

1 ***Statin use and chronic lymphocytic leukemia incidence: A nested case-control study in Manitoba,***  
2 ***Canada***

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28 advisory boards for Gilead, Janssen, and Abbvie Pharmaceuticals. VB received consulting fees from  
29 Astra Zeneca.

30 **Abbreviations:**

31 ATC: Anatomical Therapeutic Chemical

32 BCL2: B cell lymphoma-2

33 CI: Confidence interval

34 CLL: chronic lymphocytic leukemia

35 DDD: Defined daily dose

36 DPIN: Drug Program Information Network

37 HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme

38 ICD-O-3: the third edition of the International Classification of Diseases for Oncology

39 MBL: monoclonal B lymphocytosis

40 MCR: Manitoba Cancer Registry

41 MH: Manitoba Health

42 MPR: Manitoba Population Registry  
43 MVA: mevalonate  
44 NSAIDs: Nonsteroidal anti-inflammatory drugs  
45 NHL: Non-Hodgkin lymphoma  
46 OR: Odds ratio  
47 PHIN: personal health identification number  
48 SLL: small lymphocytic lymphoma  
49 WHO: World Health Organization  
50

51 **Abstract**

52 Background: Recent studies have reported reduced risk of chronic lymphocytic leukemia (CLL) among  
53 statin users. However, the possibility that the effect of statins may differ by their chemical or  
54 pharmacodynamic properties has not been investigated.

55 Methods: In this nested case-control study, all Manitobans aged  $\geq 40$  years when diagnosed with CLL  
56 (as a first cancer) from 1999 to 2014 (n=1,385) were matched (on gender, age, residence, and duration of  
57 insurance coverage) to cancer-free controls (n=6,841). Using conditional logistic regression, statin use  
58 was analyzed by individual statins and groups: hydrophilic, low-potency lipophilic (fluvastatin and  
59 lovastatin) and high-potency lipophilic statins.

60 Results: Statin users constituted 27% and 28% of the CLL cases and controls. After adjusting for  
61 potential confounding by indication, patterns of healthcare utilization and use of other drugs, CLL  
62 incidence was not associated with use of hydrophilic (odds ratio: 1.08; 95% confidence interval: 0.86-  
63 1.34) or high-potency lipophilic statins (0.94; 0.79-1.11). Low-potency lipophilic statins were associated  
64 with a lower risk of CLL (0.64; 0.45-0.92), with stronger association (0.44; 0.22-0.88) observed with  
65 more regular use (half to full standard dose on average).

66 Conclusions: We found an association between low-potency lipophilic statin use and reduced CLL risk,  
67 with a possible dose-response effect.

68 Impact: While requiring replication in future studies, our findings suggest that the effect of statins on  
69 CLL risk may depend on their specific chemical or pharmacodynamic properties.

70

71 **Introduction**

72 Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the western world, with the  
73 incidence increasing as the population ages. In Canada, 2,465 new CLL cases were reported in 2013 with  
74 90 cases from the province of Manitoba (1). The incidence rate of CLL in Canada per 100,000 population  
75 has increased steadily from 4.2 in 1992 to 6.6 in 2010 (1). The etiology of CLL remains poorly  
76 understood, although certain chemicals, infections, blood transfusions, organ transplantation, and  
77 variations in certain loci have been associated with increased CLL risk (2, 3).

78 Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors,  
79 block the mevalonate (MVA) pathway and are widely prescribed for the prevention and management of  
80 cardiovascular disease. Both *in vitro* and *in vivo* studies have shown that statins have a direct anti-tumor  
81 effect through blocking of the MVA pathway in various tumor types (4, 5). Statins have been shown to  
82 induce apoptosis in B-CLL cells (6) and lower expression of low density lipoprotein receptor activity in  
83 CLL patients (7). Statin use has also been associated with a reduced risk of various cancer types in  
84 numerous observational studies and meta-analyses (8-12).

