

## Supplementary Online Content

Zeng C, Dubreuil M, Larochelle M. Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA*. doi:10.1001/jama.2019.1347

**eTable 1.** Baseline characteristics of unmatched and propensity-score matched osteoarthritis patients ( $\geq 50$  years) initiating tramadol prescription or naproxen prescription.

**eTable 2.** Baseline characteristics of unmatched and propensity-score matched osteoarthritis patients ( $\geq 50$  years) initiating tramadol prescription or diclofenac prescription.

**eTable 3.** Baseline characteristics of unmatched and propensity-score matched osteoarthritis patients ( $\geq 50$  years) initiating tramadol prescription or celecoxib prescription.

**eTable 4.** Baseline characteristics of unmatched and propensity-score matched osteoarthritis patients ( $\geq 50$  years) initiating tramadol prescription or etoricoxib prescription.

**eTable 5.** Baseline characteristics of unmatched and propensity-score matched osteoarthritis patients ( $\geq 50$  years) initiating tramadol prescription or codeine prescription.

This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1. Baseline characteristics of unmatched and propensity-score matched osteoarthritis patients (≥ 50 years) initiating tramadol prescription or naproxen prescription**

Variable list	Unmatched		Standardized difference	Propensity-score matched		Standardized difference
	Tramadol (n=31,087)	Naproxen (n=26,731)		Tramadol (n=12,397)	Naproxen (n=12,397)	
<b>Demographics</b>						
Age, mean (SD), y	71.0 (9.7)	67.6 (9.4)	0.362	69.4 (9.6)	69.4 (9.5)	0.002
Socioeconomic deprivation index score, mean (SD) <sup>a</sup>	2.6 (1.4)	2.4 (1.3)	0.170	2.5 (1.4)	2.5 (1.4)	0.010
Female (%)	63.1	55.5	0.154	59.2	59.6	0.009
<b>Time block</b>						
01/01/2000-12/31/2000	2.1	1.8	0.019	1.8	1.8	0.000
01/01/2001-12/31/2001	3.2	1.8	0.090	2.0	2.0	0.000
01/01/2002-12/31/2002	4.3	1.7	0.151	2.1	2.1	0.000
01/01/2003-12/31/2003	5.2	1.7	0.191	2.3	2.3	0.000
01/01/2004-12/31/2004	6.0	2.0	0.207	3.1	3.1	0.000
01/01/2005-12/31/2005	8.5	3.0	0.235	4.7	4.7	0.000
01/01/2006-12/31/2006	8.7	3.0	0.244	4.8	4.8	0.000
01/01/2007-12/31/2007	9.0	3.6	0.221	5.8	5.8	0.000
01/01/2008-12/31/2008	9.3	6.8	0.093	9.9	9.9	0.000
01/01/2009-12/31/2009	9.1	8.0	0.042	11.0	11.0	0.000
01/01/2010-12/31/2010	8.5	8.6	0.002	10.7	10.7	0.000
01/01/2011-12/31/2011	7.7	13.1	0.179	12.0	12.0	0.000

01/01/2012-12/31/2012	6.7	12.7	0.203		10.6	10.6	0.000
01/01/2013-12/31/2013	5.5	12.5	0.249		8.7	8.7	0.000
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=31,087)	Naproxen (n=26,731)			Tramadol (n=12,397)	Naproxen (n=12,397)	
01/01/2014-12/31/2014	3.8	11.0	0.276		6.5	6.5	0.000
01/01/2015-12/31/2015	2.5	8.7	0.273		4.0	4.0	0.000
<b>BMI, mean (SD), kg/m<sup>2</sup></b>	29.3 (5.9)	28.9 (5.5)	0.061		29.1 (5.7)	29.2 (5.6)	0.012
<b>OA duration, mean (SD), y</b>	6.8 (6.9)	6.6 (6.5)	0.034		6.8 (6.8)	6.8 (6.6)	0.002
<b>Site of OA</b>							
Knee OA only	53.2	56.2	0.062		56.3	56.4	0.002
Hip OA only	30.5	24.1	0.145		25.8	26.2	0.009
Hand OA only	7.7	13.3	0.185		10.1	9.7	0.016
Knee and hip OA	5.5	3.5	0.096		4.6	4.6	0.002
Knee and hand OA	1.9	1.9	0.003		2.1	2.0	0.002
Hip and hand OA	0.9	0.7	0.024		0.9	0.9	0.000
Knee, hip, and hand OA	0.3	0.2	0.027		0.3	0.2	0.002
<b>Lifestyle factors</b>							
Drinking (%)							
None	22.8	17.0	0.128		19.1	19.2	0.003
Past	3.2	2.3	0.050		2.8	2.8	0.001
Current	74.0	80.7	0.164		78.1	78.0	0.003
Smoking (%)							
None	53.5	56.8	0.081		53.5	53.7	0.003
Past	32.9	31.2	0.025		33.9	33.7	0.003

Current	13.6	12.0	0.041		12.6	12.6	0.001
<b>Comorbidity (%)</b>							
Peptic ulcer	9.8	4.5	0.206		6.5	6.1	0.014
<b>Variable list</b>	<b>Unmatched</b>		<b>Standardized difference</b>		<b>Propensity-score matched</b>		<b>Standardized difference</b>
	<b>Tramadol (n=31,087)</b>	<b>Naproxen (n=26,731)</b>			<b>Tramadol (n=12,397)</b>	<b>Naproxen (n=12,397)</b>	
Gastrointestinal bleeding	3.3	1.4	0.125		2.1	2.0	0.006
<b>CKD</b>							
Non-CKD	86.7	90.0	0.100		87.1	87.1	0.000
CKD stage 1	0.1	0.1	0.007		0.1	0.1	0.005
CKD stage 2	1.1	1.4	0.024		1.5	1.6	0.005
CKD stage 3	9.7	7.8	0.069		10.1	10.1	0.001
CKD stage 4	0.8	0.2	0.082		0.4	0.4	0.000
CKD stage 5	0.5	0.1	0.065		0.3	0.2	0.011
CKD stage unknown	1.0	0.4	0.072		0.6	0.5	0.001
Diabetes	15.4	12.1	0.096		14.6	14.5	0.002
Hypertension	54.3	44.6	0.196		52.1	52.4	0.005
Liver disease	2.8	2.2	0.033		2.5	2.5	0.001
Transient ischaemic attack	4.6	2.4	0.120		3.2	3.3	0.007
Ischaemic heart disease	19.5	10.0	0.271		14.2	14.6	0.010
Congestive heart failure	5.4	1.7	0.199		2.8	2.6	0.017
Myocardial infarction	6.9	3.5	0.157		4.9	5.0	0.005
Stroke	4.5	2.3	0.122		3.3	3.2	0.002
Angina	13.2	6.5	0.227		9.4	9.7	0.010
Peripheral vascular disease	2.6	1.1	0.113		1.7	1.7	0.003

