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Medical History, Lifestyle, Family History, and Occupational Risk Factors for Follicular Lymphoma: The InterLymph Non-Hodgkin Lymphoma Subtypes Project

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Background Follicular lymphoma (FL) has been linked with cigarette smoking and, inconsistently, with other risk factors.

Methods We assessed associations of medical, hormonal, family history, lifestyle, and occupational factors with FL risk in 3530 cases and 22 639 controls from 19 case–control studies in the InterLymph consortium. Age-, race/ethnicity-, sex- and study-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression.

Results Most risk factors that were evaluated showed no association, except for a few modest or sex-specific relationships. FL risk was increased in persons: with a first-degree relative with non-Hodgkin lymphoma (OR = 1.99; 95% CI = 1.55 to 2.54); with greater body mass index as a young adult (OR = 1.15; 95% CI = 1.04 to 1.27 per 5 kg/m^2 increase); who worked as spray painters (OR = 2.66; 95% CI = 1.36 to 5.24); and among women with Sjögren syndrome (OR = 3.37; 95% CI = 1.23 to 9.19). Lower FL risks were observed in persons: with asthma, hay fever, and food allergy (ORs = 0.79–0.85); blood transfusions (OR = 0.78; 95% CI = 0.68 to 0.89); high recreational sun exposure (OR = 0.74; 95% CI = 0.65 to 0.86, fourth vs first quartile); who worked as bakers or millers (OR = 0.51; 95% CI = 0.28 to 0.93) or university/higher education teachers (OR = 0.58; 95% CI = 0.41 to 0.83). Elevated risks specific to women included current and longer duration of cigarette use, whereas reduced risks included current alcohol use, hay fever, and food allergies. Other factors, including other autoimmune diseases, eczema, hepatitis C virus seropositivity, hormonal drugs, hair dye use, sun exposure, and farming, were not associated with FL risk.

Conclusions The few relationships observed provide clues suggesting a multifactorial etiology of FL but are limited in the extent to which they explain FL occurrence.

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Follicular lymphoma (FL), the second most common form of lymphoma in the United States and western Europe, is a lymphoproliferative disorder of germinal center B cells (1). The US age-adjusted incidence rate for FL during 1992–2001 was 3.18 per 100 000, with a 3.6-fold variation between the highest and lowest rates (in white males and American Indian/Alaska Native males, respectively) (2) and a 2.8-fold variation in rates among Asian Americans of different origins (3). Age-adjusted FL rates are slightly higher in males than in females. Most patients present with indolent disease, although 2%–3% of FL cases transform annually to diffuse large B-cell lymphoma (4).

Few epidemiologic studies published before 2004 evaluated risk factors separately for subtypes of non-Hodgkin lymphoma (NHL) based on the Revised European-American Lymphoma (REAL)/ World Health Organization (WHO) classification (5–10). Subsequently, an expanding literature has examined risk factors for the common NHL subtypes, although most of these studies have assessed specific or related categories of exposure but did not evaluate risks across a broad range of exposures. Cigarette smoking has repeatedly been associated with a higher risk of FL (11–13), and some reports, including previous InterLymph pooled analyses, have linked excess risk of FL with Sjögren syndrome (14), blood transfusions (15), family history of hematopoietic malignancies (16,17), hair dyes (18,19), and greater height (20). A few reports have linked occupational exposure to benzene, oils/greases, and other solvents such as styrene and trichloroethylene with increased risks of FL (9,21–23). Reduced risks of FL have been linked with atopic disorders (24), oral contraceptive use (25), alcohol consumption (26,27), and sun exposure (28–30).

We have pooled data from 19 case–control studies conducted in Europe, North America, and Australia to examine associations between medical and family history, lifestyle, hormonal drugs, and occupation. The broad range of risk factors available provided an opportunity to assess multivariate associations, and the large study size, 3530 FL cases and 22639 controls, provided an opportunity to examine relatively rare exposures and weak associations overall and in subgroups defined by sex, race/ethnicity, region, and source of controls.

Methods

Study Population

Detailed methodology for the InterLymph NHL Subtypes Project is provided elsewhere in this issue. Studies eligible for inclusion in this pooled analysis were case–control studies, with incident, histologically confirmed cases of FL defined according to the WHO classification (31,32); each study collected individual-level data for at least several risk factors of interest and these were submitted to the pooling project by December 31, 2011. Most studies excluded individuals with a known history of solid organ transplantation or HIV/AIDS. Contributing studies were approved by local ethics review committees, and all participants provided written, informed consent prior to participation.

Risk Factors and NHL Subtype Ascertainment and Harmonization

Each study collected data on potential NHL risk factors in a standardized, structured format by in-person or telephone interviews, and/or self-administered questionnaires. Risk factors included were those where data were available from at least four studies. Each variable was harmonized individually, then related exposure variables were reviewed for consistency as detailed elsewhere (33).

Cases were classified according to the WHO classification (31,32) using guidelines from the InterLymph Pathology Working Group (34,35).

Statistical Analysis

Risk of FL associated with each exposure variable was evaluated using logistic regression models, adjusting for age, race/ethnicity, sex, and study in a basic adjusted model. The significance of each association was evaluated by a likelihood ratio test, comparing models with and without the exposure variable of interest, with *P* values less than 0.05 identifying putatively influential factors. To quantify the magnitude of the association, we estimated the relative risk using odds ratios (ORs) and 95% confidence intervals (CIs) derived from the logistic regression models. Individuals with missing data for a variable of interest were excluded. To evaluate effect heterogeneity among the studies, we performed a separate logistic regression within each study and then quantified the variability of the coefficients by the H statistic, adapting the definition by Higgins and Thompson to categorical variables (36).

To consider possible effect modification, we repeated the above logistic regression analyses but stratified individuals by age, sex, race/ethnicity, region (ie, North America vs Europe vs Australia), study design (ie, population-based vs hospital-based), or other putative risk factors identified in the analysis. To assess confounding, we first evaluated the risk estimate for each putative risk factor in a series of models that adjusted for one other putative risk factor individually in addition to the basic adjusted model. Next, we conducted a single logistic regression model including all putative risk factors, this time including a separate missing category for each variable to ensure that the entire study population was included in the analysis. Finally, we conducted a forward step-wise logistic regression with all putative risk factors, adjusting for age, sex, race/ethnicity, and study. Results from this series of multivariate adjusted logistic regression models showed little difference from the findings based on the basic adjusted models (ie, adjusted for age, sex, race/ethnicity, and study). We therefore report the results for the basic adjusted models only.

Because controls for most original studies were frequency matched by age and sex to all cases, we conducted sensitivity analyses using a subset of controls individually matched by age and sex to the FL cases. The results were similar to those using the full set of controls and, thus, we retained all controls for the main analyses to increase statistical power.