85 The results of studies of statin use and the risk of non-Hodgkin lymphoma (NHL), a heterogeneous  
86 group of cancers of the immune system that includes CLL, are mixed, with some studies identifying a  
87 risk reduction and others detecting no association (10-15). Thus, it is possible that the effects of statins  
88 depend on the subtype of NHL studied. A small (~15% reduction) non-statistically significant  
89 association between statin use and CLL risk has been found in two previous studies (16, 17). These  
90 studies were, however, limited by small sample size: 410 CLL cases including 22 statin users (16) and  
91 326 cases including 114 users (17). They were further limited by reliance on questionnaires for  
92 measuring statin use; by lack of information about dose, duration and timing of use; and by grouping all  
93 statins regardless of their chemical or pharmacokinetic properties. We recently studied the effects of  
94 statins, as a class, on the incidence of several NHL subtypes, including CLL, and estimated an odds  
95 ratio(OR) of 0.89 (95% confidence interval [CI] 0.77–1.04) for CLL (18). In this paper, we report on the

96 association between CLL and use of several commonly used statins with different chemical structures,  
97 pharmacodynamics and lipid-lowering effects.

## 98 **Methods**

99 We conducted a population-based nested case-control study using the cancer registry and health service  
100 administrative databases of Manitoba.

### 101 Data sources

102 Manitoba Health (MH) is the publicly funded health insurance agency providing comprehensive health  
103 insurance, including coverage for hospital and outpatient physician services, to the province's 1.3 million  
104 residents. Coverage is universal, with no eligibility distinction based on age or income, and participation  
105 rates are very high (>99%) (19). Insured services include hospital, physician and preventive services  
106 including vaccinations. MH maintains several centralized, administrative electronic databases that are  
107 linkable using a unique personal health identification number (PHIN). The completeness and accuracy  
108 of MH administrative databases are well established (20, 21). These databases have been used  
109 extensively in studies of cancer epidemiology and post-marketing evaluation of various vaccines and  
110 drugs.

111 CancerCare Manitoba maintains one of the oldest population-based cancer registries in the world  
112 (Manitoba Cancer Registry [MCR], in operation since 1956). Reporting of cancer cases is mandated by  
113 provincial regulations and required for payment of physicians' service claims. The MCR is regularly  
114 audited by the North American Association of Central Cancer Registries. The quality of cancer  
115 registration has been consistently very high (21). Most cases are pathologically-confirmed (94% for  
116 cases registered between 2003 and 2007) and less than 2% of registrations originate from death  
117 certificates (21).

118 The MH Population Registry (MHPR) tracks addresses and insurance status (including end of coverage  
119 due to death or emigration) for all insured persons. Since 1971, the Hospital Abstracts database

120 recorded virtually all services provided by hospitals in the province, including admissions and day  
121 surgeries (20). The data collected comprise demographic as well as diagnosis and treatment information  
122 including primary diagnosis and service or procedure codes, coded using the International Classification  
123 of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) before April 2004, and the ICD-10-CA  
124 (Canadian adaptation of the ICD-10) and the Canadian Classification of Health Interventions (CCI)  
125 afterwards. The Medical Services database, also in operation since 1971, collects similar information on  
126 services provided by physicians in offices, hospitals and outpatient departments across the province (20).  
127 The Drug Program Information Network (DPIN), in operation since 1995, records all prescription  
128 drugs dispensed to Manitoba residents, including most personal care home residents (22). The DPIN  
129 database captures data from pharmacy claims for formulary drugs dispensed to all Manitobans even  
130 those without prescription drug coverage. However, prescriptions dispensed to Registered First  
131 Nations, who receive their prescription benefits from the federal government, tend to be under-reported  
132 by up to 20% (22). Because information is submitted electronically at the “point-of-sale”, the accuracy of  
133 the recorded prescription information is excellent (22).

134 This study was approved by the University of Manitoba Research Ethics Board and by MH’s Health  
135 Information Privacy Committee.