Pneumonia or infection	8.2	6.6	0.060		7.3	7.2	0.002
Hyperlipidaemia	17.9	16.3	0.043		18.4	18.2	0.004
Dementia	1.2	1.0	0.019		1.0	1.1	0.007
Varicose veins	14.1	12.6	0.045		14.0	14.1	0.002
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=31,087)	Naproxen (n=26,731)			Tramadol (n=12,397)	Naproxen (n=12,397)	
Other circulatory disease	34.5	29.2	0.113		32.7	32.4	0.008
Depression	15.3	12.7	0.073		14.4	14.5	0.002
Venous thromboembolism	5.5	2.9	0.128		4.0	3.9	0.007
Chronic obstructive pulmonary disease	7.2	3.6	0.163		5.0	4.8	0.006
Atrial fibrillation	8.2	2.9	0.232		4.8	4.5	0.016
Anxiety	16.1	13.7	0.232		15.8	15.6	0.016
Seizure	0.5	0.5	0.006		0.5	0.5	0.000
Sleep disorder or sleep apnea	2.1	1.9	0.016		2.0	2.1	0.003
<b>Medication (%)</b>							
Other NSAIDs	85.4	84.7	0.021		85.7	86.2	0.015
Other opioids	40.7	27.4	0.283		35.4	35.9	0.011
Aspirin	42.0	28.6	0.284		36.1	36.7	0.011
Statin	48.1	41.5	0.133		47.6	47.9	0.005
Glucocorticoids	25.5	18.6	0.166		22.7	22.9	0.004
Nitrates	18.2	9.9	0.239		13.5	13.7	0.008
Antihypertensive medicine	72.2	57.8	0.307		67.0	67.6	0.013
Antidiabetic medicine	11.1	8.4	0.090		10.2	10.2	0.000
ACE inhibitors	39.3	30.4	0.188		36.7	36.9	0.005

Angiotensin receptor blocker	15.0	11.6	0.100		14.2	14.3	0.001
Beta receptor inhibitor	38.0	29.8	0.175		35.8	36.0	0.004
Calcium channel blockers	38.2	28.3	0.211		34.9	35.0	0.001
Loop diuretics	26.7	12.8	0.355		17.9	18.0	0.003
Thiazide-like diuretics	6.3	4.6	0.073		5.5	5.5	0.000
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=31,087)	Naproxen (n=26,731)			Tramadol (n=12,397)	Naproxen (n=12,397)	
Potassium-sparing diuretics	12.4	5.3	0.251		7.6	7.6	0.000
Insulin	3.0	1.8	0.079		2.2	2.2	0.004
Anticoagulants	10.9	4.0	0.268		6.4	6.1	0.014
Benzodiazepines	39.2	31.4	0.164		35.7	35.8	0.003
SSRI	23.3	20.4	0.070		22.1	22.5	0.011
SNRI	6.3	5.2	0.048		5.8	6.0	0.006
Healthcare utilization, mean (SD)							
Hospitalizations <sup>b</sup>	0.8 (1.6)	0.5 (1.1)	0.210		0.7 (1.3)	0.7 (1.4)	0.015
General practice visits <sup>b</sup>	14.2 (12.3)	10.7 (9.0)	0.324		12.8 (10.0)	12.7 (10.3)	0.008
Specialist referrals <sup>b</sup>	1.3 (1.7)	1.1 (1.5)	0.107		1.3 (1.6)	1.3 (1.7)	0.008

Abbreviations: BMI, body mass index; n, number; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin converting enzyme; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin–norepinephrine reuptake inhibitor; OA, osteoarthritis; y, years; SD, standard deviation.

<sup>a</sup> The Socioeconomic deprivation index score (i.e., Townsend Deprivation Index) ranged from 1 (least deprived) to 5 (most deprived).

<sup>b</sup> Frequency during the past two years.

**eTable 2. Baseline characteristics of unmatched and propensity-score matched osteoarthritis patients (≥ 50 years) initiating tramadol prescription or diclofenac prescription**

Variable list	Unmatched		Standardized difference	Propensity-score matched		Standardized difference
	Tramadol (n=16,372)	Diclofenac (n=21,675)		Tramadol (n=6,512)	Diclofenac (n=6,512)	
<b>Demographics</b>						
Age, mean (SD), y	72.1 (9.7)	67.5 (9.7)	0.479	70.3 (9.6)	70.3 (9.5)	0.001
Socioeconomic deprivation index score, mean (SD) <sup>a</sup>	2.6 (1.4)	2.4 (1.3)	0.137	2.5 (1.4)	2.5 (1.4)	0.012
Female (%)	63.7	55.4	0.169	61.5	62.5	0.021
<b>Time block</b>						
01/01/2000-12/31/2000	2.1	7.4	0.253	2.8	2.8	0.000
01/01/2001-12/31/2001	2.9	8.4	0.239	4.0	4.0	0.000
01/01/2002-12/31/2002	4.0	8.1	0.174	5.3	5.3	0.000
01/01/2003-12/31/2003	4.8	8.7	0.157	6.1	6.1	0.000
01/01/2004-12/31/2004	5.5	9.4	0.148	7.7	7.7	0.000
01/01/2005-12/31/2005	7.8	12.5	0.157	11.1	11.1	0.000
01/01/2006-12/31/2006	7.3	9.6	0.083	10.6	10.6	0.000
01/01/2007-12/31/2007	7.3	9.3	0.074	10.4	10.4	0.000
01/01/2008-12/31/2008	8.0	7.4	0.021	10.1	10.1	0.000
01/01/2009-12/31/2009	8.2	6.3	0.073	9.5	9.5	0.000
01/01/2010-12/31/2010	7.9	5.0	0.119	7.4	7.4	0.000
01/01/2011-12/31/2011	8.3	3.3	0.218	6.1	6.1	0.000
01/01/2012-12/31/2012	7.7	2.3	0.250	4.5	4.5	0.000

