Published in final edited form as:
Ann Epidemiol. 2012 December ; 22(12): 855–862. doi:10.1016/j.annepidem.2012.10.002.

The Association between Early Life and Adult Body Mass Index and Physical Activity with Risk of non-Hodgkin Lymphoma: Impact of Gender

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Abstract

Purpose—To evaluate the association of body mass index (BMI) and physical activity (PA) during adulthood and at age 18 with risk of non-Hodgkin lymphoma (NHL).

Methods—We enrolled 950 newly diagnosed NHL patients and 1146 frequency-matched clinic-based controls. Height, weight, and PA (recent adult and at age 18) were self-reported. Odds ratios (OR), 95% confidence intervals (CI), and tests for trend were estimated using unconditional logistic regression adjusted for age, gender, and residence.

Results—BMI at age 18 was associated with an increased NHL risk (OR=1.38 for highest vs. lowest quartile, p-trend=0.0012), which on stratified analysis was specific to females (OR=1.90, p-trend=0.00025). There was no association of adult BMI with NHL risk. Higher physical activity in adulthood (OR=1.03, p-trend=0.85) or at age 18 (OR=0.88, 95%CI: 0.72–1.07) was not associated with risk, but there was an inverse association for adult physical activity that was specific to females (OR=0.71, p-trend=0.039). Only BMI at age 18 remained significantly associated with NHL risk when modeled together with adult or age 18 physical activity. There was little evidence for heterogeneity in these results for the common NHL subtypes.

Conclusions—Early adult BMI may be of greatest relevance to NHL risk, particularly in females.

MeSH Keywords

body mass index; exercise; lymphoma; non-Hodgkin; etiology; case-control studies

BACKGROUND

The lifetime risk of developing non-Hodgkin lymphoma (NHL) is 1 in 44 for men and 1 in 52 for women, making this malignancy the 6th most common cancer in the United States (1–

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2). The best characterized risk factors to date are immune deficiency and immune suppression (3–6). The incidence of NHL rose markedly over the past several decades, with an estimated 80% increase in incidence rates between 1970 and the late 1990s (7–9). Concurrently, the prevalence of adult obesity (body mass index (BMI) ≥30 kg/m^2) in the US has doubled between 1980 and 2002 (10), and was most recently estimated at 35.9% (11). With an additional 33.3% of adults having BMIs between 25 and 30 kg/m^2, 69.2% of the adult US population is estimated to be overweight or obese (12). While regular physical activity has increased slightly between 2000 and 2005, a majority of US adults remain physically inactive (13).

Obesity has been established as a causal factor in several cancers, including breast cancer in postmenopausal women, endometrial, kidney, and esophageal cancers (14). There is also sufficient evidence to conclude that physical inactivity increases the risk of colon and breast cancer (14). The exact mechanisms linking obesity and physical activity to cancer have yet to be fully elucidated, and appear to be variable by cancer site (15). However, obesity and associated excess adipose tissue have been associated with elevated levels of several markers of chronic low-grade systemic inflammation, including C-reactive protein, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and leptin (16–17); decreased levels of the proapoptotic and antiproliferative adipokine adiponectin (17); and impaired immune function (18). Conversely, physical activity is associated with decreased weight and central adiposity (19), as well as inhibition of proinflammatory cytokines (16).

The link between obesity and NHL risk has been evaluated in multiple epidemiologic studies. This literature has recently been comprehensively reviewed (20), and three meta-analyses report a weak but statistically significant association between obesity and NHL risk (21). Fewer studies have evaluated BMI in early adulthood and NHL risk (22–32). Data are also more limited for physical activity and NHL risk (25, 27, 30–31, 33–36), particularly in early adulthood (27, 30). The purpose of this study was to evaluate the association of BMI, physical activity, and NHL risk, with particular attention to the life period of exposure and patterns of association for the most common NHL subtypes.