Results

The median age was similar for FL cases at diagnosis (median: 58 years, range: 18–91 years) and controls at the time of interview (median: 59 years, range: 16–98 years). FL cases were more likely to be female, but FL cases and controls were similar by race/ethnicity (with >90% non-Hispanic whites) and socioeconomic status (Table 1). Most cases and controls were from North America or northern Europe and from population-based studies.

Medical Conditions and Treatments

Overall, participants with a history of autoimmune diseases involving B-cell or T-cell activation were not at an increased risk of FL, except for those with Sjögren syndrome (Table 2). History of any atopic condition (OR = 0.87; 95% CI = 0.80 to 0.94) or any specific allergies (ORs ranged from 0.82 to 0.88), but not eczema, was associated with a reduced risk of FL (Table 2). Hay fever and food allergy were associated with significantly reduced FL risk in females but not males (*P* heterogeneity = .01 and .04, respectively; Table 3).

History of a blood transfusion was associated with a 22% lower risk of FL (Table 4). Reductions in FL risk were most notable for those who received a transfusion after age 55 years and within 40 years before the diagnosis of FL/interview. Positive hepatitis C virus serology was not linked with FL risk (OR = 1.28; 95% CI = 0.64 to 2.57, based on 11 exposed cases and 34 exposed controls). Neither use of oral contraceptives nor use of hormonal replacement therapy was linked with FL risk (data not shown).

Family History of Hematopoietic Malignancies

Participants with a first-degree relative with a history of NHL experienced approximately a twofold greater risk of FL than participants without such a history (Table 5), and risks were elevated in both male and female participants except females with affected male relatives (Table 3). Male and female participants with first-degree male, but not female, relatives with multiple myeloma had an increased risk of FL (Table 5). FL was not increased in participants with first-degree relatives with leukemia or Hodgkin lymphoma (Table 5).

Table 1. Descriptive characteristics of follicular lymphoma cases and controls

	Controls	Cases
	No. (%)	No. (%)
Total	22 639 (86.5)	3530 (13.5)
Age at diagnosis/interview, y		
<30	1356 (6.0)	38 (1.1)
30–39	2143 (9.5)	253 (7.2)
40–49	3090 (13.6)	655 (18.6)
50–59	4870 (21.5)	1003 (28.4)
60–69	6277 (27.7)	1011 (28.6)
70–79	4048 (17.9)	508 (14.4)
≥80	839 (3.7)	58 (1.6)
Missing	16 (0.1)	4 (0.1)
Sex		
Male	13 228 (58.4)	1785 (50.6)
Female	9411 (41.6)	1745 (49.4)
Race		
White non-Hispanic	21 145 (93.4)	3231 (91.5)
Black	351 (1.6)	37 (1.0)
Asian	321 (1.4)	70 (2.0)
Hispanic	334 (1.5)	59 (1.7)
Other/unknown/missing	488 (2.2)	133 (3.8)
Socioeconomic status		
Low	9266 (40.9)	1384 (39.2)
Medium	6577 (29.1)	1061 (30.1)
High	6386 (28.2)	1019 (28.9)
Other/missing	410 (1.8)	66 (1.9)
Region		
North America	11 005 (48.6)	1854 (52.5)
Northern Europe	6542 (28.9)	1100 (31.2)
Southern Europe	4398 (19.4)	324 (9.2)
Australia	694 (3.1)	252 (7.1)
Study design		
Population-based	17 389 (76.8)	2908 (82.4)
Hospital-based	5250 (23.2)	622 (17.6)

Lifestyle Factors

Risks for FL were increased in those who were overweight (OR = 1.49; 95% CI = 1.21 to 1.83) or obese (OR = 1.46; 95% CI = 0.98 to 2.17) as young adults and rose 15% with each five kg/m^2 increase in young adult body mass index (BMI) (Table 6). No significant relationship was observed for usual adult BMI or weight. Greater adult height in males, but not females, was associated with increased risk of FL (data not shown).

History of cigarette smoking was positively associated with FL risk in females but not males (P heterogeneity = .004; Table 3). Among women, a modest increase in risk of FL in those who ever smoked cigarettes was limited to current smokers, along with a significant positive trend for duration of smoking (data not shown). The trend in pack-years of smoking in women was more clearly related to duration than frequency of cigarettes smoked (data not shown). FL risks were reduced modestly in women, but not men, who ever drank alcohol, particularly current drinkers (Table 3), but there was no clear pattern with duration, number of drinks per week, or cumulative alcohol consumption (data not shown); we note, however, that many studies did not collect these data.

A lower risk of FL was associated with increasing number of hours per week of recreational sun exposure for both men and women (Table 3) but was attenuated for total sun exposure hours (Table 6). FL risk, examined in females only, was not linked with hair dye use overall or by type, duration, or frequency (data not shown), except for a modest increase in those who used hair dyes before 1980 (OR = 1.40, 95% CI = 1.10 to 1.78).

Occupational Factors

Working or living on a farm was not associated with risk of FL (Table 7). Bakers and millers, and those working as university or higher education teachers, experienced reduced risks, whereas spray painters had increased risks of FL. A modest, nonsignificant increase in risk of FL was seen for those ever working as medical doctors, but those working more than 10 years in this occupation had a significantly elevated risk (OR = 2.06, 95% CI = 1.08 to 3.92, based on 38 cases vs 13 controls). Employment in other occupations was not associated with risk of FL (Table 7).

Risks According to Race/Ethnicity, Source of Population, and Region

For the associations observed in all FL patients, patterns were generally similar by race/ethnicity, except for increased risks for any atopic disorder and hay fever, and a trend in recreational sun exposure in Asians (Supplementary Table 1, available online). Comparison of FL risks in population-based versus hospital-based studies revealed that the findings were mainly driven by the former (Supplementary Table 2, available online). Risks according to region were mostly consistent, although risks for combined and individual atopic allergic disorders showed greater reductions in risk in Australia than in Europe or North America (Supplementary Table 3, available online).

Discussion

In the largest pooled analysis of case–control studies focused on FL and the first to assess a broad range of exposures simultaneously, most risk factors examined were not associated with risk of FL specifically, except for a few mostly modest or sex-specific relationships. We found novel associations with FL risk for certain occupations, including reduced risk in bakers/millers, and university/higher education teachers, and increased risk in spray painters. With our larger number of studies and strong evidence for independence in multivariate models, this analysis extends earlier InterLymph observations of an increased risk of FL for those with Sjögren syndrome (37), a first-degree relative with a history of NHL (17), and reduced risks among those with allergic diseases (24) and greater recreational hours spent per week in the sun (30). Increased FL risks among current cigarette smokers, in conjunction with a positive trend with duration of smoking, were restricted to women, as were the significantly reduced risks of FL in those with a history of hay fever or food allergy. We also found a reduced risk of FL with a history of blood transfusion.