01/01/2013-12/31/2013	7.6	1.0	0.327		2.1	2.1	0.000
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=16,372)	Diclofenac (n=21,675)			Tramadol (n=6,512)	Diclofenac (n=6,512)	
01/01/2014-12/31/2014	6.2	0.7	0.304		1.5	1.5	0.000
01/01/2015-12/31/2015	4.4	0.5	0.257		0.8	0.8	0.000
<b>BMI, mean (SD), kg/m<sup>2</sup></b>	29.2 (5.9)	28.3 (5.2)	0.168		28.7 (5.6)	28.8 (5.6)	0.009
<b>OA duration, mean (SD), y</b>	6.8 (7.1)	5.8 (6.5)	0.138		6.4 (6.8)	6.4 (6.8)	0.003
<b>Site of OA</b>							
Knee OA only	52.9	56.4	0.071		55.9	55.9	0.002
Hip OA only	31.3	26.4	0.109		28.9	28.7	0.005
Hand OA only	7.3	12.1	0.162		8.7	8.3	0.014
Knee and hip OA	5.3	2.9	0.120		3.9	4.2	0.019
Knee and hand OA	1.8	1.3	0.041		1.6	1.8	0.009
Hip and hand OA	1.0	0.6	0.037		0.8	0.8	0.003
Knee, hip, and hand OA	0.3	0.2	0.035		0.2	0.3	0.006
<b>Lifestyle factors</b>							
Drinking (%)							
None	23.8	17.4	0.166		20.9	21.9	0.023
Past	3.4	1.6	0.115		2.4	2.5	0.003
Current	72.8	81.0	0.095		76.7	75.7	0.023
Smoking (%)							
None	53.6	56.7	0.026		54.8	54.1	0.012
Past	33.6	28.7	0.123		32.4	32.9	0.011
Current	12.7	14.6	0.042		12.8	12.9	0.002



<b>Comorbidity (%)</b>							
Peptic ulcer	11.1	5.3	0.213		8.9	8.6	0.011
<b>Variable list</b>	<b>Unmatched</b>		<b>Standardized difference</b>	<b>Propensity-score matched</b>		<b>Standardized difference</b>	
	<b>Tramadol (n=16,372)</b>	<b>Diclofenac (n=21,675)</b>		<b>Tramadol (n=6,512)</b>	<b>Diclofenac (n=6,512)</b>		
Gastrointestinal bleeding	3.8	1.3	0.157		2.7	2.5	0.017
CKD							
Non-CKD	85.4	95.6	0.355		91.2	91.3	0.005
CKD stage 1	0.1	0.1	0.009		0.0	0.1	0.012
CKD stage 2	1.2	0.5	0.075		0.9	1.0	0.014
CKD stage 3	10.6	3.0	0.302		6.4	6.2	0.01
CKD stage 4	1.0	0.1	0.116		0.3	0.3	0.003
CKD stage 5	0.6	0.2	0.071		0.3	0.3	0.000
CKD stage unknown	1.1	0.4	0.079		0.8	0.8	0.005
Diabetes	16.6	9.2	0.221		13.2	13.8	0.018
Hypertension	56.7	39.8	0.343		52.5	52.9	0.009
Liver disease	2.9	1.6	0.085		2.3	2.2	0.008
Transient ischaemic attack	5.1	2.6	0.133		4.2	4.1	0.006
Ischaemic heart disease	21.0	11.8	0.252		18.0	18.0	0.002
Congestive heart failure	6.3	2.4	0.191		4.5	4.3	0.009
Myocardial infarction	7.5	4.1	0.146		6.2	6.2	0.001
Stroke	5.2	2.5	0.145		3.7	3.9	0.011
Angina	13.9	8.3	0.181		12.6	12.7	0.005
Peripheral vascular disease	2.7	1.2	0.112		2.0	2.0	0.001
Pneumonia or infection	8.1	6.5	0.061		7.6	7.6	0.000

Hyperlipidaemia	18.1	12.1	0.170		17.2	17.2	0.000
Dementia	1.5	0.7	0.080		0.9	0.8	0.007
Varicose veins	13.1	12.2	0.028		12.9	13.1	0.006
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=16,372)	Diclofenac (n=21,675)			Tramadol (n=6,512)	Diclofenac (n=6,512)	
Other circulatory disease	34.9	24.5	0.228		32.3	32.5	0.004
Depression	14.9	10.3	0.140		13.7	13.9	0.008
Venous thromboembolism	5.8	2.9	0.145		4.8	4.5	0.015
Chronic obstructive pulmonary disease	8.3	3.1	0.225		6.0	5.5	0.024
Atrial fibrillation	9.8	2.8	0.292		5.6	5.3	0.014
Anxiety	15.8	11.8	0.292		15.2	14.6	0.014
Seizure	0.5	0.4	0.023		0.5	0.4	0.002
Sleep disorder or sleep apnea	1.9	1.1	0.062		1.7	1.8	0.002
<b>Medication (%)</b>							
Other NSAIDs	72.0	67.6	0.096		73.2	74.1	0.021
Other opioids	38.7	19.1	0.443		32.0	32.9	0.019
Aspirin	42.0	26.2	0.337		37.3	37.4	0.003
Statin	49.2	28.3	0.438		42.4	42.6	0.005
Glucocorticoids	26.2	13.2	0.331		21.3	21.0	0.007
Nitrates	18.9	9.8	0.262		15.5	15.7	0.006
Antihypertensive medicine	73.6	52.1	0.456		67.6	68.5	0.020
Antidiabetic medicine	11.9	6.7	0.181		9.6	10.0	0.014
ACE inhibitors	41.4	22.9	0.403		34.4	35.3	0.017
Angiotensin receptor blocker	15.9	7.2	0.276		12.7	12.6	0.003