METHODS

Study Population

This study was reviewed and approved by the Mayo Clinic Human Subjects Institutional Review Board, and all participants provided written informed consent. Full details of this clinic-based case-control study conducted at the Mayo Clinic (Rochester, MN) have been published (37). Briefly, eligible patients were within 9 months of their first lymphoma diagnosis and ≥20 years old at the time of diagnosis; clinic-based controls were randomly selected from a dynamic population of patients, age ≥20, who had prescheduled medical examinations in the Mayo Clinic general medicine practices. Controls were frequency matched to cases by 5-year age group, gender, and residence. Of the 1798 eligible cases and 1899 eligible controls recruited from 9/2002 – 2/2008, 1236 (69%) and 1315 (69%) participated in the study, respectively. Participants with NHL (N=95 Hodgkin lymphoma cases excluded) who completed the self-administered risk-factor questionnaire for BMI and physical activity (950 cases, 1146 controls) were included in this analysis. Cases and controls without a complete risk-factor questionnaire were slightly younger and slightly more likely to be male, while there were no differences by state of residence.

Exposure Assessment

Height and weight were self-reported on the risk-factor questionnaire; weight was reported for both the time period 2 years prior to case diagnosis/control selection (recent adult weight) as well as at age 18. BMI for both time periods was calculated as weight (kg) divided by height (m) squared. For recent adult BMI we used WHO categories (38) for analysis (<18.5 kg/m^2, underweight; 18.5–24.9 kg/m^2, healthy weight; 25–29.9 kg/m^2, overweight; ≥30 kg/m^2, obese). BMI at age 18 was divided into gender-specific quartiles according to the distribution among controls. Physical activity variables included duration (average number of minutes/session) and frequency (categorical; 1–3 days/month to ≥5 days/week) of walking, mild, moderate, and strenuous physical activity two years prior to case diagnosis or control selection (recent adult physical activity). An overall index of recent adult physical activity was estimated by weighting the reported duration and frequency of each physical activity intensity by the average energy requirement (defined in metabolic equivalents; METs) to obtain an average MET-minutes/week for each participant. A MET score of 3.0, 4.0, and 8.0 was used to weight the product of reported mild, moderate and strenuous exercise, respectively, and the MET score for walking varied from 2.0 for casual walking speed to 6.3 for very fast walking (39–40). Participants were also asked to self-report regular strenuous exercise (exercise that was long enough to work up a sweat and make your heart beat fast) at age 18 (yes or no).

Statistical Analysis

We used unconditional logistic regression to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for the association of BMI and physical activity with risk of NHL, adjusting for the design variables of age at enrollment, gender and residence. A p-trend was calculated in unconditional logistic models assuming an ordinal relationship among variable categories. Potential confounding variables were evaluated individually in the age period-specific logistic regression models, and included: total energy, fat calories, and physical activity (recent adult BMI main effect models only); and alcohol consumption, smoking history, and family history of NHL (all models). We also evaluated potential confounding by early life sun exposure (41) and total vegetable intake (42). Only variables that changed the main effect OR by greater than 10% were retained in the final models. We also evaluated these associations for the major NHL subtypes of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL) using polytomous logistic regression (43); a Wald-test was used to assess heterogeneity across these subtypes.

In secondary analyses, we evaluated the associations of BMI (recent and early adult) and physical activity (recent and early adult) stratified by gender. A formal test of interaction was also calculated using a likelihood ratio test comparing models with and without an interaction term. Finally, a series of multivariate models were evaluated to assess the relative contribution of recent and early adult BMI and physical activity in relation to NHL risk.

Analyses were conducted using SAS software system (SAS Institute, Cary, NC; Version 9.2).

RESULTS

Cases and controls were similar with respect to age (median age 63 years for each) and gender (58% and 53% males, respectively), residence and level of education (Table 1). Virtually all (99%) of the participants were Caucasian. The most common NHL subtypes were CLL/SLL (N=302), FL (N=242), and DLBCL (N=181). The overall prevalence of overweight or obese in this study population was 41% and 27%. The correlation between early adult and recent adult BMI was r=0.47 (p<0.0001).