Although meta-analyses of all NHL (5,38,39) found a modest up to 10% increase in risk among those who had worked in farming, few studies have evaluated occupational risks for FL specifically. A pooled analysis of studies in Kansas and Nebraska found increases in FL risk in association with employment in agriculture or farming that were not statistically significant (40). Two studies with stratification of cases by chromosomal translocation in t(14;18) found associations with certain agricultural pesticides (but not farming per se) for

Table 2. Autoimmune and allergic disorders and risk of follicular lymphoma*

	Controls†	Cases†		
	No. (%)	No. (%)	OR (95% CI)‡	*P*
History of autoimmune conditions				
History of autoimmune disease				
No autoimmune disease	19423 (95.9)	3242 (95.8)	1.00 (referent)	.358
B-cell activation	157 (0.8)	39 (1.2)	1.26 (0.88 to 1.81)	
T-cell activation	664 (3.3)	100 (3.0)	0.88 (0.71 to 1.10)	
Both	15 (0.1)	4 (0.1)	1.40 (0.45 to 4.32)	
Sjögren syndrome				
No	6917 (97.2)	1487 (96.6)	1.00 (referent)	.024
Yes	9 (0.1)	7 (0.5)	3.37 (1.23 to 9.19)	
Systematic lupus erythematosus				
No	15987 (98.6)	2807 (98.0)	1.00 (referent)	.104
Yes	33 (0.2)	12 (0.4)	1.81 (0.91 to 3.60)	
Inflammatory bowel disorder				
No	16231 (97.6)	2620 (97.2)	1.00 (referent)	.349
Yes	199 (1.2)	29 (1.1)	0.83 (0.56 to 1.24)	
Celiac disease				
No	8907 (99.4)	1459 (98.8)	1.00 (referent)	.632
Yes	25 (0.3)	7 (0.5)	1.24 (0.52 to 2.96)	
Type I diabetes				
No	13185 (95.9)	1861 (92.0)	1.00 (referent)	.982
Yes	84 (0.6)	14 (0.7)	0.99 (0.55 to 1.80)	
Atopic disorders				
Any atopic disorder§				
No	15601 (68.9)	2345 (66.4)	1.00 (referent)	<.001
Yes	6442 (28.5)	1107 (31.4)	0.87 (0.80 to 0.94)	
Allergy‖				
No	10790 (72.1)	1903 (70.0)	1.00 (referent)	.018
Yes	3309 (22.1)	590 (21.7)	0.88 (0.79 to 0.98)	
Food allergy				
No	12757 (85.2)	2180 (80.1)	1.00 (referent)	.007
Yes	988 (6.6)	171 (6.3)	0.79 (0.67 to 0.94)	
Asthma				
No	18448 (85.6)	2894 (83.9)	1.00 (referent)	.018
Yes	1698 (7.9)	260 (7.5)	0.85 (0.74 to 0.97)	
Hay fever				
No	12467 (71.3)	2086 (69.3)	1.00 (referent)	<.001
Yes	2958 (16.9)	521 (17.3)	0.82 (0.73 to 0.91)	
Eczema				
No	14766 (86.1)	2452 (82.4)	1.00 (referent)	.283
Yes	1605 (9.4)	318 (10.7)	1.08 (0.94 to 1.23)	

* CI = confidence interval; OR = odds ratio.

† The counts do not add up to the total # of cases/controls due to data missing by design or report.

‡ OR (95% CI) adjusted for age, sex, race/ethnicity, and study.

§ Atopic disorders include asthma, eczema, hay fever, or other allergies, excluding drug allergies.

‖ History of allergy excludes drug allergies, asthma, eczema, and hay fever.

t(14;18)-positive NHL, but not for *t*(14;18)-negative cases (41,42). Although *t*(14;18) is not specific to FL, this molecular feature occurs in 70%–90% of FL cases compared with 20%–30% of diffuse large B-cell lymphoma cases and 5%–10% of other NHL subtypes (31). It is possible that FL may be associated with specific exposures in farming, such as poultry (43), which were not characterized in our assessment of farming as an occupation. Unfortunately, molecular characterization according to *t*(14;18) status was not available for the majority of the FL cases in this pooled study. Our finding of an increased risk of FL in spray painters is consistent with previous reports finding that NHL risk is elevated among those working in the occupation of painter and those working with solvents used in paint product formulations (44,45). The decreased risk of FL in university/higher education teachers is not consistent with the results from a meta-analysis showing increased risk among teachers (38), but the meta-analysis included teachers at all levels, whereas our finding was restricted to university/higher education teachers. The meta-analysis did not provide separate estimates of risk for university/higher education teachers. This, and our findings for medical doctors and for bakers/millers, should be further investigated in occupational epidemiologic studies to evaluate specific exposures.

Reasons for the female-specific modest increase in FL risk associated with cigarette smoking are not clear, but these results are consistent with those of a recent meta-analysis of 24 studies which reported a 43% increased risk of FL in female smokers compared with nonsmokers, but no association of smoking status, duration,

Table 3. Sex-specific medical, lifestyle, family history, and occupational exposures and follicular lymphoma*