Beta receptor inhibitor	37.5	26.7	0.231		34.5	35.3	0.016
Calcium channel blockers	40.4	22.8	0.385		34.5	35.1	0.013
Loop diuretics	28.1	13.0	0.381		21.6	21.3	0.007
Thiazide-like diuretics	6.9	4.0	0.131		5.9	5.9	0.001
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=16,372)	Diclofenac (n=21,675)			Tramadol (n=6,512)	Diclofenac (n=6,512)	
Potassium-sparing diuretics	12.7	7.0	0.194		10.5	10.5	0.000
Insulin	3.1	1.4	0.115		2.1	2.2	0.007
Anticoagulants	12.4	3.3	0.342		7.6	6.9	0.028
Benzodiazepines	36.6	24.0	0.278		33.1	33.4	0.006
SSRI	21.6	13.7	0.207		18.7	19.0	0.009
SNRI	6.1	3.1	0.143		4.3	4.6	0.010
<b>Healthcare utilization, mean (SD)</b>							
Hospitalizations <sup>b</sup>	0.9 (1.7)	0.3 (0.9)	0.424		0.6 (1.1)	0.6 (1.3)	0.012
General practice visits <sup>b</sup>	14.3 (12.8)	9.7 (8.7)	0.425		12.8 (9.7)	12.9 (10.4)	0.008
Specialist referrals <sup>b</sup>	1.3 (1.8)	0.7 (1.1)	0.439		1.0 (1.4)	1.0 (1.4)	0.009

Abbreviations: BMI, body mass index; n, number; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin converting enzyme; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin–norepinephrine reuptake inhibitor; OA, osteoarthritis; y, years; SD, standard deviation.

<sup>a</sup> The Socioeconomic deprivation index score (i.e., Townsend Deprivation Index) ranged from 1 (least deprived) to 5 (most deprived).

<sup>b</sup> Frequency during the past two years.

**eTable 3. Baseline characteristics of unmatched and propensity-score matched osteoarthritis patients (≥ 50 years) initiating tramadol prescription or celecoxib prescription**

Variable list	Unmatched		Standardized difference	Propensity-score matched		Standardized difference
	Tramadol (n=39,075)	Celecoxib (n=11,625)		Tramadol (n=5,674)	Celecoxib (n=5,674)	
<b>Demographics</b>						
Age, mean (SD), y	70.2 (9.7)	70.8 (9.6)	0.069	69.9 (9.5)	69.8 (9.5)	0.008
Socioeconomic deprivation index score, mean (SD) <sup>a</sup>	2.6 (1.4)	2.5 (1.3)	0.074	2.6 (1.4)	2.6 (1.4)	0.006
Female (%)	61.0	66.9	0.121	65.5	65.2	0.006
<b>Time block</b>						
01/01/2000-12/31/2000	2.4	2.3	0.009	3.1	3.1	0.000
01/01/2001-12/31/2001	3.4	12.3	0.337	12.8	12.8	0.000
01/01/2002-12/31/2002	4.0	19.4	0.494	16.7	16.7	0.000
01/01/2003-12/31/2003	4.4	21.7	0.532	18.4	18.4	0.000
01/01/2004-12/31/2004	4.9	27.5	0.645	21.9	21.9	0.000
01/01/2005-12/31/2005	6.7	1.8	0.245	2.9	2.9	0.000
01/01/2006-12/31/2006	7.3	2.1	0.252	3.5	3.5	0.000
01/01/2007-12/31/2007	7.8	2.3	0.255	3.8	3.8	0.000
01/01/2008-12/31/2008	8.2	2.1	0.281	3.3	3.3	0.000
01/01/2009-12/31/2009	8.6	2.2	0.288	3.4	3.4	0.000
01/01/2010-12/31/2010	8.6	1.8	0.308	2.8	2.8	0.000
01/01/2011-12/31/2011	8.4	1.2	0.340	2.1	2.1	0.000
01/01/2012-12/31/2012	8.1	1.2	0.334	1.9	1.9	0.000

01/01/2013-12/31/2013	7.3	0.7	0.340		1.0	1.0	0.000
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=39,075)	Celecoxib (n=11,625)			Tramadol (n=5,674)	Celecoxib (n=5,674)	
01/01/2014-12/31/2014	5.7	0.7	0.283		1.2	1.2	0.000
01/01/2015-12/31/2015	4.1	0.8	0.220		1.2	1.2	0.000
<b>BMI, mean (SD), kg/m<sup>2</sup></b>	29.5 (5.9)	28.2 (5.1)	0.229		28.6 (5.5)	28.6 (5.3)	0.001
<b>OA duration, mean (SD), y</b>	6.9 (6.9)	6.4 (6.5)	0.084		6.6 (6.4)	6.6 (6.6)	0.002
<b>Site of OA</b>							
Knee OA only	54.1	54.3	0.005		54.0	53.9	0.001
Hip OA only	29.2	26.1	0.069		27.9	27.5	0.008
Hand OA only	7.9	11.0	0.106		8.9	9.2	0.009
Knee and hip OA	5.6	4.8	0.034		5.9	5.9	0.001
Knee and hand OA	2.0	2.4	0.026		2.2	2.2	0.001
Hip and hand OA	0.9	1.1	0.018		0.8	0.9	0.013
Knee, hip, and hand OA	0.4	0.3	0.009		0.3	0.3	0.003
<b>Lifestyle factors</b>							
Drinking (%)							
None	21.4	21.3	0.028		21.6	21.5	0.003
Past	3.1	2.0	0.077		2.6	2.4	0.016
Current	75.4	76.7	0.048		75.7	76.1	0.009
Smoking (%)							
None	52.8	59.5	0.079		56.2	55.7	0.010
Past	33.2	27.1	0.159		29.6	30.0	0.009
Current	13.9	13.4	0.033		14.2	14.3	0.002