We observed a stronger association of early adult BMI with overall NHL risk (OR=1.38, 95%CI: 1.08–1.76; p-trend=0.0012) as compared to recent adult BMI (OR=1.15, 95%CI:

0.91–1.45; p-trend=0.23) (Table 2). These results were similar after restricting cases to those who enrolled closest to diagnosis (<median time of 61 days), those presenting without B symptoms, and those with advanced stage disease (III/IV), providing some evidence against major recall bias or reverse causality. The strongest association for early adult BMI was with risk of DLBCL (OR=1.77, 95%CI: 1.13–2.77; p-trend=0.004), although ORs were above 1 for the other subtypes and the test for heterogeneity among subtypes was not statistically significant (p=0.47). When we stratified by gender for both early and recent adult BMI, we found that the increased overall NHL risk with early adult BMI was specific to females (OR=1.90, 95%CI: 1.29–2.79; p-trend=0.00025), with a suggestive p-interaction=0.097. There was a similar but weaker trend also specific to females for recent adult BMI (OR=1.27, 95%CI: 0.90–1.78; p-trend=0.17), but the interaction was not statistically significant (p-interaction=0.53). In subtype analysis, associations for BMI at age 18 years were specific to females for FL (OR=1.81, 95%CI: 1.01–3.25; p-trend=0.029) and CLL/SLL (OR=1.52, 95%CI: 0.82–2.80; p-trend=0.093), while for DLBCL they were observed for both males (OR=1.57, 95%CI: 0.87–2.83; p-trend=0.078) and females (OR=2.16, 95%CI: 1.06–4.38; p-trend=0.017). A similar, although weaker, pattern in subtype risk between females and males was observed for recent adult BMI.

There was no association of the summary adult physical activity index with overall NHL risk (OR=1.03, 95%CI: 0.80–1.33; p-trend=0.85) (Table 3); frequency of walking, mild, moderate, and strenuous activity in adulthood showed no associated when evaluated individually (data not shown). There was some suggestion of reduced NHL risk associated with strenuous physical activity in early adulthood (OR=0.88, 95%CI: 0.72–1.07). There was no evidence of heterogeneity by subtype for the adult physical activity index (p=0.82) or strenuous physical activity at age 18 (p=0.93). However, after stratification by gender, we found that there was an inverse association of recent adult physical activity among females (OR=0.71, 95%CI: 0.47–1.07; p-trend 0.039) but not males (OR=1.37, 95%CI: 0.98–1.92; p-trend=0.15), with overall NHL risk (p-interaction=0.059). Similarly, the weak inverse association with overall NHL risk for strenuous physical activity at age 18 years was observed for females (OR=0.81, 95%CI 0.61–1.07) but not males (OR=1.00, 95%CI: 0.72–1.07), p-interaction=0.30.

We next evaluated a series of multivariate models to assess the relative importance of BMI and physical activity, as well as timing of each exposure, with regard to overall NHL risk and NHL risk by gender (Table 4). Models 1 and 2 evaluated the relative significance of BMI and physical activity, each within the same life period. At age 18, physical activity was not associated with NHL risk after adjusting for BMI (OR=1.45, 95%CI: 1.12–1.87), and this finding was limited to females (OR=2.06, 95%CI: 1.36–3.11). For recent adult exposures, neither BMI nor physical activity was strongly associated with NHL risk; the decreased risk of NHL with high physical activity observed among females in the univariate analyses remained only marginally significant in a model with BMI. Models 3 and 4 evaluated the relative significance of exposure timing (i.e., early life versus recent adult) for BMI and physical activity, respectively. For BMI, early adult exposure was more relevant with regard to NHL risk overall (OR=1.41, 95%CI: 1.08–1.83, p=0.0019), and even more so for females (OR=1.82, 95%CI: 1.20–2.77, p=0.0014); neither early nor recent adult BMI was strongly associated with NHL risk among males. When early and recent adult physical activity were modeled simultaneously, neither was significantly associated with NHL risk. Finally, in a model with BMI at age 18 and adult physical activity (model 5), only BMI at age 18 remained significant, and this association remained specific to females (BMI at age 18 OR=2.02, 95%CI: 1.34–3.05, p=0.0003).

