

Supplementary material to “**Statin use and chronic lymphocytic leukemia incidence: A nested case-control study in Manitoba, Canada**” by Christiaan H. Righolt, Geng Zhang, Xibiao Ye, James B. Johnston, Versha Banerji, Spencer Gibson, and Salaheddin M. Mahmud.

Supplementary tables

Supplemental table 1. Statin information

ATC code	Name	DDD ^a	Year available	Potency	Lipophilic
C10AA01	Simvastatin	30 mg	1991	High	Yes
C10AA02	Lovastatin	45 mg	1989	Low	Yes
C10AA03	Pravastatin	30 mg	1991	Med	No
C10AA04	Fluvastatin	60 mg	1994	Low	Yes ^b
C10AA05	Atorvastatin	20 mg	1997	High	Yes
C10AA06	Cerivastatin ^c	0.2 mg	1998	High	Yes
C10AA07	Rosuvastatin	10 mg	2003	High	No
C10AA08	Pitavastatin ^d	2 mg	~2004	High	Yes

a: DDD = defined daily dose. b: Fluvastatin has intermediate physicochemical characteristics.¹ Although some authors classify it as hydrophilic,² most classify it as lipophilic.^{3,4} c: Cerivastatin was withdrawn from market in 2001 due to side effects. d: Pitavastatin was not prescribed in Manitoba during this study.

Supplemental table 2. Anatomical therapeutic chemical (ATC) codes used to identify other prescribed drugs.

Drug category	ATC codes
Non-statin lipid-lowering drugs	C10AB, C10AC, C10AD, C10AX
Metformin	A10BA02
Insulins	A10A
Other oral hypoglycemic drugs	A10BA01, A10BA03, A10BB, A10BC, A10BF, A10BG, A10BH, A10BX, A10X
Aspirin	N02BA01
Non-aspirin NSAIDs	M01, N02BA02-N02BA16, N02BA51, N02BA55, N02BA57, N02BA59, N02BA65, N02BA71, N01A75, N02BA77, N02BA79
Any NSAIDs	M01A, N02BA

Supplemental table 3. International classification of diseases (ICD) codes used to identify^a comorbidities.

Disease	ICD-9 codes	ICD-10 codes
Diabetes ^b	250	E10-E14, O24, G590, G632, H280, H360, M142, M146, N083
Chronic cardiovascular disease (excluding hypertension)	39, 41-45	I0, I2-I5, I60-I66, I670-I673, I675-I679, I68-I69, I7-I9
Ischemic heart diseases	410-414	I20-I25
Stroke	431-434, 438	I61-I64, I69

a: One hospitalization or two physician visits are required to identify a comorbidity. b: Diabetes is also identified by prescription drug use with Anatomical Therapeutic Chemical Classification System codes for drugs used in diabetes (A10).

Supplemental table 4: Number (%) of statin users among CLL cases and their matched controls by ever-use of statin subgroups according to certain socio-economic and clinical characteristics

	Never-use (N=5,937)	Hydrophilic (N=722)	High-potency lipophilic (N=1,790)	Low-potency lipophilic (N=327)
CLL	1,014 (17.1%)	131 (18.1%)	290 (16.2%)	40 (12.2%)
Male	3,471 (58.5%)	471 (65.2%)	1,149 (64.2%)	185 (56.6%)
Age group				
40 - 54	794 (13.4%)	26 (3.6%)	73 (4.1%)	8 (2.4%)
55 - 64	1,486 (25.0%)	162 (22.4%)	350 (19.6%)	45 (13.8%)
65 - 74	1,623 (27.3%)	254 (35.2%)	624 (34.9%)	110 (33.6%)
75+	2,034 (34.3%)	280 (38.8%)	743 (41.5%)	164 (50.2%)
In top 60% of household income distribution	3,349 (56.4%)	401 (55.5%)	976 (54.5%)	171 (52.3%)
Rural residence	2,139 (36.0%)	271 (37.5%)	685 (38.3%)	109 (33.3%)
Comorbidities				
Diabetes	736 (12.4%)	206 (28.5%)	597 (33.4%)	95 (29.1%)
Chronic cardiovascular disease (excluding hypertension)	1,971 (33.2%)	411 (56.9%)	1,050 (58.7%)	222 (67.9%)
Ischemic heart diseases	657 (11.1%)	285 (39.5%)	716 (40.0%)	159 (48.6%)
Stroke	112 (1.9%)	35 (4.8%)	100 (5.6%)	16 (4.9%)
Ever-use of prescription drugs				
Non-statin lipid-lowering drugs	141 (2.4%)	153 (21.2%)	363 (20.3%)	71 (21.7%)
Metformin	331 (5.6%)	146 (20.2%)	398 (22.2%)	50 (15.3%)
Insulins	79 (1.3%)	39 (5.4%)	99 (5.5%)	17 (5.2%)

