#### SUPPLEMENTAL MATERIAL

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Supplemental Table 1. CPRD codes for nephrotic syndrome and the clinical events

Med Read			codes for nephrotic syndrome and the clinical events	Frequency,
No	code	code	Read term	n (%)
1	2999	K0100	NS	1972 (75)
2	2471	K01X100	NS in DM	172 (7)
3	22205	K01X411	Lupus nephritis	138 (5)
4	1803	K011.00	NS with membranous glomerulonephritis	78 (3)
5	22852	K015.00	NS, focal and segmental glomerular lesions	69 (3)
6	17365	K01B.00	NS, diffuse crescentic glomerulonephritis	31 (1)
7	29634	K013.00	NS with minimal change glomerulonephritis	28 (1)
8	21989	K019.00	NS, diffuse mesangio-capillary glomerulonephritis	25 (1)
9	27427	K01z.00	NS NOS	24 (1)
10	19316	K016.00	NS, diffuse membranous glomerulonephritis	20 (1)
11	21947	K017.00	NS, diffuse mesangial proliferative glomerulonephritis	17 (1)
12	23913	K014.00	NS, minor glomerular abnormality	12 (1)
13	47922	K01x000	NS in amyloidosis	10 (0)
14	47672	K01x400	NS in systemic lupus erythematosus	9 (0)
15	15 50472	50472 K018.00	NS, diffuse endocapillary proliferative	3 (0)
13	30472	KU16.UU	glomerulonephritis	3 (0)
16	45499	K01X111	Kimmelstiel-Wilson Disease	2 (0)
17	56987	K01A.00	NS, dense deposit disease	2 (0)
18	57926	K013.12	Steroid sensitive NS	2 (0)
19	108816	K01x.00	NS in diseases EC	2 (0)
20	40349	K013.11	Lipoid nephrosis	1 (0)
21	58750	K01x300	NS in poly-arthritis nodosa	1 (0)
22	94373	K01y.00	NS with other pathological kidney lesions	1 (0)
23	110794	K01w200	Congenital NS with focal glomerulosclerosis	1 (0)
24	63786	K01w.00	Congenital NS	0 (0)
25	72303	K01w000	Finnish NS	0 (0)
26	9840	K010.00	NS with proliferative glomerulonephritis	0 (0)
27	99201	K01x200	NS in malaria	0 (0)
28	99644	K012.00	NS + membrano-proliferative glomerulonephritis	0 (0)
29	108591	K01w100	Drash syndrome	0 (0)
30	108922	K01w112	Wilms' tumor + NS + pseudohermaphroditism	0 (0)
31	111370	K01wz00	Congenital NS NOS	0 (0)
			TOTAL	2620 (100)

CPRD = the Clinical Practice Research Datalink; DM = diabetes mellitus; EC = elsewhere classified; NS

<sup>=</sup> nephrotic syndrome; NOS = Not Otherwise specified;

#### **Supplemental Table 2.** The Anatomical Therapeutic Chemical Classification system for NSAIDs

No	NSAIDs according to COX enzyme selectivity and chemical structures	ATC codes
1	Conventional NSAIDs	
	Butylpyrazolidines	M01AA
	Acetic acid derivatives and related substances	M01AB
	Oxicams	M01AC
	Propionic acid derivatives	M01AE
	Fenamates	M01AG
	Other anti-inflammatory and anti-rheumatoid agents, non-steroid	M01AX
2	Selective COX-2 inhibitors	M01AH

Abbreviations: ATC = The Anatomical Therapeutic Chemical; COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs

Supplemental Table 3. Odds ratios of nephrotic syndrome for NSAID users stratified by age