DISCUSSION

In this case-control study, we observed an association of high BMI in early adulthood with increased NHL risk, which was specific to females and showed little heterogeneity by common NHL subtypes. After accounting for BMI at age 18, recent adult BMI, recent adult physical activity, and early adult physical activity were not associated with NHL risk.

The association between recent adult BMI and NHL risk has been investigated in numerous cohort and case-control studies, and has been examined recently in a comprehensive literature review (20), three meta-analyses (21, 44–45), and a pooled analysis (46). All three meta-analyses report a weak but statistically significant association between increased BMI and NHL risk, with relative risk estimates ranging from 1.06 (95%CI: 1.03–1.09) (45) per 5 kg/m^2 to 1.20 (95%CI: 1.07–1.34) with BMI ≥30 kg/m^2 (21). The InterLymph pooled analysis reported an association between BMI ≥40 kg/m^2 and lymphoma risk that was limited to the DLBCL subtype (OR=1.80; 95%CI 1.24–2.62) (46). Our results for all NHL are broadly consistent, showing a very weak overall effect for recent adult BMI ≥30 kg/m^2 (OR=1.15; 95%CI 0.91–1.45) and the strongest effect for DLBCL (OR=1.35; 95%CI 0.89–2.04), although neither estimate was statistically significant.

Thirteen studies evaluated the association of BMI at younger ages with NHL risk (22–32, 47–48). Consistent with our findings, the cumulative evidence suggests that high BMI in early adulthood (ages 18–20) may be more relevant with regard to NHL risk (23, 25, 27–29). Six of these studies also evaluated the association between early adult BMI and NHL risk by gender (23–24, 28–29, 32, 48), and two were limited to females (25, 31). Of these studies, one reported a slightly stronger association among females (24), two studies reported a stronger association in males (28–29) and three studies reported similar associations by gender (23, 32, 48); early adult BMI was associated with NHL risk in only one (25) of the studies among females. Significant regional and study-specific heterogeneity of the association between recent adult BMI and NHL risk was noted in the InterLymph pooled analysis (46), and could potentially explain some of the inconsistency in the literature. However, we acknowledge that the observed association of early adult BMI with NHL risk limited to females in our study may be a false positive.

Multiple hypotheses have been proposed for mechanisms linking BMI with NHL risk, and all remain speculative. A low level chronic inflammatory state has been associated with higher BMI levels, which could support B cell growth and increase NHL risk (16–17). There is some evidence to support a positive, direct effect of BMI on hyperinsulinema, which leads to growth factor potentiation and anti-apoptotic signaling as a result of increased free IGF-1 (17). A recent analysis conducted in the Nurses' Health Study Cohorts demonstrated an association between high BMI at age 18 and IGF-1 levels in adulthood (49). Additionally, the adipokine leptin is a hormone secreted from adipocytes with serum levels closely correlated to adiposity, and leptin gene expression is also upregulated by insulin (17, 50). Variation in both the leptin and leptin receptor (*LEP* and *LEPR*) genes have been associated NHL risk (24).

While the rise in obesity prevalence among adolescents has paralleled the rapid rise in obesity observed in US adults, evidence from NHANES indicates that the increase in obesity prevalence from 1971–2000 is similar between adolescent girls and boys (51). However, the proposed biologic mechanisms linking BMI and cancer risk may vary by gender (17). Perhaps of most relevance to the gender difference observed between early adult BMI and NHL risk, there is evidence of a significant gender difference in serum leptin levels, with higher levels in females as compared to males (52).