<b>Comorbidity (%)</b>							
Peptic ulcer	8.9	7.6	0.046		8.9	8.8	0.002
<b>Variable list</b>	<b>Unmatched</b>		<b>Standardized difference</b>		<b>Propensity-score matched</b>		<b>Standardized difference</b>
	<b>Tramadol (n=39,075)</b>	<b>Celecoxib (n=11,625)</b>			<b>Tramadol (n=5,674)</b>	<b>Celecoxib (n=5,674)</b>	
Gastrointestinal bleeding	3.1	2.2	0.061		2.9	2.7	0.012
CKD							
Non-CKD	86.9	97.5	0.400		96.5	96.3	0.008
CKD stage 1	0.1	0.1	0.015		0.1	0.0	0.015
CKD stage 2	1.2	0.2	0.115		0.5	0.4	0.011
CKD stage 3	9.7	1.3	0.376		1.8	2.0	0.014
CKD stage 4	0.7	0.1	0.098		0.1	0.1	0.005
CKD stage 5	0.5	0.3	0.028		0.4	0.4	0.008
CKD stage unknown	0.9	0.6	0.038		0.6	0.8	0.015
Diabetes	15.8	9.0	0.207		11.7	11.4	0.009
Hypertension	53.6	44.6	0.181		47.4	48.1	0.013
Liver disease	2.8	1.9	0.059		2.7	2.4	0.018
Transient ischaemic attack	4.2	3.6	0.031		4.0	4.0	0.001
Ischaemic heart disease	18.5	15.5	0.079		17.9	18.1	0.005
Congestive heart failure	5.0	3.9	0.049		4.6	4.5	0.004
Myocardial infarction	6.5	4.7	0.077		5.6	5.8	0.008
Stroke	4.2	3.1	0.058		3.6	3.6	0.001
Angina	12.6	11.6	0.029		13.3	13.5	0.004
Peripheral vascular disease	2.5	1.7	0.052		2.0	2.1	0.005
Pneumonia or infection	8.7	8.0	0.025		9.5	9.2	0.011

Hyperlipidaemia	18.1	12.2	0.164		14.1	14.9	0.021
Dementia	1.1	0.7	0.033		0.6	0.7	0.007
Varicose veins	13.9	14.6	0.018		14.8	14.5	0.007
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=39,075)	Celecoxib (n=11,625)			Tramadol (n=5,674)	Celecoxib (n=5,674)	
Other circulatory disease	34.9	31.4	0.075		34.9	34.1	0.016
Depression	15.6	13.1	0.073		15.3	15.2	0.001
Venous thromboembolism	5.3	4.3	0.048		4.9	4.9	0.002
Chronic obstructive pulmonary disease	6.8	4.2	0.114		5.5	5.1	0.015
Atrial fibrillation	7.7	3.7	0.172		4.8	4.7	0.005
Anxiety	16.7	15.2	0.172		17.2	17.6	0.005
Seizure	0.5	0.3	0.042		0.4	0.4	0.003
Sleep disorder or sleep apnea	2.2	1.5	0.049		1.9	1.7	0.011
<b>Medication (%)</b>							
Other NSAIDs	88.4	88.8	0.013		90.6	91.3	0.025
Other opioids	42.6	30.0	0.264		39.6	39.5	0.003
Aspirin	40.7	31.1	0.200		34.1	34.9	0.016
Statin	47.9	28.3	0.413		33.7	34.2	0.010
Glucocorticoids	25.9	19.9	0.145		23.9	22.7	0.028
Nitrates	17.4	13.9	0.097		16.7	17.2	0.014
Antihypertensive medicine	71.4	63.8	0.164		68.2	68.3	0.002
Antidiabetic medicine	11.4	6.6	0.170		8.4	8.6	0.005
ACE inhibitors	39.3	24.3	0.325		28.6	28.9	0.007
Angiotensin receptor blocker	14.4	8.3	0.193		8.8	8.9	0.002

Beta receptor inhibitor	37.9	32.6	0.112		35.2	35.6	0.007
Calcium channel blockers	38.0	27.8	0.218		32.3	32.4	0.002
Loop diuretics	25.4	21.6	0.089		24.8	25.0	0.004
Thiazide-like diuretics	6.4	5.6	0.035		5.6	5.9	0.012
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=39,075)	Celecoxib (n=11,625)			Tramadol (n=5,674)	Celecoxib (n=5,674)	
Potassium-sparing diuretics	11.4	12.6	0.037		13.8	13.5	0.008
Insulin	3.0	1.5	0.100		2.2	2.0	0.007
Anticoagulants	10.5	4.2	0.244		6.3	6.2	0.004
Benzodiazepines	40.2	34.1	0.126		39.9	39.7	0.006
SSRI	23.9	17.6	0.156		21.4	21.0	0.010
SNRI	6.5	4.8	0.075		5.5	5.4	0.001
<b>Healthcare utilization, mean (SD)</b>							
Hospitalizations <sup>b</sup>	0.8 (1.6)	0.3 (0.9)	0.440		0.4 (1.0)	0.4 (1.0)	0.023
General practice visits <sup>b</sup>	14.2 (11.9)	12.2 (10.1)	0.181		14.1 (10.7)	13.9 (11.1)	0.018
Specialist referrals <sup>b</sup>	1.3 (1.8)	0.8 (1.3)	0.352		1.0 (1.3)	1.0 (1.4)	0.002

Abbreviations: BMI, body mass index; n, number; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin converting enzyme; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin–norepinephrine reuptake inhibitor; OA, osteoarthritis; y, years; SD, standard deviation.

<sup>a</sup> The Socioeconomic deprivation index score (i.e., Townsend Deprivation Index) ranged from 1 (least deprived) to 5 (most deprived).

<sup>b</sup> Frequency during the past two years.



**eTable 4. Baseline characteristics of unmatched and propensity-score matched osteoarthritis patients (≥ 50 years) initiating tramadol prescription or etoricoxib prescription**

