

	Major CVD events			Any CVD event			Major CVD mortality			Any CVD mortality			All-cause mortality		
Model parameter	Estimate	95% confidence interval		Estimate	95% confidence interval		Estimate	95% confidence interval		Estimate	95% confidence interval		Estimate	95% confidence interval	
Initial rate (April 2006)	0.539	0.519	0.559	1.316	1.274	1.358	0.155	0.145	0.166	0.325	0.305	0.345	1.316	1.241	1.391
Initial trend per year (April 2006 - March 2011)	0.001	-0.005	0.008	0.016	0.002	0.030	-0.009	-0.012	-0.006	-0.017	-0.023	-0.011	-0.032	-0.057	-0.007
Predicted rate (April 2012)	0.546	0.522	0.571	1.413	1.360	1.466	0.101	0.089	0.114	0.220	0.196	0.244	1.122	1.025	1.219
Post-intervention rate (April 2012)	0.530	0.508	0.551	1.369	1.321	1.417	0.101	0.093	0.108	0.204	0.191	0.217	1.109	1.043	1.176
Post-intervention trend per year (April 2012 - March 2017)	-0.003	-0.011	0.005	-0.001	-0.019	0.017	-0.004	-0.006	-0.001	-0.009	-0.014	-0.004	-0.015	-0.040	0.010
Change in rate	-0.017	-0.049	0.016	-0.044	-0.115	0.027	-0.001	-0.015	0.014	-0.017	-0.044	0.011	-0.013	-0.130	0.105
Change in trend	-0.004	-0.014	0.006	-0.017	-0.039	0.006	0.005	0.001	0.010	0.008	0.000	0.016	0.017	-0.019	0.052
End rate (March 2017)	0.515	0.492	0.537	1.364	1.313	1.415	0.083	0.075	0.092	0.160	0.145	0.175	1.035	0.956	1.113

Table S7: Results from interrupted time series analysis of age and sex standardized rates of new and overall antihypertensive medication use between April 2006 and March 2017, with interruption between April 2011 and March 2012

Model parameter	New use		
	Estimate (per 100 person-years)	95% confidence interval	
Initial rate (April 2006)	3.746	3.554	3.937
Initial trend per year (April 2006 - March 2011)	-0.068	-0.135	0.000
Predicted rate (April 2012)	3.335	3.080	3.589
Post-intervention rate (April 2012)	3.229	3.069	3.390
Post-intervention trend per year (April 2012 - March 2017)	0.028	-0.030	0.087
Change in rate	-0.105	-0.406	0.196
Change in trend	0.096	0.007	0.185
End rate (March 2017)	3.369	3.198	3.539

Table S8: Results from interrupted time series analysis of age and sex standardized rates for outcomes in patients with and without hypertension, between April 2007 and March 2017