#### 136 Source cohort

137 We used the MHPR to assemble a cohort comprised of all adults aged 40 years or older (statins are  
138 rarely prescribed for younger people) who were registered with MH between 1999 and 2014. Cohort  
139 members were followed from the latest of the study start date (January 1, 1999), their 40th birthday or  
140 the date of immigration to Manitoba until the study end date (December 31, 2014), or the date of  
141 diagnosis of CLL, death or emigration, whichever occurred first.

#### 142 Definition of cases and controls

143 To be eligible for inclusion in the nested case-control analysis, a participant must have been: (1) free of  
144 cancer (except non-melanoma skin cancer) before the *index date*, defined as the date of diagnosis for a  
145 case or the matching date for a control, and (2) be covered by MH for a minimum of 5 years prior to the  
146 index date (to ensure that all participants had a reasonable opportunity to fill statin prescriptions before  
147 the index date).

148 Cases, identified by linking with the MCR, were members of the source cohort diagnosed with a  
149 pathologically-confirmed CLL (ICD-O-3 histology codes 9670 and 9823) (23). We also included small  
150 lymphocytic lymphoma (SLL) in the cases group, because SLL has similar clinical and pathological  
151 characteristics to CLL (24). Using incidence density sampling (25), we matched each case to up to five  
152 controls on birth date ( $\pm 1$  year), region of residence (one of five health regions with populations  $\geq 40$   
153 between 25,000 and 375,000) and length of coverage with insurance before the *index date* (to ensure a  
154 comparable length of residence in the province).

#### 155 Measurement of prescription drug use

156 For each participant, detailed histories of dispensed statins and other drug classes were obtained from  
157 the DPIN for the period between January 1, 1995, or the coverage initiation date if it was later, and the  
158 index date. The length of these histories was  $\geq 10$  years in 59% of participants (median 11.4 years,  
159 interquartile range 7.7–15.2 years). The WHO Anatomic Therapeutic Chemical (ATC)  
160 classification was used to classify drugs, e.g., statins were defined as all drugs in the Manitoba drug  
161 formulary with ATC codes C10AA (Supplementary Table 1-2). Statins were further classified, a priori,  
162 according to their potency and lipophilicity, into hydrophilic (pravastatin and rosuvastatin), high-  
163 potency (simvastatin and atorvastatin) and low-potency (lovastatin and fluvastatin) statins.

164 Exposure to individual and grouped statins (henceforth the index class) was characterized in two ways:  
165 (1) As a binary (“ever-use”) variable indicating whether a participant ever filled a prescription of any  
166 drug in the index class at any point before the index date, and (2) as continuous and ordinal variable

167 representations of the average annual dose of the index class calculated by dividing the total dispensed  
168 quantity of the class by its overall duration of use (measured from the dispensing date of the first  
169 prescription that included a drug in that class). All drug use in the year immediately prior to the index  
170 date was excluded to avoid protopathic bias (26). Because different drugs in the same class may have  
171 different pharmacologic potency, the total dispensed quantity for each drug was expressed as a  
172 proportion of the WHO's defined daily dose (DDD) for that drug before summing up all these  
173 proportions as the total dispensed quantity of the class (see Supplementary Table 1 for list of DDDs).  
174 The DDD is "the assumed average maintenance dose per day for a drug used for its main indication in  
175 adults" (27).

#### 176 Covariates

177 We identified ischemic and other chronic cardiovascular diseases and diabetes (indications or proxies for  
178 indications for statin use) from the hospital abstracts and medical services databases, using previously  
179 validated algorithms (Supplementary Table 3). We also measured the number of physician visits within  
180 the 5-year period before the index date as a proxy for propensity to access healthcare services.  
181 Neighborhood average household income quintiles, which are correlated with self-reported household  
182 incomes, were determined based on place of residence and 2011 Canadian census data (28, 29).