Based on our observations, physical activity appears to be less relevant to NHL risk as compared to BMI. There has only been limited evaluation of physical activity and risk of NHL (25, 27, 30–31, 33–36), particularly physical activity earlier in life (27, 30). With the exception of a decreased NHL risk among women with higher levels of reported physical activity (OR=0.59; 95%CI: 0.42–0.81) reported in a Canadian case-control study (34), there is little evidence to support an association between physical activity and NHL risk, consistent with our observations. Of note, recent adult physical activity was self-reported at the time of study enrollment, and it is possible that latent NHL could have led to decreased physical activity in the time preceding diagnosis. Furthermore, physical activity at age 18 was assessed via a single dichotomous measure, likely resulting in exposure misclassification that could have limited our ability to detect an association with NHL risk. Future evaluation of physical activity at this age should take into account exercise intensity, frequency, and duration.

While underpowered to assess NHL subtypes, our data provide some evidence that there may be subtype-specific associations with BMI. NHL subtypes are known to be very clinically (53), and likely etiologically (54) heterogeneous. While most studies have evaluated the association between BMI and all NHL subtypes combined, in subtype analysis BMI has been most consistently linked to DLBCL (21, 44, 46), and high BMI (≥35 kg/m^2) was associated with increased risk of DLBCL alone in a study designed specifically to evaluate subtype heterogeneity (54). For early adult BMI, we observed the strongest association for DLBCL, although there were associations for FL and CLL/SLL as well, but only among female participants.

Our analysis is a result of a carefully designed case-control study with central pathology review. Although this study was not population-based, the effects of referral and selection bias were minimized by restricting both case and control participation to those residing in the region surrounding Mayo Clinic (Minnesota, Iowa, and Wisconsin). Participation rates for both cases and controls were relatively high, and the controls were well balanced to cases in regard to geographic characteristics (distance and rural/urban), marital status, education, and SES, supporting the internal validity of the control group (37). Broad consistency of results from this study with pooled results from InterLymph studies further supports internal validity. Demographic and disease characteristics of cases are similar to population-based cancer registry data, and the controls had similar characteristics for anthropometrics and other lifestyle factors when compared to a population-based control group from Iowa, all providing evidence of external validity (37).

Our measure of physical activity ascertained frequency, duration, and type of physical activity, and this is one of the first studies to evaluate the gender-specific main effects of both recent adult and early adult physical activity level with regard to NHL risk. Our analysis was limited by self-report of BMI and physical activity, and remote recall of early adult exposures. Misclassification of exposure is most likely to be non-differential between cases and controls, with bias most likely towards the null. More specific estimates of body size and fat distribution, such as waist-to-hip ratio, should be considered for future studies (55–56). Finally, while we did not find evidence that the observed association of higher BMI in early adulthood with NHL risk was confounded by total calories, fat calories, alcohol, smoking, height, family history of NHL, early life sun exposure, or total vegetable intake, residual and unmeasured confounding remains a possibility.

In conclusion, we report evidence that BMI may be of greater relevance than physical activity with regard to NHL risk. Higher BMI in early adulthood may be most relevant to NHL risk, particularly among females. Further analysis of specific etiologic mechanism and relevant pattern of lifetime exposure by which high BMI may increase NHL risk differentially by gender is warranted.

Acknowledgments

We thank Sondra Buehler for her editorial assistance. This work was supported by awards from the National Institutes of Health National, Cancer Institute [R01 CA92153; P50 CA97274]. Dr. Kelly was supported by the National Institutes of Health, National Heart Lung and Blood Institute [HL007152], National Cancer Institute [P50 CA130805; K07 CA157580], and the Lymphoma Research Foundation Fellowship Program.