	In patients with hypertension			In patients without hypertension		
Model parameter	Estimate (per 100 person-years)	95% confidence interval		Estimate (per 100 person-years)	95% confidence interval	
Ambulatory BP monitoring						
Initial rate (April 2007)	3.888	3.353	4.422	0.272	0.251	0.293
Initial trend per year (April 2007 - March 2011)	-0.171	-0.241	-0.100	0.001	-0.002	0.004
Predicted rate (April 2012)	1.285	0.665	1.905	0.288	0.254	0.323
Post-intervention rate (April 2012)	3.486	3.099	3.873	0.787	0.719	0.856
Post-intervention trend per year (April 2012 - March 2017)	-0.027	-0.071	0.017	-0.002	-0.009	0.006
Change in rate	2.201	1.470	2.932	0.499	0.422	0.575
Change in trend	0.144	0.061	0.227	-0.003	-0.011	0.005
End rate (March 2017)	3.092	2.696	3.487	0.761	0.704	0.818
Home BP monitoring						
Initial rate (April 2007)	0.815	0.645	0.985	0.051	0.045	0.057
Initial trend per year (April 2007 - March 2011)	-0.010	-0.034	0.013	0.001	0.000	0.002
Predicted rate (April 2012)	0.658	0.436	0.880	0.070	0.062	0.077
Post-intervention rate (April 2012)	1.209	0.989	1.428	0.196	0.165	0.227
Post-intervention trend per year (April 2012 - March 2017)	0.130	0.101	0.159	0.016	0.012	0.021
Change in rate	0.551	0.239	0.863	0.126	0.095	0.158
Change in trend	0.140	0.103	0.177	0.015	0.011	0.020
End rate (March 2017)	3.128	2.830	3.425	0.439	0.397	0.481
Office BP monitoring						
Initial rate (April 2007)	349.590	332.804	366.376	78.221	74.464	81.978
Initial trend per year (April 2007 - March 2011)	-7.979	-10.324	-5.634	-0.283	-0.835	0.269
Predicted rate (April 2012)	227.906	205.802	250.011	73.903	68.373	79.433
Post-intervention rate (April 2012)	242.229	231.905	252.553	74.099	70.882	77.316
Post-intervention trend per year (April 2012 - March 2017)	-4.958	-6.121	-3.795	-0.813	-1.177	-0.448
Change in rate	14.322	-10.074	38.719	0.195	-6.202	6.593
Change in trend	3.021	0.403	5.639	-0.530	-1.191	0.132
End rate (March 2017)	169.096	159.724	178.469	62.110	59.206	65.015
Hard CVD events						
Initial rate (April 2007)	0.770	0.690	0.850	0.514	0.494	0.535
Initial trend per year (April 2007 - March 2011)	0.002	-0.008	0.012	0.002	-0.001	0.004
Predicted rate (April 2012)	0.801	0.719	0.884	0.540	0.513	0.568
Post-intervention rate (April 2012)	0.719	0.649	0.789	0.515	0.494	0.537
Post-intervention trend per year (April 2012 - March 2017)	0.000	-0.008	0.008	-0.002	-0.004	0.001
Change in rate	-0.082	-0.191	0.026	-0.025	-0.060	0.010
Change in trend	-0.002	-0.015	0.010	-0.003	-0.007	0.001
End rate (March 2017)	0.714	0.653	0.775	0.493	0.469	0.516
First antihypertensive use						
Initial rate (April 2007)	46.445	43.337	49.553	3.429	3.278	3.580
Initial trend per year (April 2007 - March 2011)	-2.393	-2.818	-1.967	-0.014	-0.039	0.011
Predicted rate (April 2012)	9.957	6.104	13.811	3.218	2.949	3.486
Post-intervention rate (April 2012)	19.796	18.292	21.300	3.067	2.915	3.220
Post-intervention trend per year (April 2012 - March 2017)	-0.366	-0.545	-0.186	0.010	-0.008	0.029
Change in rate	9.839	5.702	13.975	-0.150	-0.459	0.158
Change in trend	2.027	1.565	2.489	0.024	-0.007	0.055
End rate (March 2017)	14.405	12.819	15.991	3.220	3.057	3.383

Figure S1: Age and sex standardized incidence of asthma (per 100 person-years) between April 2007 and March 2017 with interruption between April 2011 and March 2012.