	Male				Female				
	Controls†	Cases†			Controls†	Cases†			
	No. (%)	No. (%)	OR (95% CI)‡	*P*	No. (%)	No. (%)	OR (95% CI)‡	*P*	*P* heterogeneity
Medical conditions									
Sjögren's syndrome									
No	—	—	—	—	3555 (97.5)	829 (96.4)	1.00 (referent)	.028	.0030
Yes	0	0	—	—	9 (0.2)	7 (0.8)	3.24 (1.19 to 8.80)	—	—
Any atopic disorder§									
No	9660 (73.0)	1247 (69.9)	1.00 (referent)	.180	5941 (63.1)	1098 (62.9)	1.00 (referent)	<.001	.0587
Yes	3187 (24.1)	497 (27.8)	0.92 (0.82 to 1.04)		3255 (34.6)	610 (35.0)	0.82 (0.73 to 0.92)	—	—
Allergy‖									
No	6682 (76.8)	1049 (73.9)	1.00 (referent)	.596	4108 (65.5)	854 (65.7)	1.00 (referent)	.006	.0947
Yes	1556 (17.9)	255 (18.0)	0.96 (0.82 to 1.12)	—	1753 (28.0)	335 (25.8)	0.82 (0.70 to 0.94)	—	—
Food allergy									
No	6704 (86.1)	1078 (79.7)	1.00 (referent)	.744	5141 (82.0)	1034 (79.5)	1.00 (referent)	.002	.0409
Yes	405 (5.2)	71 (5.3)	0.96 (0.73 to 1.25)	—	583 (9.3)	100 (7.7)	0.70 (0.56 to 0.88)	—	—
Asthma									
No	10548 (86.3)	1468 (85.1)	1.00 (referent)	.112	7900 (84.6)	1426 (82.7)	1.00 (referent)	.079	.8354
Yes	909 (7.4)	120 (7.0)	0.85 (0.69 to 1.04)	—	789 (8.5)	140 (8.1)	0.84 (0.69 to 1.02)	—	—
Hay fever									
No	7000 (72.9)	1031 (69.1)	1.00 (referent)	.256	5467 (69.3)	1055 (69.6)	1.00 (referent)	<.001	.0124
Yes	1475 (15.4)	249 (16.7)	0.91 (0.78 to 1.07)	—	1483 (18.8)	272 (18.0)	0.74 (0.63 to 0.86)	—	—
Eczema									
No	8722 (88.2)	1272 (85.0)	1.00 (referent)	.583	6044 (83.3)	1180 (79.7)	1.00 (referent)	.321	.8818
Yes	737 (7.5)	125 (8.4)	1.06 (0.86 to 1.30)	—	868 (12.0)	193 (13.0)	1.09 (0.92 to 1.30)	—	—
Blood transfusion									
No	6085 (75.1)	996 (77.3)	1.00 (referent)	.005	4657 (78.9)	1020 (81.5)	1.00 (referent)	.011	.4838
Yes	878 (10.8)	101 (7.8)	0.74 (0.59 to 0.92)	—	1088 (18.4)	196 (15.7)	0.80 (0.68 to 0.95)	—	—
Family history									
NHL									
No	8544 (86.2)	1095 (85.5)	1.00 (referent)	<.001	5572 (80.0)	1050 (83.6)	1.00 (referent)	.022	.385
Yes	132 (1.3)	52 (4.1)	2.54 (1.81 to 3.58)	—	146 (2.1)	44 (3.5)	1.54 (1.08 to 2.20)	—	—
NHL in male relatives									
No	7003 (84.5)	923 (85.8)	1.00 (referent)	<.001	4756 (78.5)	889 (83.6)	1.00 (referent)	.777	.0263
Yes	54 (0.7)	23 (1.9)	2.73 (1.63 to 4.60)	—	59 (1.0)	12 (1.1)	1.10 (0.58 to 2.08)	—	—
NHL in female relatives									
No	6661 (83.9)	906 (85.8)	1.00 (referent)	.008	4744 (78.3)	877 (82.5)	1.00 (referent)	.043	.5794
Yes	55 (0.7)	20 (1.9)	2.14 (1.26 to 3.65)	—	71 (1.2)	24 (2.3)	1.69 (1.04 to 2.75)	—	—
Lifestyle factors									
BMI as a young adult (kg/m^2)									
Continuous	13228 (100.0)	1785 (100.0)	1.09 (0.94 to 1.27)	.275	9411 (100.0)	1745 (100.0)	1.25 (1.09 to 1.44)	.948	.0606
Physical activity									
None	319 (9.5)	41 (6.8)	1.00 (referent)	.153	397 (10.7)	57 (7.4)	1.00 (referent)	.190	.7835
Mild	210 (6.2)	52 (8.6)	1.30 (0.81 to 2.07)	—	264 (7.1)	82 (10.7)	1.53 (1.02 to 2.30)	—	—
Moderate	424 (12.6)	84 (13.9)	1.06 (0.69 to 1.62)	—	510 (13.8)	125 (16.3)	1.16 (0.79 to 1.69)	—	—
Vigorous	1380 (41.0)	255 (42.1)	1.37 (0.95 to 1.98)	—	1657 (44.8)	330 (43.0)	1.19 (0.86 to 1.66)	—	—

(Table continues)

Table 3 (Continued).

	Male				Female				
	Controls†	Cases†			Controls†	Cases†			
	No. (%)	No. (%)	OR (95% CI)‡	*P*	No. (%)	No. (%)	OR (95% CI)‡	*P*	*P* heterogeneity
History of cigarette smoking¶									
No	3934 (30.8)	520 (31.0)	1.00 (referent)	.695	4945 (54.9)	744 (45.8)	1.00 (referent)	<.001	.0038
Yes	8047 (63.0)	987 (58.8)	0.98 (0.87 to 1.10)	—	3643 (40.4)	762 (46.9)	1.22 (1.09 to 1.37)	—	—
History of alcohol consumption									
Nondrinker	1995 (17.1)	239 (16.1)	1.00 (referent)	.551	2282 (28.5)	404 (27.7)	1.00 (referent)	.002	.1969
Drinker (at least 1 drink per month)	7245 (62.2)	833 (56.3)	0.95 (0.80 to 1.12)	—	3749 (46.8)	630 (43.2)	0.79 (0.68 to 0.91)	—	—
Recreational sun exposure (h/wk)									
Quartile 1 (low)	1003 (18.1)	195 (20.4)	1.00 (referent)	.034	1231 (23.3)	327 (28.4)	1.00 (referent)	.002	.8752
Quartile 2	1112 (20.1)	176 (18.4)	0.77 (0.61 to 0.96)	—	1220 (23.1)	245 (21.3)	0.77 (0.64 to 0.93)	—	—
Quartile 3	1121 (20.2)	177 (18.5)	0.74 (0.58 to 0.93)	—	1038 (19.7)	216 (18.8)	0.78 (0.64 to 0.95)	—	—
Quartile 4 (high)	1745 (31.5)	277 (29.0)	0.77 (0.62 to 0.95)	—	1238 (23.5)	228 (19.8)	0.70 (0.58 to 0.85)	—	—
Occupational exposures									
Bakers and millers									
No	6124 (93.7)	970 (98.1)	1.00 (referent)	.143	5222 (98.7)	1001 (99.5)	1.00 (referent)	.040	.6802
Yes	97 (1.5)	7 (0.7)	0.58 (0.27 to 1.27)	—	61 (1.2)	5 (0.5)	0.42 (0.17 to 1.06)	—	—
Chemists and chemical workers									
No	5804 (92.8)	884 (95.7)	1.00 (referent)	.090	5090 (99.3)	989 (99.4)	1.00 (referent)	.968	.5551
Yes	136 (2.2)	28 (3.0)	1.46 (0.96 to 2.23)	—	31 (0.6)	6 (0.6)	1.02 (0.42 to 2.49)	—	—
Medical worker									
No	5996 (91.7)	934 (94.4)	1.00 (referent)	.489	5124 (88.3)	1023 (87.7)	1.00 (referent)	.489	.3100
Yes	225 (3.4)	43 (4.3)	1.13 (0.80 to 1.59)	—	670 (11.6)	144 (12.3)	0.93 (0.77 to 1.14)	—	—
Medical doctor									
No	5709 (93.7)	912 (97.1)	1.00 (referent)	.480	5515 (99.4)	1103 (99.5)	1.00 (referent)	.765	.9556
Yes	63 (1.0)	13 (1.4)	1.25 (0.68 to 2.32)	—	19 (0.3)	5 (0.5)	1.17 (0.42 to 3.24)	—	—
Spray-painter (except construction)									
No	5465 (94.1)	790 (96.7)	1.00 (referent)	<.001	4854 (99.6)	936 (99.9)	1.00 (referent)	.111	.8588
Yes	22 (0.4)	13 (1.6)	3.83 (1.87 to 7.84)	—	7 (0.1)	0 (0.0)	—		—
University and higher education teachers									
No	6063 (92.7)	959 (97.0)	1.00 (referent)	.011	5666 (97.7)	1145 (98.1)	1.00 (referent)	.066	.6104
Yes	154 (2.4)	16 (1.6)	0.53 (0.31 to 0.90)	—	120 (2.1)	21 (1.8)	0.65 (0.40 to 1.05)	—	—

* BMI = body mass index; CI = confidence interval; NHL = non-Hodgkin lymphoma; OR = odds ratio.