Variable list	Unmatched		Standardized difference	Propensity-score matched		Standardized difference
	Tramadol (n=44,036)	Etoricoxib (n=4,006)		Tramadol (n=2,946)	Etoricoxib (n=2,946)	
<b>Demographics</b>						
Age, mean (SD), y	70.4 (9.7)	69.0 (9.6)	0.142	68.9 (9.4)	68.9 (9.4)	0.002
Socioeconomic deprivation index score, mean (SD) <sup>a</sup>	2.6 (1.4)	2.5 (1.4)	0.063	2.5 (1.4)	2.5 (1.4)	0.028
Female (%)	62.4	61.4	0.022	62.5	62.2	0.006
<b>Time block</b>						
01/01/2000-12/31/2000	2.2	-	0.210	-	-	-
01/01/2001-12/31/2001	3.2	-	0.258	-	-	-
01/01/2002-12/31/2002	4.1	4.4	0.017	4.2	4.2	0.000
01/01/2003-12/31/2003	4.8	14.7	0.337	14.2	14.2	0.000
01/01/2004-12/31/2004	5.4	24.3	0.549	24.3	24.3	0.000
01/01/2005-12/31/2005	7.4	7.7	0.013	7.5	7.5	0.000
01/01/2006-12/31/2006	7.7	7.0	0.026	7.3	7.3	0.000
01/01/2007-12/31/2007	8.1	8.7	0.022	8.7	8.7	0.000
01/01/2008-12/31/2008	8.3	7.5	0.031	8.1	8.1	0.000
01/01/2009-12/31/2009	8.4	6.2	0.084	6.7	6.7	0.000
01/01/2010-12/31/2010	8.4	5.8	0.101	5.6	5.6	0.000
01/01/2011-12/31/2011	8.2	4.4	0.156	4.2	4.2	0.000
01/01/2012-12/31/2012	7.8	2.9	0.216	3.1	3.1	0.000

01/01/2013-12/31/2013	6.9	2.3	0.219		2.5	2.5	0.000
<b>Variable list</b>	<b>Unmatched</b>		<b>Standardized difference</b>		<b>Propensity-score matched</b>		<b>Standardized difference</b>
	<b>Tramadol (n=44,036)</b>	<b>Etoricoxib (n=4,006)</b>			<b>Tramadol (n=2,946)</b>	<b>Etoricoxib (n=2,946)</b>	
01/01/2014-12/31/2014	5.3	2.0	0.180		1.8	1.8	0.000
01/01/2015-12/31/2015	3.8	2.0	0.106		1.7	1.7	0.000
<b>BMI, mean (SD), kg/m<sup>2</sup></b>	29.5 (5.9)	28.6 (5.3)	0.154		28.7 (5.7)	28.6 (5.3)	0.004
<b>OA duration, mean (SD), y</b>	7.0 (6.9)	6.2 (6.3)	0.121		6.3 (6.3)	6.3 (6.3)	0.003
<b>Site of OA</b>							
Knee OA only	54.0	54.9	0.018		56.1	56.0	0.001
Hip OA only	28.9	23.5	0.122		22.2	22.2	0.001
Hand OA only	7.8	12.8	0.164		12.9	12.5	0.013
Knee and hip OA	5.7	4.8	0.043		4.7	5.0	0.017
Knee and hand OA	2.2	2.4	0.019		2.6	2.7	0.006
Hip and hand OA	1.0	1.1	0.012		1.0	1.1	0.003
Knee, hip, and hand OA	0.4	0.4	0.000		0.5	0.4	0.005
<b>Lifestyle factors</b>							
<b>Drinking (%)</b>							
None	21.8	20.9	0.034		20.5	20.7	0.004
Past	3.1	2.3	0.051		2.9	2.4	0.027
Current	75.1	76.8	0.009		76.6	76.8	0.006
<b>Smoking (%)</b>							
None	53.3	57.1	0.064		57.8	56.4	0.029
Past	33.0	30.7	0.055		30.9	31.9	0.023
Current	13.7	12.2	0.046		11.3	11.6	0.011

<b>Comorbidity (%)</b>							
Peptic ulcer	9.0	7.0	0.072		6.1	6.6	0.017
<b>Variable list</b>	<b>Unmatched</b>		<b>Standardized difference</b>		<b>Propensity-score matched</b>		<b>Standardized difference</b>
	<b>Tramadol (n=44,036)</b>	<b>Etoricoxib (n=4,006)</b>			<b>Tramadol (n=2,946)</b>	<b>Etoricoxib (n=2,946)</b>	
Gastrointestinal bleeding	3.1	1.8	0.087		2.0	1.8	0.015
CKD							
Non-CKD	87.0	93.3	0.214		92.6	93.0	0.013
CKD stage 1	0.1	0.0	0.020		0.1	0.1	0.012
CKD stage 2	1.2	0.6	0.055		0.7	0.8	0.012
CKD stage 3	9.7	4.9	0.182		5.5	5.1	0.021
CKD stage 4	0.7	0.2	0.064		0.3	0.3	0.000
CKD stage 5	0.5	0.2	0.052		0.2	0.2	0.015
CKD stage unknown	0.9	0.6	0.036		0.6	0.6	0.000
Diabetes	15.5	9.8	0.171		11.2	10.8	0.014
Hypertension	53.8	46.8	0.141		47.8	47.8	0.001
Liver disease	2.7	2.1	0.040		2.6	2.3	0.020
Transient ischaemic attack	4.3	2.6	0.090		2.1	2.7	0.044
Ischaemic heart disease	18.6	13.0	0.154		13.1	13.7	0.016
Congestive heart failure	5.0	3.2	0.093		3.3	3.2	0.010
Myocardial infarction	6.5	4.3	0.099		4.3	4.7	0.018
Stroke	4.3	2.6	0.093		2.5	2.6	0.011
Angina	12.6	9.3	0.106		9.9	10.0	0.005
Peripheral vascular disease	2.5	1.4	0.077		1.3	1.5	0.012
Pneumonia or infection	8.6	7.8	0.029		8.8	8.4	0.016

Hyperlipidaemia	18.0	15.3	0.075		16.5	16.3	0.005
Dementia	1.1	0.5	0.067		0.4	0.3	0.011
Varicose veins	14.2	14.2	0.001		15.6	15.2	0.010
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=44,036)	Etoricoxib (n=4,006)			Tramadol (n=2,946)	Etoricoxib (n=2,946)	
Other circulatory disease	35.4	30.0	0.117		33.1	31.7	0.029
Depression	15.8	13.9	0.055		14.5	14.8	0.008
Venous thromboembolism	5.4	3.8	0.073		4.2	3.8	0.023
Chronic obstructive pulmonary disease	6.8	4.3	0.111		5.0	4.2	0.041
Atrial fibrillation	7.5	3.6	0.170		3.6	3.9	0.013
Anxiety	16.9	14.0	0.170		15.3	15.1	0.013
Seizure	0.5	0.3	0.040		0.2	0.3	0.020
Sleep disorder or sleep apnea	2.3	1.6	0.050		1.8	1.7	0.008
<b>Medication (%)</b>							
Other NSAIDs	89.7	93.4	0.135		94.7	94.1	0.028
Other opioids	43.4	30.8	0.264		33.3	32.5	0.017
Aspirin	41.0	30.4	0.223		30.2	31.3	0.024
Statin	48.0	37.1	0.222		39.5	39.5	0.001
Glucocorticoids	26.3	22.5	0.089		22.6	23.2	0.012
Nitrates	17.8	12.0	0.165		12.7	12.8	0.005
Antihypertensive medicine	71.8	64.2	0.165		64.8	65.1	0.008
Antidiabetic medicine	11.1	7.1	0.142		8.4	7.9	0.020
ACE inhibitors	39.1	27.8	0.241		28.8	29.2	0.010
Angiotensin receptor blocker	14.6	12.2	0.069		11.8	12.1	0.008