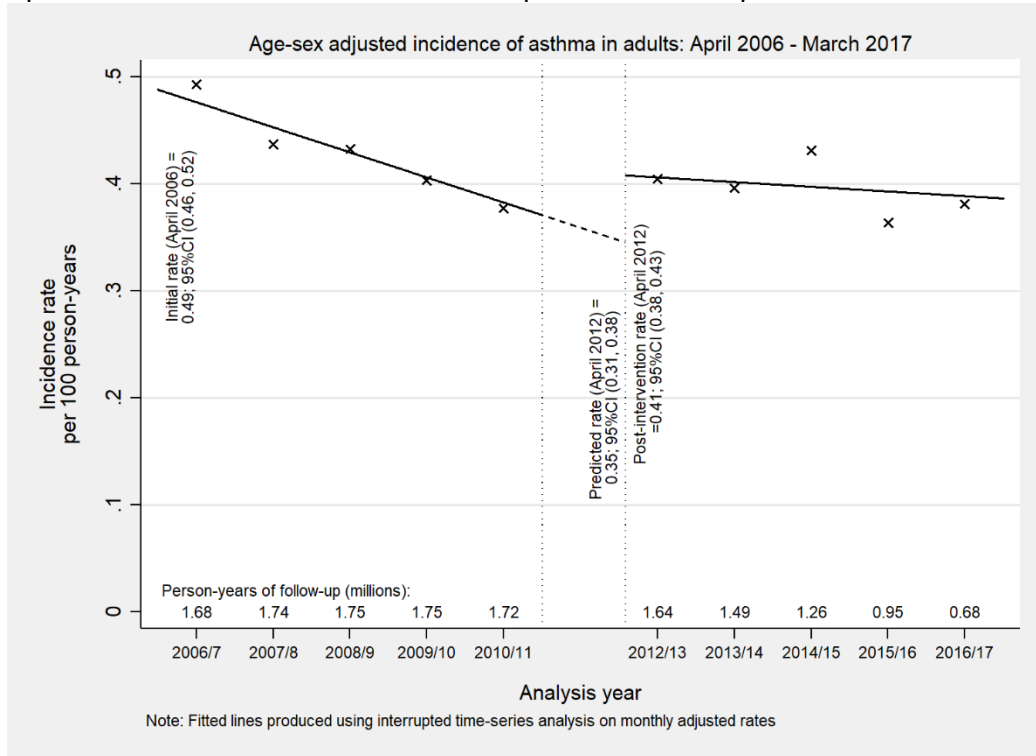


Figure S2: Age and sex standardized rate of new antihypertensive medication use (per 100 person-years) between April 2006 and March 2017 with interruption between April 2011 and March 2012.

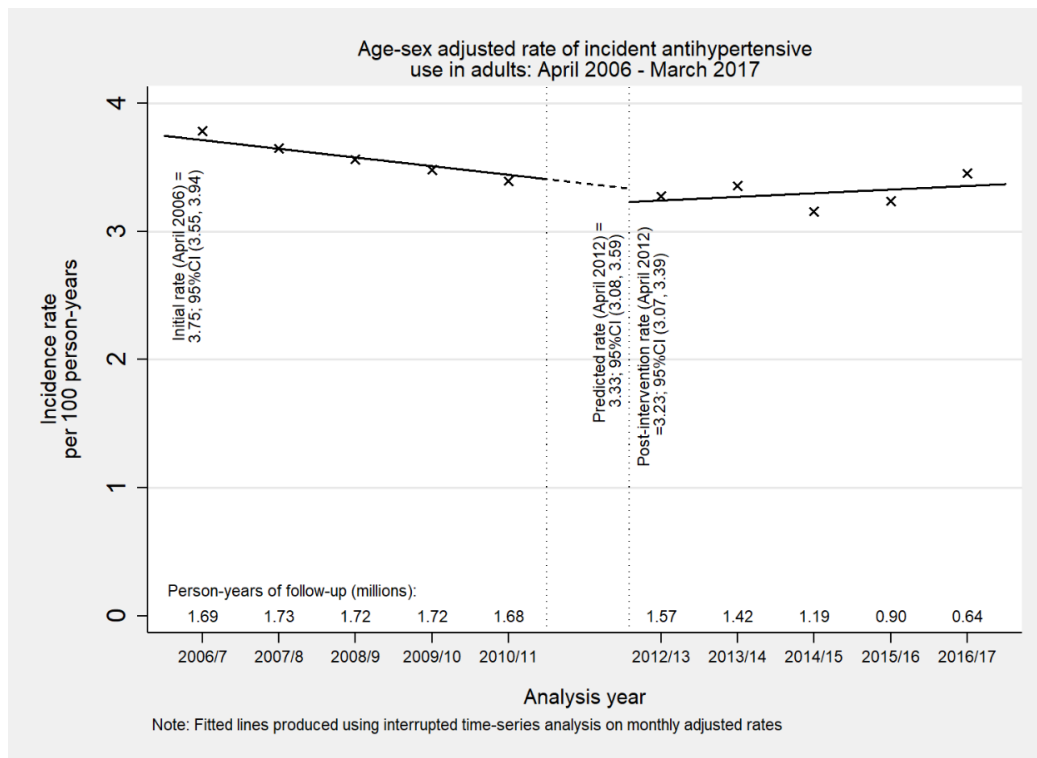


Figure S3: Age and sex standardized rate of use of at least one antihypertensive medication by class (per 100 person-years) between April 2006 and March 2017 with interruption between April 2011 and March 2012.