† The counts do not add up to the total # of cases/controls due to data missing by design or report.

‡ OR (95% CI) adjusted for age, sex, race/ethnicity, and study.

§ Atopic disorders include asthma, eczema, hay fever, or other allergies, excluding drug allergies.

‖ History of allergy excludes drug allergies, asthma, eczema, and hay fever.

¶ Smoked longer than 6 months or more than 100 cigarettes in lifetime.

Table 4. History of blood transfusions and risk of follicular lymphoma*

	Controls†	Cases†		
	No. (%)	No. (%)	OR (95% CI)‡	*P*
Blood transfusion				
No	10 742 (76.7)	2016 (79.4)	1.00 (referent)	<.001
Yes	1966 (14.0)	297 (11.7)	0.78 (0.68 to 0.89)	
Age at first transfusion				
No transfusion	10 742 (76.7)	2016 (79.4)	1.00 (referent)	.003
<25 y	483 (3.4)	82 (3.2)	0.83 (0.65 to 1.06)	
25–39 y	579 (4.1)	99 (3.9)	0.80 (0.64 to 1.00)	
40–54 y	449 (3.2)	71 (2.8)	0.82 (0.63 to 1.06)	
55 or older	455 (3.2)	45 (1.8)	0.62 (0.45 to 0.85)	
Total number of blood transfusions				
No transfusion	10 742 (76.7)	2016 (79.4)	1.00 (referent)	.003
1 transfusion	1306 (9.3)	202 (8.0)	0.83 (0.71 to 0.97)	
2 transfusions	361 (2.6)	47 (1.9)	0.63 (0.46 to 0.86)	
3 or more transfusions	229 (1.6)	35 (1.4)	0.73 (0.50 to 1.05)	
Transfusion, but number unknown	70 (0.5)	13 (0.5)	0.88 (0.48 to 1.62)	
Number of years from 1st transfusion to date of diagnosis/interview				
No transfusion	10 742 (76.7)	2016 (79.4)	1.00 (referent)	.003
<20 y	878 (6.3)	121 (4.8)	0.77 (0.63 to 0.94)	
20–39 y	748 (5.3)	118 (4.6)	0.76 (0.62 to 0.93)	
≥40 y	340 (2.4)	58 (2.3)	0.86 (0.64 to 1.14)	
Blood transfusion before 1990				
No transfusion	10 742 (76.7)	2016 (79.4)	1.00 (referent)	<.001
Before 1990	1457 (10.4)	235 (9.3)	0.83 (0.71 to 0.96)	
After 1990	404 (2.9)	44 (1.7)	0.62 (0.45 to 0.86)	
Transfusion year unknown	105 (0.7)	18 (0.7)	0.68 (0.39 to 1.17)	

* CI = confidence interval; OR = odds ratio.

† The counts do not add up to the total # of cases/controls due to data missing by design or report.

‡ OR (95% CI) adjusted for age, sex, race/ethnicity, and study.

or intensity in males (46). Findings from cohort studies (11,27,47) also provide some support for this association. An association of cigarette smoking with FL is biologically plausible in that increased rates of *t*(14;18) translocations have been observed in heavy smokers (48). The current analysis, with more than twice as many studies and threefold more FL cases than our earlier InterLymph consortium analysis (13), provides more precise estimates of FL risk (20% increase in our analysis of "current" smokers vs 31% in our earlier assessment), and identified a similar significant relationship with increasing duration of smoking, establishing that this association is not likely to be confounded by alcohol, BMI, or a variety of other risk factors evaluated here.

Our finding of an excess risk of FL associated with Sjögren's syndrome is consistent with our earlier InterLymph pooled analysis (12 studies, 12 982 NHL cases (14)) in which Sjögren's syndrome was the only autoimmune disease associated with FL.

We found reductions in risk of FL in relation to history of allergic conditions except for eczema. These findings are consistent with our earlier pooled analysis (2842 FL) (24). However, this first sex-specific assessment revealed that the significant reductions in risks for any allergy, hay fever, and food allergy were restricted to females. Our findings of increased risks for atopic disorders and hay fever in Asian participants require further evaluation.

Our results also mirror those from our previous pooled InterLymph analysis (1703 FL) (17) that found a twofold increased FL risk among participants with a first-degree relative with a history of NHL, with risks elevated in both male and female participants, except females with affected male relatives (17). Our data also support findings from other studies of a stronger familial association of NHL risk in male relatives, which is consistent for FL and other lymphoma subtypes (49–51).

The present study reveals a reduced risk of FL only in current drinkers who were female, but not related to the frequency or duration of their alcohol consumption. In our earlier InterLymph pooled evaluation based on nine studies (1307 FL) (26), we observed a reduced risk of FL associated with alcohol consumption, particularly in current drinkers, but with no evidence of dose–response relationships with frequency or duration of alcohol use. Prospective studies have shown mixed results with moderate (52–56) and heavy (27) alcohol intake associated with reductions in FL risk ranging from 23% to 41% in some studies, but not in others (57–59). One cohort study found an elevated risk of FL among women who were former alcohol drinkers (60). It has been postulated that these findings may be due to effects of alcohol in modulating immune function (61) but because immune deficiency has not been shown to be important for FL risk, chronic inflammation may be a potential biologic mechanism, although alcohol has many other biologic effects. An alternative explanation is that the association is not causal but may reflect differences in other characteristics between alcohol drinkers and nondrinkers.