Other oral hypoglycemic drugs	331 (5.6%)	112 (15.5%)	323 (18.0%)	52 (15.9%)
Aspirin	717 (12.1%)	289 (40.0%)	757 (42.3%)	124 (37.9%)
Non-aspirin NSAID	3,521 (59.3%)	550 (76.2%)	1,317 (73.6%)	232 (70.9%)
Any NSAID	3,741 (63.0%)	609 (84.3%)	1,495 (83.5%)	263 (80.4%)
No. of physician visits in the 5-year period before index date				
0 - 19	1,622 (27.3%)	33 (4.6%)	103 (5.8%)	19 (5.8%)
20 - 39	1,786 (30.1%)	200 (27.7%)	467 (26.1%)	75 (22.9%)
40 - 64	1,302 (21.9%)	228 (31.6%)	578 (32.3%)	110 (33.6%)
65+	1,227 (20.7%)	261 (36.1%)	642 (35.9%)	123 (37.6%)

Supplemental table 5. Adjusted^a odds ratios (95% confidence interval) of the association between CLL diagnosis and statin use, excluding the year before the index date, by individual statins according to period, duration and dose.

Statin use	Simvastatin	Lovastatin	Pravastatin	Fluvastatin	Atorvastatin	Rosuvastatin
Time of first use (years prior to the index date) ^b						
2-5	1.25 (0.88-1.79)	0.77 (0.26-2.27)	0.88 (0.50-1.55)	0.55 (0.19-1.60)	0.88 (0.70-1.12)	1.08 (0.77-1.51)
6-10	0.89 (0.63-1.27)	0.66 (0.32-1.34)	1.06 (0.66-1.70)	0.86 (0.33-2.26)	0.99 (0.75-1.30)	0.90 (0.53-1.52)
11+	0.88 (0.57-1.37)	0.63 (0.34-1.17)	1.38 (0.87-2.20)	0.63 (0.24-1.65)	1.09 (0.73-1.64)	1.20 (0.13-10.95)
Relative duration (fraction of drug history) ^b						
1 - 25%	0.95 (0.70-1.28)	0.79 (0.44-1.43)	0.97 (0.66-1.43)	0.74 (0.37-1.46)	0.94 (0.76-1.17)	1.07 (0.78-1.47)
26 - 50%	1.10 (0.71-1.71)	0.72 (0.25-2.09)	1.21 (0.65-2.26)	0.24 (0.03-1.84)	0.82 (0.59-1.15)	1.02 (0.49-2.13)
51 - 75%	0.74 (0.38-1.47)	0.47 (0.14-1.55)	1.48 (0.77-2.86)	1.50 (0.40-5.66)	1.35 (0.87-2.09)	N/A
>= 76%	1.52 (0.80-2.89)	0.53 (0.19-1.50)	1.10 (0.37-3.28)	N/A	N/A	N/A
Continuous use ^b						
< 12 months	1.01 (0.77-1.32)	0.73 (0.43-1.22)	1.10 (0.77-1.57)	0.66 (0.35-1.27)	0.98 (0.79-1.21)	0.91 (0.65-1.29)
>= 12 months	0.98 (0.66-1.45)	0.57 (0.27-1.20)	1.11 (0.69-1.80)	0.74 (0.21-2.52)	0.89 (0.67-1.18)	1.51 (0.90-2.54)
Duration (months) ^b						
1 - 6	0.86 (0.55-1.34)	0.55 (0.16-1.86)	1.03 (0.58-1.83)	0.51 (0.18-1.47)	1.09 (0.80-1.49)	0.78 (0.45-1.38)
7 - 24	1.14 (0.74-1.74)	0.81 (0.38-1.73)	1.09 (0.65-1.84)	0.92 (0.35-2.44)	0.74 (0.53-1.03)	1.07 (0.68-1.68)
25 - 48	1.22 (0.77-1.95)	0.59 (0.23-1.50)	0.93 (0.45-1.94)	0.54 (0.12-2.42)	0.99 (0.71-1.39)	1.19 (0.67-2.14)
>= 49	0.93 (0.63-1.39)	0.69 (0.34-1.40)	1.34 (0.81-2.20)	0.78 (0.23-2.68)	1.01 (0.73-1.38)	1.49 (0.74-2.98)
Cumulative dose (DDD) ^b						