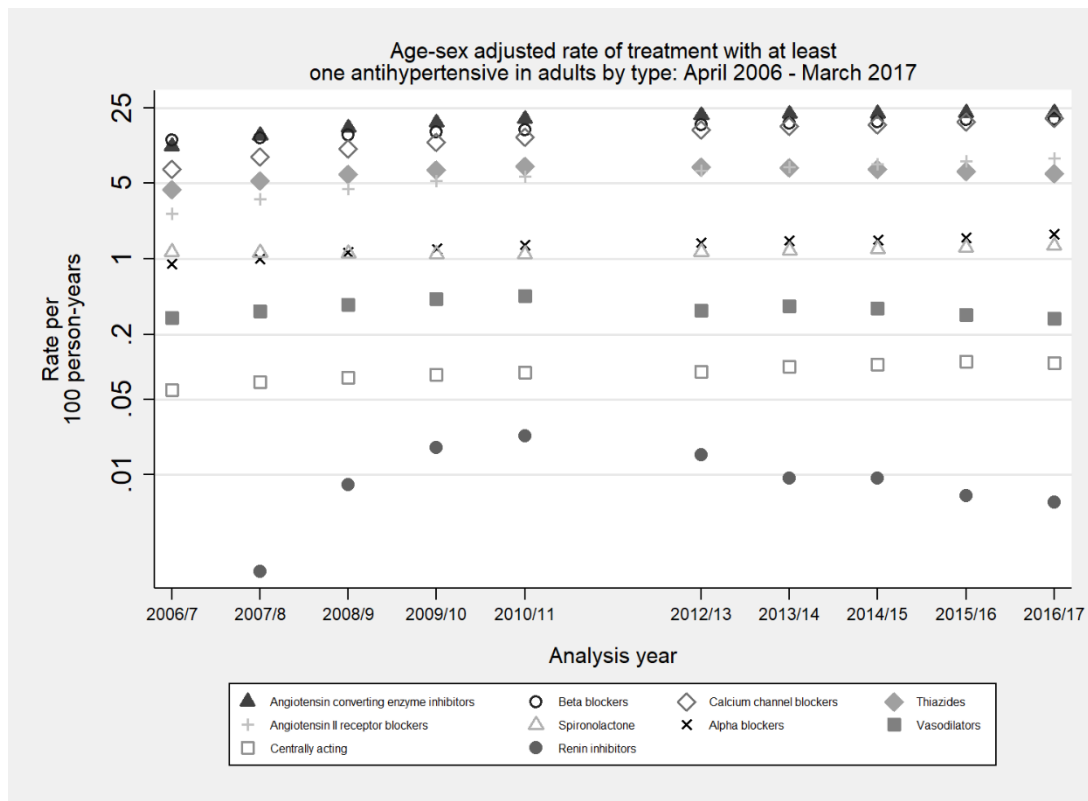


Figure S4: Age and sex standardized rate of ambulatory BP monitoring (per 100 person-years), in hypertensive and normotensive patients, between April 2007 and March 2017 with interruption between April 2011 and March 2012.