#### 183 Statistical analysis

184 We used conditional (to account for individual matching) logistic regression (CLR) models to calculate  
185 ORs and 95% CIs of the association between statin use and CLL diagnosis. Selection of covariates for  
186 the final models was driven by a causal diagram analysis (30) and an empirical search for confounders: a  
187 variable was considered a confounder if its inclusion in adjusted models resulted in a >10% change in  
188 OR estimates of the main exposure. The final model was adjusted for history of chronic cardiovascular  
189 disease, ever-use of non-statin lipid-lowering drugs, aspirin, non-aspirin NSAIDs, household income,  
190 and number of physician visits in the 5-year period before the index date. To test for effect modification,



191 we stratified our analysis by each confounder and used likelihood-ratio tests to assess the statistical  
192 significance of the interaction terms. When appropriate, models also included mutual adjustment for  
193 statin groups and individual statins.

194 Given the long exposure histories in this cohort, participants had highly variable statin use histories. To  
195 reduce the effect of this heterogeneity, and to assess the presence of an “induction period” for statin  
196 effects (the time interval between an exposure exerting its causal effects and disease initiation or  
197 prevention (31)), we repeated all analyses after dividing the exposure history into 3 successive periods:  
198 2–5, 6–10, and 11+ years before the index date. A separate exposure index was computed for each  
199 period by limiting exposure measurements to prescriptions dispensed during that period (32). As before,  
200 CLR models were used to estimate ORs associated with drug use in each period with mutual  
201 adjustment for exposure in other periods. We used SAS 9.4 (SAS Institute, Cary, North Carolina) and  
202 Stata 14 (Stata Corp. LLC., College Station, Texas) for all analyses.

## 203 **Results**

204 We included 1,385 CLL patients, matched to 6,841 cancer-free controls (Table 1). Most patients were  
205 male (60%) and older than 65 (65%), but CLL incidence seemed unrelated to income. CLL patients had a  
206 slightly higher prevalence, at diagnosis, of chronic cardiovascular disease than controls (42% vs 40%)  
207 and more physician visits in the 5-year period before the index date.

208 About 27% of cases and 28% of controls received at least one statin prescription prior to the index date,  
209 mostly atorvastatin (~16%). A similar percentage of cases and controls received hydrophilic and high-  
210 potency lipophilic statins (Table 1). There were only minor differences in the relative duration of use or  
211 the average dose between cases and controls. The dose was the typical dose for hydrophilic statins  
212 (median use of 365 DDD/year) but lower than the typical dose for high-potency lipophilic (243  
213 DDD/year) and low-potency lipophilic statins (162 DDD/year) (Table 2). Low-potency lipophilic statin  
214 users were typically older (50% were 75+ compared to 42% for high-potency lipophilic statin users) and

215 more likely to have chronic cardiovascular disease (68% versus 57%-59% for users of other statins and  
216 33% for never-users) (Supplementary Table 4).

217 After adjusting for several variables, including cardiovascular disease, propensity to use healthcare, and  
218 use of non-statin lipid-lowering drugs, aspirin and other NSAIDs (Table 3), ever-use of any statin was  
219 associated with small non-statistically significant reduced risk of CLL (OR = 0.89; 95% CI 0.76-1.04).  
220 When grouped by lipophilicity and potency, only use of low-potency lipophilic statins (lovastatin and  
221 fluvastatin) was associated with reduced risk, 0.64 (0.45-0.92). Neither high-potency lipophilic statins  
222 (0.94; 0.79-1.11) nor hydrophilic statins (1.08; 0.86-1.34) were associated with CLL risk. The analysis  
223 lacked power to detect a statistically significant association of individual statins use and CLL. However,  
224 the effects of individual low-potency statins, fluvastatin (0.71; 0.40-1.26) and lovastatin (0.66; 0.43-1.02),  
225 were consistent with their group effect.