Beta receptor inhibitor	38.4	32.7	0.118		34.2	34.0	0.004
Calcium channel blockers	38.1	29.3	0.187		30.8	30.8	0.000
Loop diuretics	25.9	19.6	0.151		19.1	20.0	0.022
Thiazide-like diuretics	6.5	6.7	0.007		6.7	7.0	0.012
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=44,036)	Etoricoxib (n=4,006)			Tramadol (n=2,946)	Etoricoxib (n=2,946)	
Potassium-sparing diuretics	11.8	10.5	0.043		10.6	10.6	0.000
Insulin	2.9	1.3	0.115		1.6	1.5	0.006
Anticoagulants	10.3	4.5	0.222		4.9	4.9	0.003
Benzodiazepines	41.0	36.4	0.094		39.1	38.1	0.021
SSRI	24.3	21.2	0.074		23.2	22.5	0.015
SNRI	6.7	6.0	0.028		5.7	5.9	0.010
<b>Healthcare utilization, mean (SD)</b>							
Hospitalizations <sup>b</sup>	0.8 (1.6)	0.4 (1.0)	0.312		0.5 (1.0)	0.4 (1.0)	0.036
General practice visits <sup>b</sup>	14.5 (12.2)	12.2 (9.4)	0.211		13.0 (9.7)	12.8 (9.2)	0.017
Specialist referrals <sup>b</sup>	1.3 (1.8)	0.9 (1.4)	0.269		1.0 (1.4)	1.0 (1.4)	0.003

Abbreviations: BMI, body mass index; n, number; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin converting enzyme; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin–norepinephrine reuptake inhibitor; OA, osteoarthritis; y, years; SD, standard deviation.

<sup>a</sup> The Socioeconomic deprivation index score (i.e., Townsend Deprivation Index) ranged from 1 (least deprived) to 5 (most deprived).

<sup>b</sup> Frequency during the past two years.

**eTable 5. Baseline characteristics of unmatched and propensity-score matched osteoarthritis patients (≥ 50 years) initiating tramadol prescription or codeine prescription**

Variable list	Unmatched		Standardized difference	Propensity-score matched		Standardized difference
	Tramadol (n=34,353)	Codeine (n=23,899)		Tramadol (n=16,922)	Codeine (n=16,922)	
<b>Demographics</b>						
Age, mean (SD), y	70.0 (9.7)	71.6 (9.7)	0.172	70.9 (9.5)	71.0 (9.5)	0.002
Socioeconomic deprivation index score, mean (SD) <sup>a</sup>	2.6 (1.4)	2.5 (1.3)	0.082	2.5 (1.3)	2.5 (1.4)	0.008
Female (%)	60.9	61.4	0.011	60.8	60.5	0.007
<b>Time block</b>						
01/01/2000-12/31/2000	2.3	3.5	0.075	2.4	2.4	0.000
01/01/2001-12/31/2001	3.3	4.4	0.058	3.4	3.4	0.000
01/01/2002-12/31/2002	4.1	4.5	0.016	3.9	3.9	0.000
01/01/2003-12/31/2003	4.8	5.3	0.025	5.0	5.0	0.000
01/01/2004-12/31/2004	5.7	5.6	0.004	5.5	5.5	0.000
01/01/2005-12/31/2005	7.7	7.0	0.027	7.6	7.6	0.000
01/01/2006-12/31/2006	7.8	7.0	0.032	7.5	7.5	0.000
01/01/2007-12/31/2007	8.2	6.9	0.048	7.7	7.7	0.000
01/01/2008-12/31/2008	8.5	7.5	0.039	8.2	8.2	0.000
01/01/2009-12/31/2009	8.5	7.2	0.048	7.9	7.9	0.000
01/01/2010-12/31/2010	8.4	7.0	0.049	7.6	7.6	0.000
01/01/2011-12/31/2011	7.9	7.3	0.023	8.1	8.1	0.000
01/01/2012-12/31/2012	7.4	7.5	0.002	7.9	7.9	0.000

01/01/2013-12/31/2013	6.6	6.9	0.009		7.2	7.2	0.000
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=34,353)	Codeine (n=23,899)			Tramadol (n=16,922)	Codeine (n=16,922)	
01/01/2014-12/31/2014	5.1	6.8	0.069		6.0	6.0	0.000
01/01/2015-12/31/2015	3.6	5.7	0.097		4.1	4.1	0.000
<b>BMI, mean (SD), kg/m<sup>2</sup></b>	29.5 (5.9)	28.6 (5.4)	0.144		28.8 (5.5)	28.8 (5.5)	0.006
<b>OA duration, mean (SD), y</b>	6.8 (6.8)	7.3 (7.0)	0.084		7.2 (7.0)	7.1 (6.8)	0.004
<b>Site of OA</b>							
Knee OA only	53.8	55.1	0.025		55.6	56.1	0.010
Hip OA only	29.8	26.6	0.071		26.5	26.1	0.009
Hand OA only	7.7	10.2	0.087		9.5	9.4	0.003
Knee and hip OA	5.3	4.8	0.024		5.1	5.1	0.001
Knee and hand OA	2.0	2.0	0.002		2.1	2.1	0.003
Hip and hand OA	1.0	1.0	0.007		1.0	0.9	0.007
Knee, hip, and hand OA	0.4	0.2	0.024		0.2	0.2	0.001
<b>Lifestyle factors</b>							
Drinking (%)							
None	21.2	20.4	0.011		20.0	20.2	0.004
Past	2.8	3.1	0.019		2.9	3.0	0.006
Current	76.0	76.5	0.025		77.1	76.8	0.006
Smoking (%)							
None	53.3	56.4	0.063		54.9	55.1	0.005
Past	32.6	32.8	0.007		34.0	33.9	0.001
Current	14.0	10.8	0.095		11.1	11.0	0.005

