

Appendix A – Data sources

The Danish Cancer Registry has recorded incident cases of cancer on a nationwide basis since 1943 and has been shown to have accurate and almost complete ascertainment of cancer cases. Cancer diagnoses in the Cancer Registry are recorded according to the International Classification of Diseases, version 10 (ICD-10), and the ICD for Oncology (ICD-O-1-3) for topography and morphology codes.

The Danish National Prescription Registry contains data on all prescription drugs dispensed to Danish citizens since 1995. The data include the type of drug, date of dispensing, and quantity. The dosing information and the indication for prescribing are not available. Drugs are categorized according to the Anatomic Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the WHO, and the quantity dispensed for each prescription is given by the number and strength of the pharmaceutical entities (e.g., tablets), as well as the defined daily doses (DDD).

The Danish National Patient Register contains nationwide data on all non-psychiatric hospital admissions since 1977 and both psychiatric and non-psychiatric outpatient contacts since 1995. Discharge/contact diagnoses have been coded according to ICD-8 from 1977 to 1993 and ICD-10 since 1994.

Statistics Denmark hosts registries on education and income. The Population Education Register contains information on nearly all adult Danes and provides the highest completed level of education, defined as that with the longest duration of schooling. The Income Statistics Register contains more than 160 variables describing different aspects of income for all Danish citizens since 1970.

The Danish Civil Registration System contains data on date of death and migration to and from Denmark, which allowed us to extract population controls and to keep track of all subjects during the study period.

Appendix B – Confounders

Use of drugs (≥ 2 fillings prior to index date)

<u>Drug</u>	<u>ATC-code</u>
Non-aspirin NSAIDs	M01A excl. M01AX
Paracetamol	N02BE01
Low-dose aspirin	B01AC06; B01AC30
Statins	C10AA
Thiazides	C03A
Beta-blockers	C07
Vascular calcium-channel blockers	C08CA
Inhibitors of the RAS system	C09
Loop diuretics	C03C

Prior diagnoses (either a diagnostic code or a drug marker)

<u>Disease</u>	<u>ICD-8 code</u>	<u>ICD-10 code</u>	<u>Drug markers</u>
Hypertension	401.99	I10-15	-
Diabetes type 1	249	E10	-
Diabetes type 2	250	E11	A10B (≥ 500 DDD)
COPD	490.00, 491.00, 491.01, 491.03	J42-44	R03BB (≥ 500 DDD)
Alcohol abuse	291, 303, 577.10, 979, 980	F10, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, R78.0, T51, Z72.1	N07BB01, N07BB03, N07BB04 (ever use)
Moderate-severe renal disease	403-4, 580-584, 590.09, 593.19, 753.10-753.19, 792*	I12-3, N00-N05, N07, N11, N14, N17-N19	-

Socioeconomic status (education)

<u>Educational level</u>	<u>Duration of education</u>
Basic	10 years
Short/medium	11-13 years
Long	>13 years
Missing/unknown	-

Appendix C – Analysis of lamotrigine and valproate

Lamotrigine

Association between exposure to lamotrigine and risk of upper urinary tract cancer, specified by exposure pattern within the entire follow-up-period, excluding the last year prior to the index date

Exposure group	Cases	Controls	Adjusted OR ¹	Adjusted OR ²
Non-use	6,441	257,525		
Ever use	36	1,555	0.9 (0.7-1.3)	0.9 (0.6-1.2)
Long-term use (≥ 5 years)	6,438	257,543	0.6 (0.3-1.2)	0.7 (0.4-1.3)
Duration of use:				
< 1 year	17	706	1.0 (0.6-1.6)	0.9 (0.5-1.4)
1-4.99 years	14	543	1.0 (0.6-1.8)	1.0 (0.6-1.6)
5-9.99 years	4	206	0.8 (0.3-2.1)	0.7 (0.3-1.9)
≥ 10 years	3	66	1.8 (0.6-5.7)	1.7 (0.5-5.5)

1) Adjusted for age and gender (by design; risk-set matching).

2) Fully adjusted model, see section 'Main analysis'.

Valproate

Association between exposure to valproate and risk of upper urinary tract cancer, specified by exposure pattern within the entire follow-up-period, excluding the last year prior to the index date

Exposure group	Cases	Controls	Adjusted OR ¹	Adjusted OR ²
Non-use	6,437	257,684	1.0 (ref.)	1.0 (ref.)
Ever use	40	1,396	1.1 (0.8-1.6)	1.1 (0.8-1.4)
Long-term use (≥ 5 years)	6,428	257,467	0.8 (0.5-1.4)	0.9 (0.6-1.5)
Duration of use:				
< 1 year	24	883	1.1 (0.7-1.6)	1.0 (0.6-1.5)
1-4.99 years	10	518	0.8 (0.4-1.4)	0.7 (0.4-1.3)
5-9.99 years	4	199	0.8 (0.3-2.2)	0.8 (0.3-2.0)
≥ 10 years	2	85	0.9 (0.2-3.8)	0.9 (0.2-3.7)

1) Adjusted for age and gender (by design; risk-set matching).

2) Fully adjusted model, see section 'Main analysis'.