226 More regular use (181–365 DDDs/year) of low-potency lipophilic statins was associated with a  
227 clinically and statistically significant reduction in CLL risk (0.44; 0.22-0.88) (Table 4). Both higher  
228 cumulative dose ( $\geq 1201$  DDDs) and longer relative duration of use ( $\geq 76\%$  of the time) of low-potency  
229 lipophilic statins were associated with greater risk reduction, possibly suggesting a dose- and duration-  
230 response effect. Individual low-potency statins displayed similar trends (Supplementary Table 5),  
231 although the estimates were not precise. Generally, there were no clear dose or duration-response  
232 trends for use of other statins. None of the variables we adjusted for in our analysis was an effect  
233 modifier (Supplementary Table 6).

## 234 **Discussion**

235 In an a priori hypothesis-driven analysis, we found that use of low-potency lipophilic statins was  
236 associated with lower CLL risk, OR=0.64 (0.45-0.92), with some indication of a dose-response effect.  
237 We did not detect a similar association with the use of either high-potency lipophilic statins or  
238 hydrophilic statins.

239 The association between statin use and CLL risk has been studied before. Employing questionnaires to  
240 measure statin use, a study conducted in 6 European nations (including 410 CLL patients) reported an  
241 OR of 0.83 (0.51-1.34) for all statins combined (16). A prospective US cohort study found, based on  
242 biannual questionnaires, that cholesterol-lowering drugs (93% of which were statins) had a risk ratio of  
243 1.01 (0.59-1.74) for former users, and 0.91 (0.66-1.27) and 0.85 (0.58-1.23) for current users for less and  
244 more than five years of use, respectively (17). The number of CLL patients in this study was relatively  
245 small (326) with only 50 recent statin users and 49 long-term users) (17). Our estimates for statin use as  
246 a class (OR=0.89; 0.76-1.04) are in line with these results, despite differences in study design and data  
247 sources.

248 To the best of our knowledge, this is the first study to examine the association between low-potency  
249 lipophilic statins and CLL incidence (the analyses in the abovementioned studies were limited to  
250 studying the effects of statins as a class). Pharmacokinetic differences between lipophilic and hydrophilic  
251 statins may explain the differences in their association with CLL risk. The water solubility of statins  
252 affects their absorption and distribution in tissue (33, 34). Hydrophilic statins cannot easily penetrate  
253 cell plasma membranes through passive transport and their distribution is more hepatoselective (4, 35).  
254 However, this does not explain differences we observed between low-potency and high-potency  
255 lipophilic statins. The indications for individual statins are overlapping and clinical guidelines do not  
256 recommend certain types over others (36, 37), even though high-potency statins are prescribed when a  
257 larger reduction of low-density lipoprotein cholesterol (LDL-C) levels is desired (38). There is no clear  
258 connection between the type of statin and its effect on the MVA pathway in CLL cells. But this remains  
259 unexamined area as most animal and laboratory studies are often limited to studying a particular statin  
260 (39).

261 Simvastatin has shown cytotoxicity against cultured B-CLL cells with higher levels of apoptosis with  
262 increased dosage (6). Fluvastatin showed higher cytotoxicity against lymphoma cells than atorvastatin  
263 and simvastatin (39). The statins have been shown to down-regulate the anti-apoptotic protein BCL2 in

264 some leukemias (40), and the complete remission rate in CLL is increased when simvastatin is combined  
265 with venetoclax, another agent that selectively reduces BCL2 levels in CLL cells (41, 42). Elevated LDL  
266 levels in CLL cells may decrease apoptosis of CLL cells; this was not observed for acute leukemia cells  
267 or normal lymphocytes (43).

#### 268 Strengths and limitations

269 A major strength of this study is the availability of high-quality, population-based health administrative  
270 databases in Manitoba. The completeness and accuracy of the MCR and MH databases are well  
271 established (20, 21). We had a relatively large number of cases compared to other CLL studies, but some  
272 of our estimates were imprecise due to infrequent use of certain statins (especially low-potency lipophilic  
273 statins). Reporting of cancer cases to the MCR is mandated by provincial law (44). The MCR currently  
274 obtains data for all persons diagnosed with CLL cells using flow cytometry (but excludes cases with  
275 monoclonal B lymphocytosis). CLL incidence was underreported before reporting of flow cytometry  
276 became a standard practice (45). It is possible that some diagnosed cases during that time were not  
277 included in the MCR, this misclassification was likely non-differential with respect to statin use.