Supplemental Table 3: Odds ratios	<b>Supplemental Table 3.</b> Odds ratios of nephrotic syndrome for NSAID users stratified by age					
18-64 years old	Cases	Controls	Crude OR	Adj. OR <sup>∓</sup>		
·	(n = 1,579)	(n = 6,316)	(95% CI)	(95% CI)		
Nonuse, n (%)	715 (45)	3,375 (53)	1	1		
Current use, n (%)						
Conventional NSAIDs <sup>1</sup>	40 (3)	123 (2)	1.54 (1.07-2.13)	1.08 (0.69-1.68)		
Selective COX-2 inhibitors	6 (0)	20 (0)	1.42 (0.57-3.54)	0.38 (0.21-0.70)		
Recent use, n (%)						
Conventional NSAIDs <sup>1</sup>	47 (3)	91 (1)	2.44 (1.70-3.50)	1.59 (1.03-2.47)		
Selective COX-2 inhibitors	2 (0)	5 (0)	NA	NA		
Past use (discontinuation between 2 months – 2 years), n (%)						
Conventional NSAIDs1	300 (19)	900 (14)	1.57 (1.35-1.84)	1.13 (0.94-1.36)		
Selective COX-2 inhibitors	17 (1)	25 (0)	3.21 (1.72-5.98)	1.43 (0.92-2.23)		
Past use (discontinuation >2	ì	• • • • • • • • • • • • • • • • • • • •	·	,		
years), n (%)						
Conventional NSAIDs <sup>1</sup>	443 (28)	1734 (28)	1.21 (1.06-1.38)	0.91 (0.77-1.07)		
Selective COX-2 inhibitors	9 (1)	43 (1)	0.99 (0.48-2.04)	0.32 (0.13-0.80)		
≥65 years old	Cases	Controls	Crude OR	Adj. OR <sup>∓</sup>		
203 years old	(n = 1041)	(n = 4138)	(95% CI)	(95% CI)		
Nonuse, n (%)	403 (39)	1,767 (43)	1	1		
Current use, n (%)						
Conventional NSAIDs <sup>1</sup>	34 (3)	141 (3)	1.06 (0.72-1.56)	1.02 (0.67-1.55)		
Selective COX-2 inhibitors	2 (0)	19 (1)	NA	NA		
Recent use, n (%)						
Conventional NSAIDs <sup>1</sup>	26 (3)	92 (2)	1.25 (0.80-1.96)	1.31 (0.80-2.15)		
Selective COX-2 inhibitors	2 (0)	10 (0)	NA	NA		
Past use (discontinuation						
between 2 months – 2 years), n						
(%)						
Conventional NSAIDs <sup>1</sup>	174 (17)	577 (14)	1.32 (1.08-1.62)	1.26 (1.01-1.58)		
Selective COX-2 inhibitors	20 (2)	74 (2)	1.19 (0.72-1.97)	1.15 (0.67-1.98)		
Past use (discontinuation >2						
years), n (%)						
Conventional NSAIDs <sup>1</sup>	354 (34)	1,369 (33)	1.13 (0.97-1.33)	0.97 (0.81-1.16)		
Calcati a COV 2 tabilities	26 (2)	90 (2)	1.27 (0.81-1.99)	0.98 (0.59-1.62)		
Selective COX-2 inhibitors	26 (3)	30 (2)	1.27 (0.01-1.99)	0.36 (0.33-1.02)		

Abbreviations: CI = confidence interval; COX-2 = cyclooxygenase-2; NA = non-applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds ratio

<sup>&</sup>lt;sup>1</sup>acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

<sup>&</sup>lt;sup>†</sup>adjusted for comorbidities, co-medications, body mass index, smoking, and alcohol abuse

Supplemental Table 4. Odds ratios of nephrotic syndrome for NSAID users stratified by sex