In our previous InterLymph evaluation of sun exposure (1642 FL) (30), we found a downward trend in risk with increasing total recreational sun exposure, particularly for exposures at 18–40 years of age and in the 10 years before diagnosis for all B-cell lymphomas and for FL, but no association with occupational sun exposure. This inverse association may be due partly to effects on the

Table 5. Family history of hematopoietic malignancies and risk of follicular lymphoma*

First-degree family history	Controls† No. (%)	Cases† No. (%)	OR (95% CI)‡	*P*
Any hematologic malignancy				
No	14 346 (81.5)	2144 (81.3)	1.00 (referent)	<.001
Yes	769 (4.4)	198 (7.5)	1.48 (1.25 to 1.75)	
Any hematologic malignancy in male relatives				
No	11 543 (80.5)	1759 (82.2)	1.00 (referent)	<.001
Yes	329 (2.3)	88 (4.1)	1.56 (1.22 to 2.00)	
Any hematologic malignancy in female relatives				
No	11 560 (80.6)	1764 (82.5)	1.00 (referent)	.011
Yes	312 (2.2)	83 (3.9)	1.41 (1.09 to 1.82)	
NHL				
No	14 116 (83.6)	2145 (84.6)	1.00 (referent)	<.001
Yes	278 (1.6)	96 (3.8)	1.99 (1.55 to 2.54)	
NHL in male relatives				
No	11 759 (82.0)	1812 (84.7)	1.00 (referent)	.004
Yes	113 (0.8)	35 (1.6)	1.84 (1.24 to 2.73)	
NHL in female relatives				
No	11 746 (81.9)	1803 (84.3)	1.00 (referent)	<.001
Yes	126 (0.9)	44 (2.1)	1.93 (1.35 to 2.75)	
Multiple myeloma				
No	11 327 (81.9)	1795 (85.4)	1.00 (referent)	.040
Yes	41 (0.3)	16 (0.8)	1.93 (1.06 to 3.51)	
Multiple myeloma in male relatives				
No	8048 (76.6)	1338 (81.7)	1.00 (referent)	.003
Yes	16 (0.2)	11 (0.7)	3.64 (1.65 to 8.05)	
Multiple myeloma in female relatives				
No	8842 (92.1)	1550 (91.6)	1.00 (referent)	.870
Yes	25 (0.3)	5 (0.3)	0.92 (0.35 to 2.46)	
Leukemia				
No	13 831 (92.4)	2129 (91.3)	1.00 (referent)	.853
Yes	402 (2.7)	65 (2.8)	0.98 (0.74 to 1.28)	
Leukemia in male relatives				
No	11 634 (92.6)	1811 (91.5)	1.00 (referent)	.873
Yes	197 (1.6)	31 (1.6)	0.97 (0.66 to 1.43)	
Leukemia in female relatives				
No	11 680 (92.9)	1815 (91.7)	1.00 (referent)	.933
Yes	151 (1.2)	27 (1.4)	1.02 (0.67 to 1.55)	
HL				
No	14 149 (94.5)	2173 (93.2)	1.00 (referent)	.133
Yes	84 (0.6)	21 (0.9)	1.47 (0.90 to 2.40)	
HL in male relatives				
No	11 288 (93.6)	1795 (92.3)	1.00 (referent)	.239
Yes	39 (0.3)	11 (0.6)	1.53 (0.77 to 3.04)	
HL in female relatives				
No	10 316 (94.6)	1694 (93.6)	1.00 (referent)	.456
Yes	29 (0.3)	7 (0.4)	1.39 (0.60 to 3.23)	

* CI = confidence interval; HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; OR = odds ratio.

† The counts do not add up to the total # of cases/controls due to data missing by design or report.

‡ OR (95% CI) adjusted for age, sex, race/ethnicity, and study.

immune function from sun exposure (62), vitamin D production (63), or chance. A cohort study examining ambient residential ultraviolet radiation among California teachers showed null findings for FL (28).

To our knowledge, the current study is the first to find that persons with a history of blood transfusion experienced a modestly reduced risk of FL. Blood transfusion (which suppresses cellular immunity, includes transfer of allogeneic cells, and may transmit infectious and chemical agents) has been associated with increased risk of all NHL in some (15,64–66), but not all studies (67–72). Limited data on the role of transfusions in FL suggest no risk (73–76) or a modest increase in risk (8,15). Cerhan and colleagues (15) have suggested that transfusions may be a marker for underlying medical conditions rather than directly associated with NHL or its subtypes.

The association of overweight and obesity in early adulthood with FL risk is strengthened by the significant positive dose–response trend of early adult BMI with FL risk. However, most cohort studies (7,56,58,77–82), with one exception (83), found no relationship of early adult weight or BMI with FL, although many

Table 6. Lifestyle factors and risk of follicular lymphoma*

	Controls†	Cases†		
	No. (%)	No. (%)	OR (95% CI)‡	*P*
BMI, weight, and height				
BMI as a young adult, kg/m^2				
15–<18.5	382 (2.5)	66 (2.5)	0.90 (0.67 to 1.19)	
18.5–<22.5	2800 (18.1)	464 (17.8)	1.00 (referent)	.001
22.5–<25	1391 (9.0)	201 (7.7)	1.03 (0.85 to 1.24)	
25–<30	838 (5.4)	164 (6.3)	1.49 (1.21 to 1.83)	
30–50	172 (1.1)	34 (1.3)	1.46 (0.98 to 2.17)	
Continuous (5 kg/m^2 increase in BMI)	5583	929	1.21 (1.09 to 1.35)	<.001
Usual adult BMI, kg/m^2				
15–<18.5	267 (1.6)	25 (0.9)	0.67 (0.44 to 1.03)	
18.5–<22.5	3481 (20.3)	538 (19.4)	1.00 (referent)	.143
22.5–<25	4276 (25.0)	706 (25.5)	1.09 (0.96 to 1.23)	
25–<30	6112 (35.7)	959 (34.6)	1.01 (0.89 to 1.14)	
30–<35	1760 (10.3)	325 (11.7)	1.07 (0.91 to 1.25)	
35–50	608 (3.6)	109 (3.9)	0.93 (0.73 to 1.17)	
Continuous (5 kg/m^2 increase in BMI)	16504	2662	0.99 (0.95 to 1.04)	.735
Usual adult height				
Quartile 1 (low)	4131 (24.1)	584 (21.1)	1.00 (referent)	.124
Quartile 2	3852 (22.5)	603 (21.8)	1.04 (0.92 to 1.18)	
Quartile 3	4169 (24.3)	695 (25.1)	1.05 (0.93 to 1.19)	
Quartile 4 (high)	4352 (25.4)	780 (28.1)	1.15 (1.02 to 1.30)	
Usual adult weight				
Quartile 1 (low)	4115 (24.0)	583 (21.0)	1.00 (referent)	.263
Quartile 2	3953 (23.1)	627 (22.6)	1.01 (0.89 to 1.14)	
Quartile 3	4335 (25.3)	680 (24.5)	0.94 (0.83 to 1.07)	
Quartile 4 (high)	4101 (24.0)	772 (27.8)	1.06 (0.94 to 1.20)	
Physical activity				
No	716 (10.1)	98 (7.1)	1.00 (referent)	. 055
Mild	474 (6.7)	134 (9.8)	1.41 (1.04 to 1.91)	
Moderate	934 (13.2)	209 (15.2)	1.09 (0.83 to 1.45)	
Vigorous	3037 (43.0)	585 (42.6)	1.26 (0.99 to 1.60)	
Cigarette smoking				
History of cigarette smoking§				
No	8879 (40.7)	1264 (38.3)	1.00 (referent)	.046
Yes	11690 (53.6)	1749 (53.0)	1.09 (1.00 to 1.18)	
Smoking status				
Nonsmoker	8879 (40.7)	1264 (38.3)	1.00 (referent)	.009
Former smoker	6327 (29.0)	956 (29.0)	1.02 (0.93 to 1.12)	
Current smoker	4829 (22.2)	743 (22.5)	1.19 (1.07 to 1.32)	
Smoker, status unknown	534 (2.5)	50 (1.5)	1.05 (0.76 to 1.45)	
Age started smoking cigarettes regularly				
Nonsmoker	8879 (40.7)	1264 (38.3)	1.00 (referent)	.051
<14 y	1068 (4.9)	125 (3.8)	0.88 (0.72 to 1.07)	
14–17 y	4348 (20.0)	710 (21.5)	1.12 (1.01 to 1.25)	
18–19 y	2352 (10.8)	384 (11.6)	1.11 (0.97 to 1.26)	
≥20 y	3251 (14.9)	475 (14.4)	1.11 (0.99 to 1.25)	
Smoker, age start unknown	671 (3.1)	55 (1.7)	0.94 (0.69 to 1.27)	
Frequency of cigarette smoking				
Nonsmoker	8879 (40.7)	1264 (38.3)	1.00 (referent)	.088
Smoker, 1–10 cigarettes/d	3910 (17.9)	603 (18.3)	1.09 (0.98 to 1.21)	
Smoker, 11–20 cigarettes/d	4766 (21.9)	731 (22.1)	1.13 (1.02 to 1.25)	
Smoker, 21–30 cigarettes/d	1248 (5.7)	189 (5.7)	1.09 (0.92 to 1.29)	
Smoker, >30 cigarettes/d	1339 (6.1)	155 (4.7)	0.90 (0.75 to 1.09)	
Smoker, cigarettes/day unknown	427 (2.0)	71 (2.2)	1.11 (0.84 to 1.45)	
Continuous	20173	2946	1.00 (1.00 to 1.00)	.948
Duration of cigarette smoking				
Nonsmoker	8879 (40.7)	1264 (38.3)	1.00 (referent)	.013
1–20 y	3917 (18.0)	534 (16.2)	1.02 (0.91 to 1.14)	
21–30 y	2341 (10.7)	388 (11.8)	1.10 (0.97 to 1.25)	
30–39 y	2392 (11.0)	417 (12.6)	1.13 (1.00 to 1.28)	
≥40 y	2749 (12.6)	391 (11.8)	1.18 (1.04 to 1.35)	