278 A limitation of this study is that the DPIN database started in 1995. Statins prescribed before that time  
279 could not be identified. Statins were not, however, frequently prescribed before 1995 (46, 47) and have  
280 only been available since around 1990 (Supplementary Table 1). Also, any resulting misclassification is  
281 likely non-differential with regard to the outcome (CLL diagnosis) as it excludes all exposure  
282 information before 1995. Although we adjusted our analysis for several confounding factors, we could  
283 not adjust for undiagnosed chronic cardiovascular disease. We also lacked information on aspirin use  
284 unless it was prescribed which is the likely the case for regular users. As a result, we cannot rule out  
285 residual confounding. We did not have information on some potential confounders, such as smoking,  
286 alcohol use and environmental exposures, albeit the literature suggests this does not cause significant  
287 confounding (2).

288 While dyslipidemia has been associated with the development of CLL (48), the effect of severity of  
289 dyslipidemia has not been studied. Our study is limited by a lack of data on cytokine and lipid levels; we  
290 could not stratify our analysis by severity of dyslipidemia. The low-potency statin users in our study  
291 used a relatively low dose of statins and were generally older and more likely to have chronic  
292 cardiovascular disease and other comorbidities. Confounding by indication may have biased our results  
293 if risk factors for CLL influenced statin prescriptions.

294 In summary, our results suggest that use of low-potency lipophilic statins might be associated with a  
295 lower risk of CLL, possibly in a dose-dependent manner. Even though a causal relationship cannot be  
296 proven, a 35% reduction in CLL risk is a promising, clinically relevant result that warrants further  
297 investigation into the effects of low-potency lipophilic statins on CLL risk.

298

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303 **Conflicts of Interest**

304 SMM has received unrestricted research grants from Merck, GlaxoSmithKline, Sanofi Pasteur, Pfizer  
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306 Lundbeck, Gilead and Janssen Pharmaceuticals for unrelated projects and sit on advisory boards for  
307 Gilead, Janssen, and Abbvie Pharmaceuticals. VB received consulting fees from Astra Zeneca.

308 **Data sharing**

309 Data used in this article was derived from administrative health and social data as a secondary use. The  
310 data was provided under specific data sharing agreements only for approved use at Manitoba Centre for  
311 Health Policy (MCHP). The original source data is not owned by the researchers or MCHP and as such  
312 cannot be provided to a public repository. The original data source and approval for use has been noted  
313 in the acknowledgments of the article. Where necessary, source data specific to this article or project  
314 may be reviewed at MCHP with the consent of the original data providers, along with the required  
315 privacy and ethical review bodies.

316 **Authors' contribution**

317 XY and SMM designed and supervised the study, GZ and CHR analyzed the data, CHR, GZ, and SMM  
318 wrote the manuscript, all other authors contributed to interpretation of the results and draft revisions.  
319 All authors critically revised the manuscript for intellectual content and approved the final draft for  
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329

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451 **Tables**

452 **Table 1: Number (%) of CLL cases and their matched controls by certain socio-economic and**  
 453 **clinical characteristics**

	<b>Case</b> (N=1,385)	<b>Control</b> (N=6,841)
Male	825 (59.6%)	4,100 (59.9%)
Age group		
40-54	151 (10.9%)	737 (10.8%)
55-64	328 (23.7%)	1,621 (23.7%)
65-74	403 (29.1%)	2,009 (29.4%)
75+	503 (36.3%)	2,474 (36.2%)
In top 60% of household income distribution	800 (57.8%)	3,804 (55.6%)
Rural residence	521 (37.6%)	2,472 (36.1%)
Comorbidities		
Diabetes	229 (16.5%)	1,231 (18.0%)
Chronic cardiovascular disease (excluding hypertension)	579 (41.8%)	2,719 (39.7%)
Ischemic heart diseases	261 (18.8%)	1,284 (18.8%)
Stroke	33 (2.4%)	200 (2.9%)
Ever-use of statins		
Any statin	371 (26.8%)	1,918 (28.0%)
Any statin 2-5 years prior to the index date	341 (24.6%)	1,739 (25.4%)
Any statin 6-10 years prior to the index date	219 (15.8%)	1,139 (16.6%)
Any statin 11+ years prior to the index date	93 (6.7%)	462 (6.8%)
Hydrophilic statins	131 (9.5%)	591 (8.6%)