supplemental Table 4. Odds Tatlos of Rephrotic Syndronie for NSAID users stratified by sex					
Female	Cases	Controls	Crude OR	Adj. OR <sup>∓</sup>	
	(n = 1,432)	(n = 5,714)	(95% CI)	(95% CI)	
Nonuse, n (%)	639 (45)	2984 (52)	1	1	
Current use, n (%)					
Conventional NSAIDs <sup>1</sup>	33 (2)	130 (2)	1.19 (0.80-1.75)	1.15 (0.92-1.44)	
Selective COX-2 inhibitors	18 (0)	18 (0)	0.78 (0.23-2.65)	0.51 (0.27-0.97)	
Recent use, n (%)					
Conventional NSAIDs <sup>1</sup>	40 (3)	94 (2)	1.99 (1.36-2.91)	1.80 (1.17-2.79)	
Selective COX-2 inhibitors	2 (0)	2 (0)	NA	NA	
Past use (discontinuation					
between 2 months – 2 years),					
n (%)					
Conventional NSAIDs <sup>1</sup>	240 (17)	722 (13)	1.55 (1.31-1.84)	1.35 (1.11-1.63)	
Selective COX-2 inhibitors	54 (2)	54 (1)	2.08 (1.27-3.38)	1.91 (1.24-2.94)	
Past use (discontinuation >2					
years), n (%)					
Conventional NSAIDs <sup>1</sup>	433 (30)	1654 (29)	1.22 (1.07-1.40)	1.02 (0.87-1.20)	
Selective COX-2 inhibitors	56 (1)	56 (1)	1.58 (0.94-2.69)	0.98 (0.53-1.81)	
Male	Cases	Controls	Crude OR	Adj. OR <sup>∓</sup>	
Wate	(n = 1,188)	(n = 4,740)	(95% CI)	(95% CI)	
Nonuse, n (%)	479 (40)	2158 (46)	1	1	
Current use, n (%)					
Conventional NSAIDs <sup>1</sup>	41 (4)	134 (3)	1.38 (0.96-1.98)	1.07 (0.70-1.64)	
Selective COX-2 inhibitors	5 (0)	21 (0)	1.07 (0.40-2.86)	0.26 (0.06-1.15)	
Recent use, n (%)					
Conventional NSAIDs <sup>1</sup>	33 (3)	88 (2)	1.69 (1.12-2.55)	1.31 (0.79-2.18)	
Selective COX-2 inhibitors	3 (0)	13 (0)	NA	NA	
Past use (discontinuation					
between 2 months – 2 years),					
n (%)					
Conventional NSAIDs <sup>1</sup>	234 (20)	755 (16)	1.40 (1.17-1.67)	1.12 (0.91-1.39)	
Selective COX-2 inhibitors	13 (1)	45 (1)	1.30 (0.70-2.43)	0.52 (0.21-1.28)	
Past use (discontinuation >2					
years), n (%)					
		ı ————————————————————————————————————		0.00 (0.75 4.00)	
Conventional NSAIDs <sup>1</sup>	364 (31)	1449 (31)	1.13 (0.97-1.32)	0.90 (0.75-1.09)	
Conventional NSAIDs <sup>1</sup> Selective COX-2 inhibitors	364 (31) 16 (1)	1449 (31) 77 (2)	1.13 (0.97-1.32) 0.94 (0.54-1.62)	0.62 (0.33-1.17)	

Abbreviations: CI = confidence interval; COX-2 = cyclooxygenase-2; NA = non-applicable; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds ratio

<sup>&</sup>lt;sup>1</sup>acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

<sup>&</sup>lt;sup>†</sup>adjusted for comorbidities, co-medications, body mass index, smoking, and alcohol abuse

## **Supplemental Table 5.** Odds ratios of nephrotic syndrome defined by kidney biopsy for conventional NSAID¹ users

	Cases	Controls	Crude OR	Adj. OR <sup>∓</sup>
	(n = 279)	(n = 10,168)	(95% CI)	(95% CI)
Nonuse, n (%)	121 (43)	5142 (51)	1	1
Current use, n (%)	7 (3)	264 (3)	1.13 (0.52-2.44)	1.06 (0.47-2.37)
Recent use, n (%)	10 (4)	182 (2)	2.35 (1.21-4.51)	1.83 (0.89-3.80)
Past use (stopped between 2 months – 2 years), n (%)	49 (18)	1477 (15)	1.41 (1.01-1.98)	1.23 (0.85-1.78)
Past use (stopped >2 years), n (%)	92 (33)	3103 (31)	1.26 (0.96-1.66)	1.09 (0.80-1.49)

Abbreviations: CI = confidence interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds ratio

<sup>&</sup>lt;sup>1</sup>acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs <sup>‡</sup>adjusted for matching variables (age, sex, the general practitioner practice, and index-date), comorbidities, co-medications, body mass index, smoking, and alcohol abuse

**Supplemental Table 6.** Odds ratios of nephrotic syndrome for conventional NSAID users<sup>1</sup> 3 months before the index date

	Cases	Controls	Crude OR	Adjusted OR <sup>∓</sup>
	(n =2,536)	(n = 10,168)	(95% CI)	(95% CI)
Nonuse, n (%)	1147 (45)	5208 (51)	1	1
Current use <sup>¢</sup> , n (%)				
1-14 days	36 (1)	96 (1)	1.70 (1.15-2.51)	1.38 (0.89-2.13)
15-28 days	29 (1)	95 (1)	1.38 (0.91-2.11)	1.24 (0.79-1.97)
>28 days	26 (1)	66 (1)	1.79 (1.13-2.82)	1.77 (1.09-2.89)
Recent use, n (%)	71 (3)	177 (2)	1.82 (1.37-2.41)	1.78 (1.31-2.43)
Past use (discontinuation between >2 months – 2 years), n (%)	445 (18)	1504 (15)	1.34 (1.19-1.52)	1.19 (1.03-1.36)
Past use (discontinuation >2 years), n (%)	782 (31)	3022 (30)	1.17 (1.06-1.30)	1.03 (0.92-1.15)