<b>Comorbidity (%)</b>							
Peptic ulcer	8.6	7.8	0.030		7.8	7.9	0.004
<b>Variable list</b>	<b>Unmatched</b>		<b>Standardized difference</b>	<b>Propensity-score matched</b>		<b>Standardized difference</b>	
	<b>Tramadol (n=34,353)</b>	<b>Codeine (n=23,899)</b>		<b>Tramadol (n=16,922)</b>	<b>Codeine (n=16,922)</b>		
Gastrointestinal bleeding	2.8	2.8	0.005		2.7	2.8	0.005
CKD							
Non-CKD	87.9	87.3	0.019		87.4	87.1	0.007
CKD stage 1	0.1	0.1	0.002		0.1	0.1	0.004
CKD stage 2	1.1	1.0	0.013		1.0	1.0	0.006
CKD stage 3	9.0	9.6	0.024		9.7	9.9	0.006
CKD stage 4	0.6	0.6	0.003		0.6	0.6	0.006
CKD stage 5	0.4	0.5	0.010		0.4	0.4	0.003
CKD stage unknown	0.9	0.9	0.000		0.8	0.8	0.003
Diabetes	14.6	14.8	0.004		15.3	15.4	0.003
Hypertension	52.2	53.3	0.022		54.2	54.6	0.008
Liver disease	2.6	2.6	0.005		2.5	2.6	0.006
Transient ischaemic attack	3.9	4.5	0.029		4.2	4.2	0.001
Ischaemic heart disease	17.5	17.9	0.011		18.0	18.2	0.004
Congestive heart failure	4.4	5.4	0.049		4.8	4.8	0.002
Myocardial infarction	6.2	6.6	0.018		6.6	6.6	0.002
Stroke	3.9	4.7	0.040		4.2	4.3	0.006
Angina	11.6	12.2	0.018		12.5	12.5	0.002
Peripheral vascular disease	2.4	2.1	0.018		2.1	2.1	0.002
Pneumonia or infection	7.9	8.0	0.005		7.9	8.1	0.007



Hyperlipidaemia	17.6	16.7	0.021		18.3	18.3	0.000
Dementia	1.0	2.1	0.092		1.1	1.2	0.013
Varicose veins	13.5	14.9	0.039		14.7	14.9	0.005
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=34,353)	Codeine (n=23,899)			Tramadol (n=16,922)	Codeine (n=16,922)	
Other circulatory disease	33.3	36.0	0.057		36.4	36.7	0.006
Depression	15.0	13.0	0.056		13.5	13.7	0.005
Venous thromboembolism	5.0	5.0	0.004		5.1	5.0	0.003
Chronic obstructive pulmonary disease	6.2	5.7	0.017		5.8	5.9	0.002
Atrial fibrillation	6.9	8.6	0.064		7.8	8.0	0.007
Anxiety	15.8	15.2	0.064		15.7	15.7	0.007
Seizure	0.5	0.5	0.010		0.4	0.4	0.003
Sleep disorder or sleep apnea	2.1	1.8	0.017		1.9	1.9	0.005
<b>Medication (%)</b>							
Other NSAIDs	89.5	85.4	0.125		88.0	87.8	0.007
Other opioids	23.7	15.5	0.206		17.3	17.1	0.004
Aspirin	39.0	40.0	0.020		40.0	40.3	0.006
Statin	46.1	44.9	0.025		47.0	47.2	0.004
Glucocorticoids	23.9	23.1	0.020		24.1	24.0	0.002
Nitrates	16.1	16.5	0.009		16.8	16.8	0.001
Antihypertensive medicine	69.8	69.6	0.004		70.1	70.5	0.010
Antidiabetic medicine	10.6	10.5	0.005		10.9	11.0	0.002
ACE inhibitors	37.1	38.5	0.028		39.0	39.1	0.003
Angiotensin receptor blocker	13.9	13.5	0.012		14.1	14.2	0.003

Beta receptor inhibitor	36.4	38.4	0.040		38.9	39.1	0.004
Calcium channel blockers	35.9	36.7	0.015		37.5	37.5	0.002
Loop diuretics	24.1	23.4	0.015		23.1	23.1	0.000
Thiazide-like diuretics	6.3	6.3	0.001		6.3	6.4	0.003
Variable list	Unmatched		Standardized difference		Propensity-score matched		Standardized difference
	Tramadol (n=34,353)	Codeine (n=23,899)			Tramadol (n=16,922)	Codeine (n=16,922)	
Potassium-sparing diuretics	11.0	10.4	0.019		10.3	10.3	0.001
Insulin	2.6	2.4	0.016		2.5	2.5	0.001
Anticoagulants	9.3	10.3	0.035		10.1	10.1	0.002
Benzodiazepines	38.9	33.2	0.120		34.8	34.7	0.002
SSRI	23.2	19.5	0.091		20.2	20.4	0.006
SNRI	6.2	5.2	0.046		5.2	5.3	0.007
<b>Healthcare utilization, mean (SD)</b>							
Hospitalizations <sup>b</sup>	0.8 (1.5)	0.8 (1.6)	0.011		0.8 (1.5)	0.8 (1.6)	0.009
General practice visits <sup>b</sup>	13.6 (11.5)	13.8 (11.5)	0.018		14.2 (11.5)	14.1 (10.8)	0.009
Specialist referrals <sup>b</sup>	1.3 (1.7)	1.2 (1.6)	0.051		1.3 (1.6)	1.3 (1.6)	0.002

Abbreviations: BMI, body mass index; n, number; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug; ACE, angiotensin converting enzyme; SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin–norepinephrine reuptake inhibitor; OA, osteoarthritis; y, years; SD, standard deviation.

<sup>a</sup> The Socioeconomic deprivation index score (i.e., Townsend Deprivation Index) ranged from 1 (least deprived) to 5 (most deprived).

<sup>b</sup> Frequency during the past two years.