High-potency lipophilic statins	290 (20.9%)	1,500 (21.9%)
Low-potency lipophilic statins	40 (2.9%)	287 (4.2%)
Pravastatin	67 (4.8%)	299 (4.4%)
Rosuvastatin	73 (5.3%)	330 (4.8%)
Simvastatin	113 (8.2%)	572 (8.4%)
Atorvastatin	218 (15.7%)	1,113 (16.3%)
Fluvastatin	15 (1.1%)	111 (1.6%)
Lovastatin	28 (2.0%)	199 (2.9%)
Ever-use of other prescription drugs		
Non-statin lipid-lowering drugs	101 (7.3%)	464 (6.8%)
Metformin	123 (8.9%)	681 (10.0%)
Insulin	32 (2.3%)	169 (2.5%)
Other oral hypoglycemic drugs	113 (8.2%)	604 (8.8%)
Aspirin	249 (18.0%)	1,392 (20.3%)
Non-aspirin NSAID	844 (60.9%)	4,340 (63.4%)
Any NSAID	911 (65.8%)	4,721 (69.0%)
No. of physician visits in the 5-year period before index date		
0 — 19	261 (18.8%)	1,495 (21.9%)
20 — 39	388 (28.0%)	2,014 (29.4%)
40 — 64	380 (27.4%)	1,656 (24.2%)
65+	356 (25.7%)	1,676 (24.5%)

455 **Table 2: Relative duration (percent of time) and average annual dose (DDD/year) of statin use**  
 456 **prior to the index date excluding the year before the index date, for CLL cases and their**  
 457 **matched controls according to statin subgroup.**

	Cases			Controls		
	Q1	Median	Q3	Q1	Median	Q3
<b>Average annual dose (DDD/year)</b>						
Hydrophilic	350.3	365.0	392.2	365.0	365.0	429.0
High-potency lipophilic	182.5	243.3	365.0	182.5	251.8	365.0
Low-potency lipophilic	162.2	162.2	233.4	162.2	165.1	243.3
<b>Relative duration (%)</b>						
Hydrophilic	5.1	14.5	34.2	3.4	11.8	28.6
High-potency lipophilic	6.0	20.3	42.1	6.0	20.6	41.3
Low-potency lipophilic	7.1	23.4	53.0	5.9	23.1	63.7

DDD = defined daily dose, Q1 = first quartile, Q3 = third quartile.

458

459 **Table 3: Adjusted odds ratios (95% confidence interval) of the association between CLL**  
 460 **incidence and ever-use of statins, excluding the year before the index date.**

Ever-use of statins	Model A <sup>a</sup>	Model B <sup>b</sup>
Any statin	0.94 (0.82-1.08)	0.89 (0.76-1.04)
Hydrophilic <sup>c</sup>	1.14 (0.93-1.41)	1.08 (0.86-1.34)
Pravastatin <sup>d</sup>	1.18 (0.89-1.55)	1.13 (0.84-1.51)
Rosuvastatin <sup>d</sup>	1.12 (0.85-1.47)	1.06 (0.79-1.42)
High-potency lipophilic <sup>c</sup>	0.96 (0.82-1.12)	0.94 (0.79-1.11)
Simvastatin <sup>d</sup>	1.02 (0.82-1.27)	1.03 (0.82-1.29)
Atorvastatin <sup>d</sup>	0.99 (0.84-1.18)	0.96 (0.80-1.16)
Low-potency lipophilic <sup>c</sup>	0.68 (0.48-0.96)	0.64 (0.45-0.92)
Fluvastatin <sup>d</sup>	0.72 (0.41-1.25)	0.71 (0.40-1.26)
Lovastatin <sup>d</sup>	0.70 (0.47-1.06)	0.66 (0.43-1.02)

a: Model A includes the matching variables (age, gender, residence and duration of coverage). b: Model B includes the matching variables, 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 and aspirin and derivatives. c: Also adjusted for ever-use of the other statin subgroups. d: Also adjusted for ever-use of the other individual statins.