Abbreviations: CI = confidence interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds ratio

<sup>&</sup>lt;sup>1</sup>acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

<sup>&</sup>lt;sup>ф</sup>duration of use

<sup>&</sup>lt;sup>†</sup>adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking behavior, and alcohol abuse

**Supplemental Table 7.** Odds ratios of nephrotic syndrome for conventional NSAID users<sup>1</sup> 6 months before the index date

	Cases (n =2,536)	Controls (n = 10,168)	Crude OR (95% CI)	Adjusted OR <sup>∓</sup> (95% CI)
Nonuse, n (%)	1179 (46)	5265 (52)	1	1
Current use <sup>¢</sup> , n (%)				
1-14 days	37 (2)	117 (1)	1.42 (0.98-2.07)	1.32 (1.31-1.34)
15-28 days	44 (2)	123 (1)	1.61 (1.13-2.28)	1.45 (1.00-2.12)
>28 days	23 (1)	47 (1)	2.20 (1.33-3.63)	2.03 (1.17-3.52)
Recent use, n (%)	48 (2)	193 (2)	1.09 (0.79-1.51)	0.89 (0.62-1.27)
Past use (discontinuation between >2 months – 2 years), n (%)	448 (18)	1487 (15)	1.35 (1.20-1.53)	1.22 (1.06-1.39)
Past use (discontinuation >2 years), n (%)	758 (30)	2936 (29)	1.16 (1.05-1.28)	1.03 (0.92-1.15)

Abbreviations: CI = confidence interval; COX-2 = cyclooxygenase-2; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds ratio

<sup>&</sup>lt;sup>1</sup>acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

<sup>&</sup>lt;sup>ф</sup>duration of use

<sup>&</sup>lt;sup>†</sup>adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking behavior, and alcohol abuse

**Supplemental Table 8.** Odds ratios of nephrotic syndrome for conventional NSAID users<sup>1</sup> 9 months before the index date

	Cases	Controls	Crude OR	Adjusted OR <sup>∓</sup>
	(n = 2,536)	(n = 10,168)	(95% CI)	(95% CI)
Nonuse, n (%)	1202 (47)	5323 (52)	1	1
Current use <sup>¢</sup> , n (%)				
1-14 days	35 (1)	128 (1)	1.22 (0.83-1.78)	1.16 (0.77-1.73)
15-28 days	53 (2)	113 (1)	2.09 (1.50-2.91)	2.13 (1.49-3.04)
>28 days	27 (1)	64 (1)	1.88 (1.19-2.96)	1.60 (0.97-2.62)
Recent use, n (%)	57 (2)	180 (2)	1.41 (1.04-1.91)	1.21 (0.87-1.68)
Past use (discontinuation between >2 months – 2 years), n (%)	426 (17)	1492 (15)	1.27 (1.12-1.44)	1.15 (1.00-1.31)
Past use (discontinuation >2 years), n (%)	736 (29)	2868 (28)	1.14 (1.03-1.27)	1.01 (0.90-1.14)

Abbreviations: CI = confidence interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds ratio

<sup>&</sup>lt;sup>1</sup>acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

<sup>&</sup>lt;sup>ф</sup>duration of use

<sup>&</sup>lt;sup>†</sup>adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking behavior, and alcohol abuse

**Supplemental Table 9.** Odds ratios of nephrotic syndrome for conventional NSAID users<sup>1</sup> 12 months before the index date