Abbreviations

BMI	body mass index
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
DLBCL	diffuse large B-cell lymphoma
FL	follicular lymphoma
NHL	non-Hodgkin Lymphoma
PA	physical activity
US	United States

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Table 1

Characteristics of study participants, Mayo Case-Control Study of NHL, 2002–2008

Characteristic		Cases (N=950) N (%)	Controls (N=1146) N (%)
Age, years	<40	53 (5.6)	86 (7.5)
	40–49	126 (13.3)	145 (12.7)
	50–59	197 (20.7)	232 (20.2)
	60–69	307 (32.3)	335 (29.2)
	70+	267 (28.1)	348 (30.4)
Gender	Male	550 (57.9)	611 (53.3)
Race	White	943 (99.3)	1131 (98.7)
Residence	Minnesota	636 (66.9)	775 (67.6)
	Iowa	178 (18.7)	213 (18.6)
	Wisconsin	136 (14.3)	158 (13.8)
Education Level	Some High School or less	55 (5.8)	42 (3.7)
	High School graduate or GED	217 (22.8)	262 (22.9)
	1–3 yrs vocational school or some college	273 (28.7)	319 (27.8)
	College graduate	183 (19.3)	223 (19.5)
	Graduate or professional school	171 (18.0)	242 (21.1)
	Other	51 (5.4)	58 (5.1)
Most Prevalent	CLL/SLL	302 (31.8)	
NHL Subtypes	Follicular	242 (25.5)	
	DLBCL	181 (19.1)	
Stage	I/II	232 (35.0)	
	III/IV	432 (65.0)	
PS	0–1	892 (95.4)	
	2+	43 (4.6)	
B symptoms	no	829 (89.3)	
	yes	99 (10.7)	

Table 2

Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (95% CI) for NHL risk according to height and BMI 2 years prior to diagnosis and at age 18; Mayo Case-Control Study of NHL, 2002–2008

Variable, level		Cut point Value	Controls	All NHL Cases	All NHL Odds Ratio*	All NHL 95% CI	FL Cases	FL Odds Ratio*	FL 95% CI
Recent Adult BMI (2 years prior to case diagnosis / control enrollment)									
	<18.5		13	8	0.85	0.34–2.09	3	1.08	0.30–3.89
	18.5–24.9		353	276	1	*Reference*	80	1	*Reference*
	25.0–29.9		466	378	0.96	0.78–1.18	85	0.75	0.54–1.06
	30.0+		286	273	1.15	0.91–1.45	73	1.07	0.75–1.52
	P-trend				0.23			0.84	
males	18.5–24.9		118	115	1	*Reference*	29	1	*Reference*
	25.0–29.9		302	254	0.87	0.64–1.18	56	0.75	0.46–1.24
	30.0+		174	174	1.03	0.74–1.44	38	0.89	0.52–1.52
	P-trend				0.73			0.75	
females	<18.5		13	8	0.89	0.36–2.23	3	1.06	0.29–3.90
	18.5–24.9		235	161	1	*Reference*	51	1	*Reference*
	25.0–29.9		164	124	1.05	0.77–1.43	29	0.76	0.46–1.26
	30.0+		112	99	1.27	0.90–1.78	35	1.41	0.86–2.30
	P-trend				0.17			0.31	
	P-interaction +				0.53			0.37	
Early Adult BMI (at age 18)									
	Quartile 1		289	214	1	*Reference*	63	1	*Reference*
	Quartile 2		282	188	0.88	0.68–1.14	49	0.79	0.53–1.20
	Quartile 3	*Uses gender specific cut-points below*	275	245	1.2	0.94–1.54	56	0.95	0.64–1.41
	Quartile 4		282	287	1.38	1.08–1.76	72	1.18	0.81–1.73
	P-trend				0.0012			0.27	
males	Quartile 1	<=20.94	157	145	1	*Reference*	41	1	*Reference*
	Quartile 2	20.95–22.49	145	100	0.7	0.49–0.98	22	0.56	0.32–0.98
	Quartile 3	22.5–24.37	149	133	0.91	0.66–1.27	26	0.65	0.38–1.11
	Quartile 4	>24.37	150	162	1.1	0.80–1.52	34	0.84	0.50–1.39