1 - 120	0.81 (0.52-1.27)	0.82 (0.34-2.00)	1.08 (0.56-2.06)	0.89 (0.41-1.95)	0.98 (0.71-1.35)	0.78 (0.42-1.47)
121 - 480	1.30 (0.87-1.93)	0.62 (0.28-1.38)	0.94 (0.52-1.69)	0.59 (0.18-2.00)	0.96 (0.70-1.31)	0.79 (0.44-1.41)
481 - 1200	0.99 (0.61-1.62)	1.09 (0.50-2.37)	1.19 (0.64-2.22)	0.21 (0.03-1.56)	0.89 (0.63-1.25)	1.42 (0.88-2.30)
>= 1201	0.96 (0.63-1.45)	0.37 (0.13-1.02)	1.16 (0.73-1.84)	1.07 (0.23-5.01)	0.93 (0.67-1.28)	1.26 (0.72-2.20)
Average annual dose (DDD/year) ^b						
1 - 180	0.93 (0.62-1.40)	0.77 (0.46-1.31)	2.30 (0.68-7.73)	0.78 (0.36-1.69)	1.32 (0.67-2.60)	N/A
181 - 365	1.10 (0.80-1.53)	0.51 (0.20-1.28)	1.45 (0.85-2.46)	0.47 (0.19-1.20)	0.91 (0.73-1.14)	1.48 (0.76-2.88)
>= 366	0.97 (0.64-1.45)	0.65 (0.19-2.20)	0.96 (0.67-1.37)	N/A	0.95 (0.72-1.26)	0.99 (0.72-1.36)

a: Adjusted for the matching variables (age, gender, residence and duration of coverage), chronic cardiovascular disease (excluding hypertension), income quintiles and number of physician visits 5 years before index date, non-statin lipid-lowering drugs, non-aspirin NSAIDs, aspirin and derivatives, and other individual statins. b: Compared to never use of the specific statin.

Supplemental table 6: Odds ratio (95% confidence interval) of the association between CLL incidence and ever-use of statins, excluding the year before the index date, by potential effect modifiers

	Model A^a (CI 95%)	Model B^b (CI 95%)
Overall	0.9 (0.8-1.1)	0.9 (0.8-1.0)
Chronic cardiovascular disease (excluding hypertension)		
No	1.0 (0.8-1.2)	1.0 (0.8-1.2)
Yes	0.8 (0.7-1.1)	0.8 (0.6-1.1)
p for interaction	0.397	0.614
Top 60% of income		
No	1.0 (0.8-1.3)	1.0 (0.7-1.3)
Yes	0.8 (0.7-1.0)	0.8 (0.6-0.9)
p for interaction	0.083	0.079
Number of physician visits 5 years before index date		
0 - 19	1.0 (0.5-2.1)	1.0 (0.5-2.3)
20 - 39	0.9 (0.6-1.3)	0.9 (0.6-1.4)
40 - 64	1.1 (0.8-1.5)	1.1 (0.7-1.5)
≥ 65	0.9 (0.6-1.3)	0.8 (0.6-1.2)
p for interaction	0.920	0.940
Non-statin lipid-lowering drugs		
No	0.9 (0.8-1.1)	0.9 (0.8-1.1)
Yes	1.4 (0.3-6.0)	2.8 (0.4-20.0)
p for interaction	0.983	0.990
Aspirin		
No	1.0 (0.8-1.2)	0.9 (0.8-1.1)
Yes	0.9 (0.6-1.5)	0.9 (0.6-1.5)
p for interaction	0.922	0.968
Non-aspirin NSAIDs		
No	1.0 (0.7-1.4)	0.9 (0.6-1.3)
Yes	1.0 (0.8-1.1)	0.9 (0.7-1.1)
p for interaction	0.490	0.554

a: Model A includes the matching variables (age, gender, residence and duration of coverage). b: Model B includes the matching variables and the covariates listed in the table

References

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