(Table continues)

Table 6 (Continued).

	Controls†	Cases†		
	No. (%)	No. (%)	OR (95% CI)‡	*P*
Smoker, duration unknown	291 (1.3)	19 (0.6)	0.63 (0.39 to 1.01)	
Continuous	20278	2994	1.00 (1.00 to 1.01)	.006
Lifetime cigarette exposure				
Nonsmoker	8879 (40.7)	1264 (38.3)	1.00 (referent)	.150
1–10 pack-years	3473 (15.9)	501 (15.2)	1.06 (0.95 to 1.19)	
11–20 pack-years	2272 (10.4)	341 (10.3)	1.06 (0.93 to 1.21)	
21–35 pack-years	2369 (10.9)	409 (12.4)	1.18 (1.04 to 1.34)	
≥36 pack-years	3038 (13.9)	425 (12.9)	1.10 (0.97 to 1.25)	
Smoker, pack-years unknown	538 (2.5)	73 (2.2)	0.93 (0.72 to 1.22)	
Alcohol consumption				
History of alcohol consumption				
Nondrinker	4277 (21.7)	643 (21.9)	1.00 (referent)	.009
Drinker (at least 1 drink per month)	10994 (55.9)	1463 (49.8)	0.86 (0.77 to 0.96)	
Alcohol consumption status				
Nondrinker	4277 (21.7)	643 (21.9)	1.00 (referent)	.003
Former drinker	609 (3.1)	125 (4.3)	1.16 (0.91 to 1.49)	
Current drinker	5010 (25.5)	723 (24.6)	0.88 (0.76 to 1.03)	
Drinker, status unknown	5375 (27.3)	615 (20.9)	0.81 (0.69 to 0.95)	
Age at first alcohol consumption				
Nondrinker	4277 (21.7)	643 (21.9)	1.00 (referent)	.023
<20 y	2281 (11.6)	316 (10.8)	0.92 (0.76 to 1.12)	
20–29 y	2908 (14.8)	349 (11.9)	0.88 (0.74 to 1.05)	
≥30 y	768 (3.9)	117 (4.0)	1.07 (0.85 to 1.35)	
Drinker, age start unknown	5037 (25.6)	681 (23.2)	0.80 (0.68 to 0.93)	
Duration of alcohol consumption				
Nondrinker	4277 (21.7)	643 (21.9)	1.00 (referent)	.078
1–20 y	1307 (6.6)	128 (4.4)	0.87 (0.69 to 1.11)	
21–30 y	1085 (5.5)	164 (5.6)	0.90 (0.72 to 1.13)	
30–39 y	1247 (6.3)	182 (6.2)	0.95 (0.76 to 1.17)	
≥40 y	1900 (9.7)	243 (8.3)	1.00 (0.81 to 1.22)	
Drinker, duration unknown	5455 (27.7)	746 (25.4)	0.80 (0.69 to 0.93)	
Servings of alcohol per week as an adult				
Nondrinker	4277 (21.7)	643 (21.9)	1.00 (referent)	.017
<1 drink/wk	955 (4.9)	182 (6.2)	0.89 (0.74 to 1.08)	
1–6 drinks/wk	3738 (19.0)	571 (19.4)	0.85 (0.75 to 0.97)	
7–13 drinks/wk	2216 (11.3)	288 (9.8)	0.84 (0.72 to 0.99)	
14–27 drinks/wk	2137 (10.9)	258 (8.8)	0.91 (0.77 to 1.08)	
≥28 drinks/wk or binge drinkers	1918 (9.8)	157 (5.3)	0.78 (0.64 to 0.96)	
Drinker, drinks/week unknown	30 (0.2)	7 (0.2)	3.00 (1.25 to 7.23)	
Grams of ethanol per week as an adult, consumed from any type of alcoholic beverage				
Nondrinker	4277 (21.7)	643 (21.9)	1.00 (referent)	.005
Quartile 1 (low)	2421 (12.3)	347 (11.8)	0.79 (0.68 to 0.92)	
Quartile 2	2471 (12.6)	325 (11.1)	0.83 (0.71 to 0.97)	
Quartile 3	2488 (12.6)	315 (10.7)	0.87 (0.75 to 1.02)	
Quartile 4 (high)	2534 (12.9)	230 (7.8)	0.79 (0.66 to 0.94)	
Drinker, grams consumed unknown	1080 (5.5)	246 (8.4)	1.33 (0.97 to 1.83)	
Lifetime alcohol consumption				
Nondrinker	4277 (21.7)	643 (21.9)	1.00 (referent)	.007
1–100 kg	1444 (7.3)	182 (6.2)	0.75 (0.60 to 0.93)	
101–200 kg	641 (3.3)	67 (2.3)	0.68 (0.51 to 0.91)	
201–400 kg	651 (3.3)	96 (3.3)	1.05 (0.81 to 1.37)	
>400 kg	759 (3.9)	75 (2.6)	0.85 (0.64 to 1.14)	
Drinker, lifetime consumption unknown	7499 (38.1)	1043 (35.5)	0.90 (0.79 to 1.03)	
Continuous	7886	1106	1.00 (1.00 to 1.00)	.893
Sun exposure				
Total sun exposure (h/wk)				
Quartile 1 (low)	1508 (18.7)	337 (20.6)	1.00 (referent)	.116
Quartile 2	1594 (19.8)	293 (18.0)	0.83 (0.69 to 0.99)	
Quartile 3	1633 (20.3)	307 (18.8)	0.88 (0.73 to 1.05)	
Quartile 4 (high)	1714 (21.3)	299 (18.3)	0.82 (0.69 to 0.99)	