	Cases	Controls	Crude OR	Adjusted OR <sup>∓</sup>
	(n = 2,536)	(n = 10,168)	(95% CI)	(95% CI)
Nonuse, n (%)	1215 (48)	5413 (53)	1	1
Current use <sup>¢</sup> , n (%)				
1-14 days	46 (2)	116 (1)	1.77 (1.25-2.50)	1.56 (1.07-2.27)
15-28 days	31 (1)	116 (1)	1.19 (0.80-1.78)	1.14 (0.75-1.75)
>28 days	24 (1)	55 (1)	1.94 (1.20-3.15)	1.51 (0.89-2.56)
Recent use, n (%)	62 (2)	165 (2)	1.67 (1.24-2.26)	1.51 (1.09-2.08)
Past use (discontinuation between >2 months – 2 years), n (%)	428 (17)	1510 (15)	1.26 (1.12-1.43)	1.13 (0.99-1.29)
Past use (discontinuation >2 years), n (%)	730 (29)	2795 (27)	1.16 (1.05-1.29)	1.04 (0.93-1.16)

Abbreviations: CI = confidence interval; COX-2 = cyclooxygenase-2; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds ratio

<sup>&</sup>lt;sup>1</sup>acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

<sup>&</sup>lt;sup>ф</sup>duration of use

<sup>&</sup>lt;sup>†</sup>adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking behavior, and alcohol abuse

# **Supplemental Table 10.** Odds ratios of nephrotic syndrome for conventional NSAID users among those without comorbidities<sup>1</sup> that are well-known causes of nephrotic syndrome

	Cases (n = 1,785)	Controls (n = 9,373)	Crude OR (95% CI)	Adj. OR <sup>∓</sup> (95% CI)
Nonuse, n (%)	815 (46)	4859 (52)	1	1
Current use <sup>¢</sup> , n (%)				
1-14 days	18 (1)	91 (1)	1.18 (0.71-1.97)	0.91 (0.52-1.60)
15-28 days	23 (1)	99 (1)	1.39 (0.88-2.19)	1.41 (0.86-2.31)
>28 days	14 (1)	47 (1)	1.78 (0.97-3.24)	1.60 (0.83-3.10)
Recent use, n (%)	51 (3)	166 (2)	1.83 (1.33-2.53)	1.66 (1.16-2.39)
Past use (discontinuation between >2 months – 2 years), n (%)	331 (19)	1346 (14)	1.47 (1.27-1.69)	1.29 (1.10-1.51)
Past use (discontinuation >2 years), n (%)	533 (30)	2765 (30)	1.15 (1.02-1.29)	1.01 (0.88-1.16)

Abbreviations: Adj. = Adjusted; CI = confidence interval; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds ratio

<sup>&</sup>lt;sup>1</sup>diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, amyloidosis, and leukemia <sup>6</sup>duration of use

<sup>&</sup>lt;sup>‡</sup>adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities associated with kidney toxicity, co-medications, body mass index, smoking, and alcohol abuse

## **Supplemental Table 11.** Odds ratios of hospitalized patients with nephrotic syndrome for conventional NSAID¹ users

	Cases (n = 680)	Controls (n = 10,168)	Crude OR (95% CI)	Adj. OR <sup>∓</sup> (95% CI)
Nonuse, n (%)	276 (41)	5142 (51)	1	1
Current use <sup>¢</sup> , n (%)				
1-14 days	6 (1)	104 (1)	1.08 (0.47-2.47)	0.83 (0.35-1.97)
15-28 days	9 (1)	104 (1)	1.61 (0.81-3.22)	1.61 (0.78-3.32)
>28 days	6 (1)	56 (1)	2.00 (0.85-4.67)	1.53 (0.59-3.95)
Recent use, n (%)	19 (3)	182 (2)	1.95 (1.19-3.17)	1.52 (0.89-2.59)
Past use (discontinuation between >2 months – 2 years), n (%)	130 (19)	1477 (15)	1.64 (1.32-2.04)	1.27 (1.00-1.61)
Past use (discontinuation >2 years), n (%)	234 (34)	3103 (31)	1.41 (1.17-1.68)	1.06 (0.87-1.30)

Abbreviations: CI = confidence interval; COX-2 = cyclooxygenase-2; NSAIDs = Non-Steroidal Anti-Inflammatory Drugs; OR = Odds ratio

<sup>&</sup>lt;sup>1</sup>acetic acid derivatives, propionic acid derivatives, fenamates, oxicams, and other NSAIDs

<sup>&</sup>lt;sup>ф</sup>duration of use

<sup>&</sup>lt;sup>†</sup>adjusted for matching variables (age, sex, general practitioners' practice, and the index date), comorbidities, co-medications, body mass index, smoking, and alcohol abuse