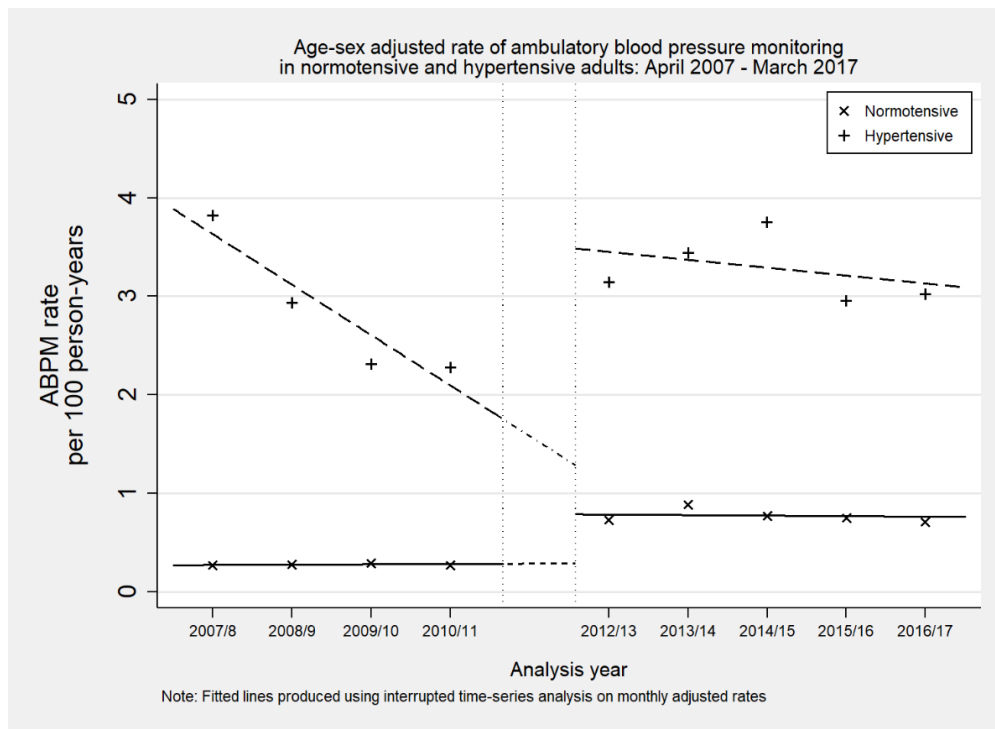


Figure S5: Age and sex standardized rate of home BP monitoring (per 100 person-years), in hypertensive and normotensive patients, between April 2007 and March 2017 with interruption between April 2011 and March 2012.

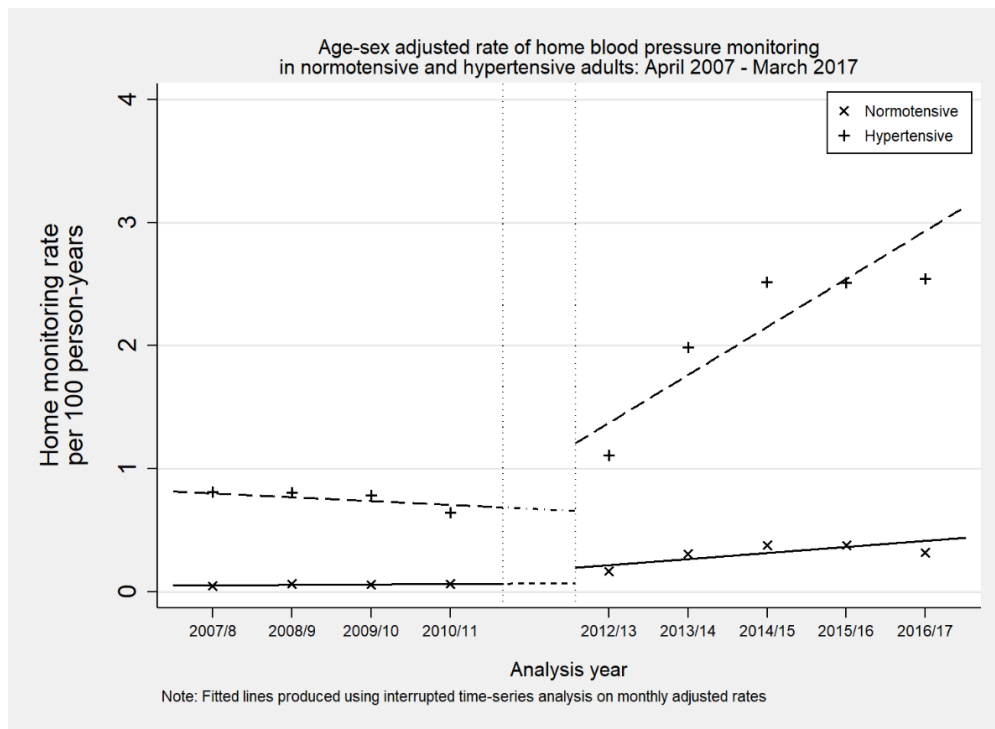


Figure S6: Age and sex standardized rate of office BP monitoring (per 100 person-years), in hypertensive and normotensive patients, between April 2007 and March 2017 with interruption between April 2011 and March 2012.