(Table continues)

Table 6 (Continued).

	Controls†	Cases†		
	No. (%)	No. (%)	OR (95% CI)‡	*P*
Recreational sun exposure (h/wk)				
Quartile 1 (low)	2234 (20.6)	522 (24.8)	1.00 (referent)	<.001
Quartile 2	2332 (21.6)	421 (20.0)	0.77 (0.67 to 0.90)	
Quartile 3	2159 (20.0)	393 (18.6)	0.77 (0.66 to 0.89)	
Quartile 4 (high)	2983 (27.6)	505 (24.0)	0.74 (0.65 to 0.86)	

* BMI = body mass index; CI = confidence interval; OR = odds ratio.
† The counts do not add up to the total # of cases/controls due to data missing by design or report.
‡ OR (95% CI) adjusted for age, sex, race/ethnicity, and study.
§ Smoked longer than 6 months or more than 100 cigarettes in lifetime.

Table 7. Occupational factors and risk of follicular lymphoma*

	Controls†	Cases†		
	No. (%)	No. (%)	OR (95% CI)‡	*P*
Farm residence and/or farming & related occupation				
Ever lived on a farm				
No	4779 (56.3)	822 (58.1)	1.00 (referent)	.592
Yes	3470 (40.9)	554 (39.1)	0.97 (0.85 to 1.09)	
Ever worked on a farm				
No	11 675 (80.0)	1978 (83.0)	1.00 (referent)	.177
Yes	2717 (18.6)	371 (15.6)	0.92 (0.81 to 1.04)	
Animal farm workers				
No	11 699 (94.8)	2092 (97.0)	1.00 (referent)	.985
Yes	316 (2.6)	52 (2.4)	1.00 (0.73 to 1.36)	
Crop farm workers				
No	11 442 (92.7)	2069 (96.0)	1.00 (referent)	.994
Yes	573 (4.6)	75 (3.5)	1.00 (0.78 to 1.29)	
Farm workers, any type				
No	10 583 (85.8)	1935 (89.7)	1.00 (referent)	.839
Yes	1432 (11.6)	209 (9.7)	0.98 (0.84 to 1.16)	
Forestry worker				
No	11 227 (96.6)	2001 (99.1)	1.00 (referent)	.580
Yes	71 (0.6)	7 (0.3)	0.81 (0.37 to 1.77)	
Meat worker				
No	11 907 (96.5)	2121 (98.4)	1.00 (referent)	.491
Yes	108 (0.9)	23 (1.1)	1.18 (0.74 to 1.88)	
Other selected occupations				
Bakers and millers				
No/never	11 857 (96.1)	2132 (98.9)	1.00 (referent)	.017
Yes	158 (1.3)	12 (0.6)	0.51 (0.28 to 0.93)	
Chemists and chemical workers				
No/never	11 848 (96.0)	2110 (97.9)	1.00 (referent)	.156
Yes	167 (1.4)	34 (1.6)	1.33 (0.91 to 1.94)	
Petroleum worker				
No/never	10 558 (96.9)	1905 (99.3)	1.00 (referent)	.518
Yes	18 (0.2)	2 (0.1)	0.63 (0.14 to 2.78)	
Medical worker				
No/never	11 120 (90.1)	1957 (90.8)	1.00 (referent)	.752
Yes	895 (7.3)	187 (8.7)	0.97 (0.82 to 1.16)	
Medical doctor				
No/never	11 921 (96.6)	2123 (98.5)	1.00 (referent)	.425
Yes	82 (0.7)	18 (0.8)	1.24 (0.74 to 2.10)	
Spray-painter (except construction)				
No/never	10 596 (96.7)	1777 (98.4)	1.00 (referent)	.008
Yes	29 (0.3)	13 (0.7)	2.66 (1.36 to 5.24)	
University and higher education teachers				
No/never	11 729 (95.1)	2104 (97.6)	1.00 (referent)	.001
Yes	274 (2.2)	37 (1.7)	0.58 (0.41 to 0.83)	

* CI = confidence interval; OR = odds ratio.
† The counts do not add up to the total # of cases/controls due to data missing by design or report.
‡ OR (95% CI) adjusted for age, sex, race/ethnicity, and study.

of these studies included relatively small numbers of FL cases. Our finding of a relationship between greater adult height in males, but not females, in relation to FL is likely a chance finding since most cohort studies (56,58,78–82) reported no relationship of height in men or women with FL except for three (20,77,83) that found a positive relationship in women.

This pooled analysis is the first and largest multivariate assessment of a broad range of putative risk factors for FL. Other strengths include assessment of effect modification (particularly gender) and confounding. The systematic nature of the subtype evaluation using the WHO classification, exposure assessment by standardized questionnaires, population-based design for most of the studies, along with careful efforts to harmonize the variables included in the pooled analyses, represent additional strengths. Limitations include the self-reported nature of the data collected, the difficulty of using retrospectively collected information, reliance on job titles instead of specific occupational exposures, the limited types of exposures evaluated, and lack of comprehensive assessment of many of the individual putative risk factors, multiple comparisons, and absence of assessment of some variables for all studies. Sex-specific associations could be due to chance or unexplained bias, although it is possible that such associations may reflect genetic variation, hormonal exposure, or occupational exposures. Other limitations include lack of independent evaluation of exposures and the potential for recall bias. Some findings (eg, female-specific associations with alcohol consumption, the inverse association with history of blood transfusions or the relationship with BMI in early adulthood) may be due to chance.

In conclusion, the majority of the factors evaluated were not associated with risk of FL. As noted above, associations with blood transfusion and BMI in early adulthood are inconsistent with prior studies. The sex-specific findings for cigarette smoking and allergic disorders, as well as the associations with some occupations, deserve further evaluation. Although this study does not identify risk factors that explain much of FL occurrence, the few relationships observed do provide clues suggesting a complex multifactorial etiology.

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