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462 **Table 4: Adjusted<sup>a</sup> odds ratios (95% confidence interval) of the association between CLL**  
 463 **diagnosis and statin use, excluding the year before the index date, by statin subgroup according**  
 464 **to period, duration and dose.**

Statin use	Hydrophilic	High-potency lipophilic	Low-potency lipophilic
Time of first use (years prior to the index date) <sup>b</sup>			
2-5	1.07 (0.79-1.44)	0.96 (0.77-1.19)	0.62 (0.28-1.40)
6-10	0.93 (0.64-1.34)	0.90 (0.71-1.14)	0.61 (0.33-1.12)
11+	1.42 (0.90-2.24)	0.96 (0.69-1.34)	0.65 (0.39-1.11)
Relative duration (fraction of drug history) <sup>b</sup>			
1 - 25%	1.03 (0.79-1.33)	0.91 (0.74-1.12)	0.69 (0.43-1.12)
26 - 50%	1.10 (0.68-1.77)	0.85 (0.64-1.13)	0.56 (0.22-1.43)
51 - 75%	1.60 (0.84-3.04)	1.10 (0.76-1.59)	0.70 (0.29-1.68)
≥ 76%	0.99 (0.34-2.91)	1.40 (0.81-2.41)	0.42 (0.15-1.17)
Continuous use <sup>b</sup>			
< 12 months	1.00 (0.77-1.30)	0.97 (0.80-1.18)	0.65 (0.43-1.01)
≥ 12 months	1.23 (0.85-1.78)	0.90 (0.70-1.15)	0.60 (0.32-1.14)
Duration (months) <sup>b</sup>			
1 - 6	0.91 (0.60-1.40)	0.95 (0.70-1.29)	0.41 (0.16-1.06)
7 - 24	1.06 (0.73-1.52)	0.85 (0.63-1.13)	0.81 (0.43-1.52)
25 - 48	1.04 (0.65-1.67)	1.00 (0.75-1.34)	0.60 (0.27-1.32)
≥ 49	1.39 (0.93-2.09)	0.97 (0.75-1.26)	0.67 (0.36-1.23)
Cumulative dose (DDD) <sup>b</sup>			
1 - 120	0.87 (0.53-1.42)	0.92 (0.67-1.25)	0.68 (0.34-1.35)
121 - 480	0.87 (0.56-1.33)	0.92 (0.70-1.22)	0.71 (0.37-1.35)
481 - 1200	1.39 (0.93-2.07)	0.97 (0.73-1.29)	0.71 (0.35-1.44)
≥ 1201	1.18 (0.83-1.70)	0.94 (0.72-1.23)	0.47 (0.20-1.09)

Average annual dose (DDD/year)<sup>b</sup>

1 - 180	2.81 (0.83-9.50)	0.97 (0.65-1.43)	0.74 (0.47-1.16)
181 - 365	1.46 (0.96-2.22)	0.96 (0.79-1.17)	0.44 (0.22-0.88)
≥ 366	0.96 (0.74-1.23)	0.89 (0.68-1.15)	0.88 (0.30-2.58)

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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 statin subgroups. b: Compared to never use of the specific statin subgroup.

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# Cancer Epidemiology, Biomarkers & Prevention

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## Statin use and chronic lymphocytic leukemia incidence: A nested case-control study in Manitoba, Canada

Christiaan H Righolt, Geng Zhang, Xibiao Ye, et al.

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