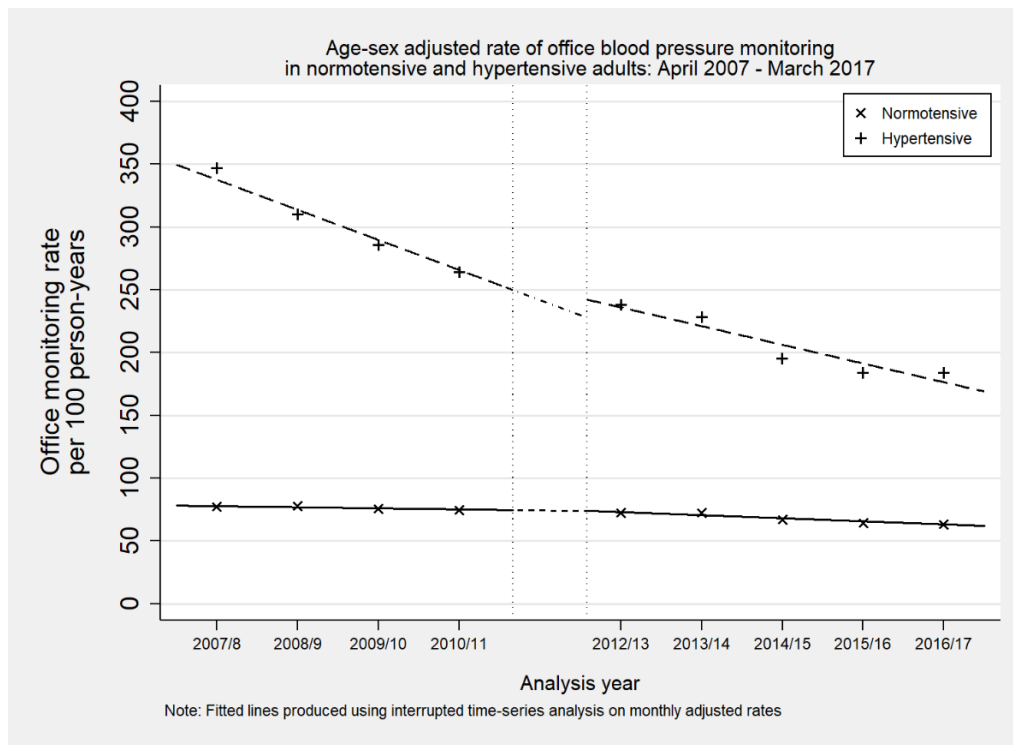


Figure S7: Age and sex standardized rate of major CVD events (per 100 person-years), in hypertensive and normotensive patients, between April 2007 and March 2017 with interruption between April 2011 and March 2012.

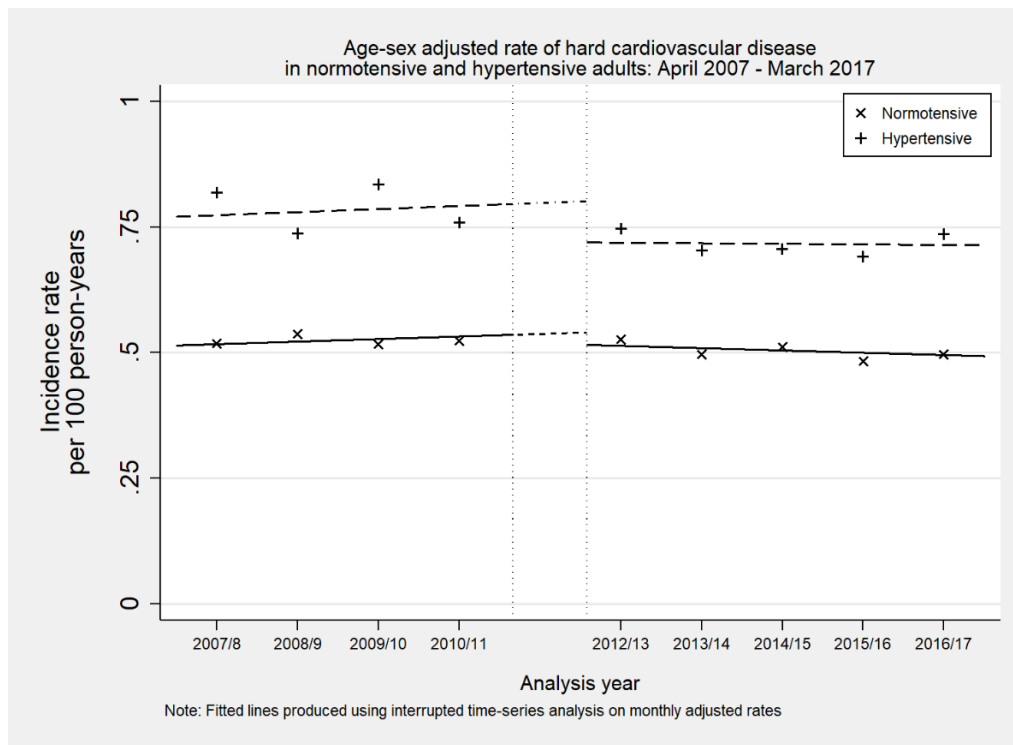


Figure S8: Age and sex standardized rate of new antihypertensive use (per 100 person-years), in hypertensive and normotensive patients, between April 2007 and March 2017 with interruption between April 2011 and March 2012.

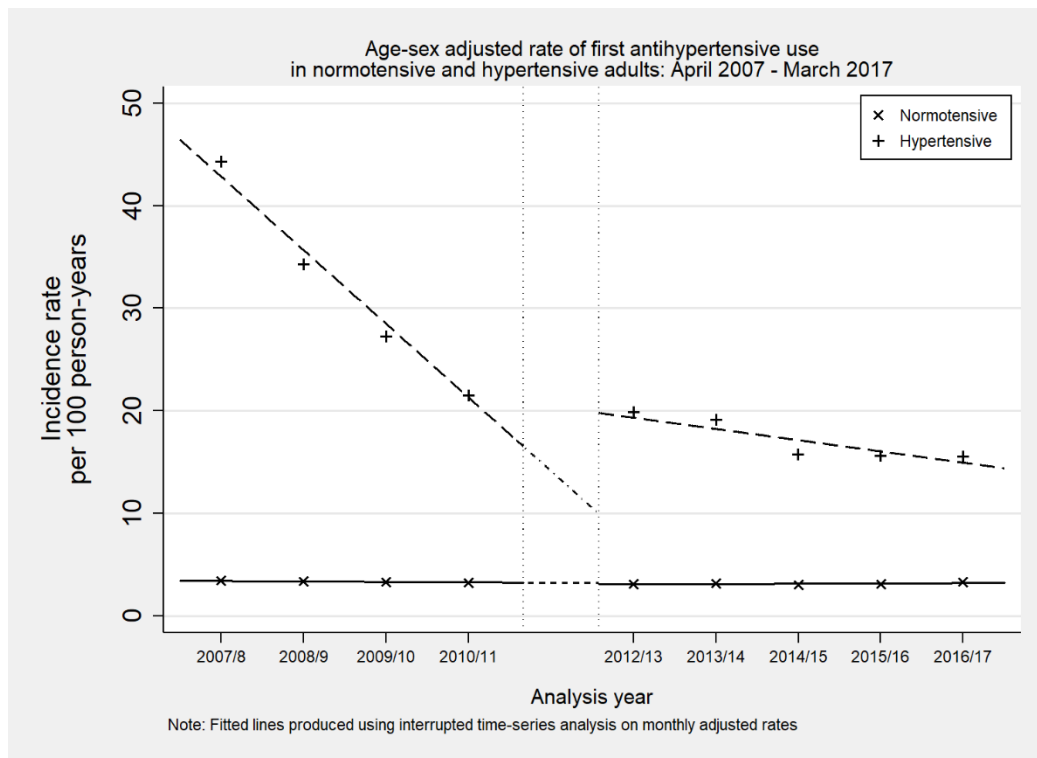


Figure S9: Age and sex standardized incidence of hypertension (per 100 person-years) between April 2007 and March 2017 with interruption between April 2011 and March 2012 (subset of practices in top 20% of out-of-office monitoring rate).

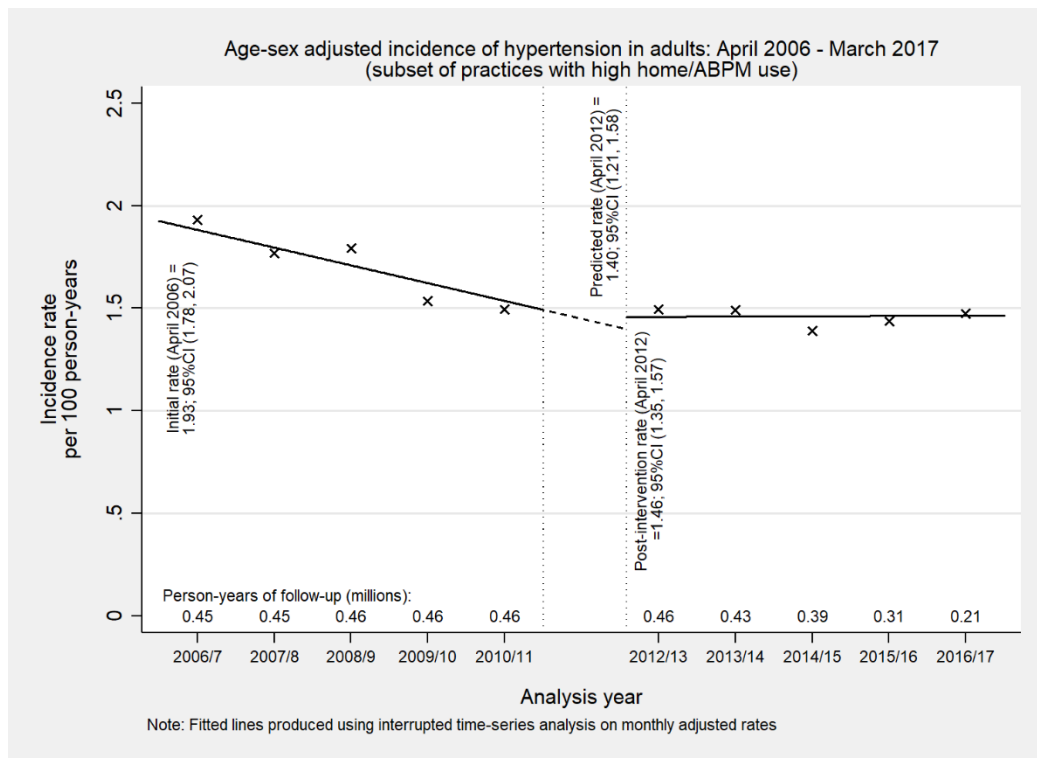


Figure S10: Age and sex standardized incidence of major CVD events (per 100 person-years) between April 2007 and March 2017 with interruption between April 2011 and March 2012 (subset of practices in top 20% of out-of-office monitoring rate).

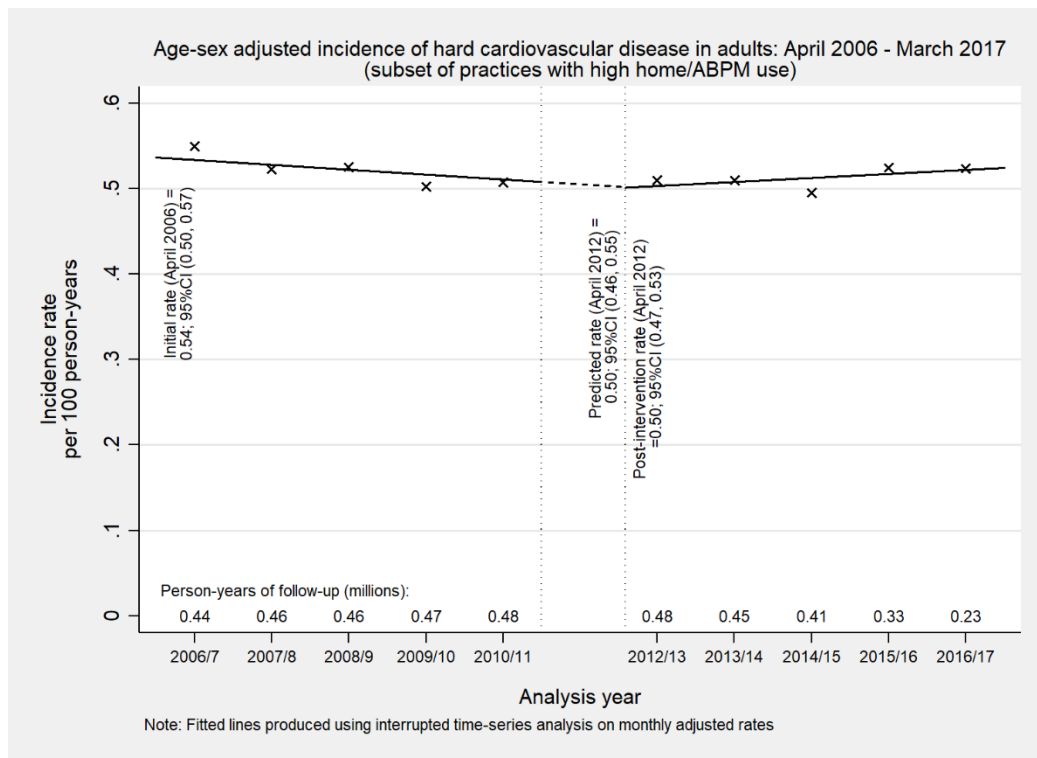


Figure S11: Age and sex standardized rate of out-of-office monitoring events (per 100 person-years) between April 2007 and March 2017 with interruption between April 2011 and March 2012 (subset of practices in top 20% of out-of-office monitoring rate).