Variable, level		Cut point Value	Controls	All NHL Cases	All NHL Odds Ratio*	All NHL 95% CI	FL Cases	FL Odds Ratio*	FL 95% CI
	P-trend				0.31			0.55	
females	Quartile 1	<=18.97	132	69	1	*Reference*	22	1	*Reference*
	Quartile 2	18.98–20.39	137	88	1.22	0.82–1.83	27	1.17	0.63–2.16
	Quartile 3	20.4–22.33	126	112	1.74	1.18–2.58	30	1.45	0.79–2.66
	Quartile 4	>22.33	132	125	1.9	1.29–2.79	38	1.81	1.01–3.25
	P-trend				0.00025			0.029	
	P-interaction+				0.097			0.18	

Variable, level		Cut point Value	Controls	CLL/SLL Cases	CLL/SLL Odds Ratio*	CLL/SLL 95% CI	DLBCL Cases	DLBCL Odds Ratio*	DLBCL 95% CI	DF^	p-value^
Recent Adult BMI (2 years prior to case diagnosis / control enrollment)											
	<18.5		13	1	0.36	0.05–2.82	2	1.14	0.25–5.22		
	18.5–24.9		353	83	1	*Reference*	49	1	*Reference*		
	25.0–29.9		466	127	1.05	0.76–1.43	69	1.03	0.69–1.53		
	30.0+		286	87	1.19	0.85–1.68	55	1.35	0.89–2.04		
	P-trend				0.22			0.18		3	0.71
males	18.5–24.9		118	39	1	*Reference*	16	1	*Reference*		
	25.0–29.9		302	89	0.9	0.58–1.39	42	1.02	0.55–1.88		
	30.0+		174	62	1.08	0.68–1.72	33	1.39	0.73–2.64		
	P-trend				0.66			0.25		3	0.62
females	<18.5		13	1	0.41	0.05–3.20	2	1.1	0.24–5.11		
	18.5–24.9		235	44	1	*Reference*	33	1	*Reference*		
	25.0–29.9		164	38	1.19	0.73–1.92	27	1.12	0.65–1.94		
	30.0+		112	25	1.17	0.68–2.02	22	1.38	0.76–2.47		
	P-trend				0.35			0.32		3	0.95
	P-interaction+				0.63			0.94			
Early Adult BMI (at age 18)											
	Quartile 1		289	70	1	*Reference*	35	1	*Reference*		
	Quartile 2	*Uses gender*	282	54	0.77	0.52–1.14	34	0.99	0.60–1.64		

Variable, level		Cut point Value	Controls	CLL/SLL Cases	CLL/SLL Odds Ratio*	CLL/SLL 95% CI	DLBCL Cases	DLBCL Odds Ratio*	DLBCL 95% CI	DF^	p-value^
	Quartile 3	*specific cut-points below*	275	86	1.29	0.90–1.84	47	1.43	0.89–2.28		
	Quartile 4		282	87	1.27	0.89–1.82	60	1.77	1.13–2.77		
	P-trend				0.04			0.0040		3	0.47
males	Quartile 1	<=20.94	157	49	1	*Reference*	22	1	*Reference*		
	Quartile 2	20.95–22.49	145	29	0.58	0.34–0.97	15	0.74	0.37–1.49		
	Quartile 3	22.5–24.37	149	53	1.05	0.67–1.65	21	1.01	0.53–1.92		
	Quartile 4	>24.37	150	57	1.11	0.71–1.74	33	1.57	0.87–2.83		
	P-trend				0.26			0.078		3	0.28
females	Quartile 1	<=18.97	132	21	1	*Reference*	13	1	*Reference*		
	Quartile 2	18.98–20.39	137	25	1.18	0.63–2.22	19	1.39	0.66–2.94		
	Quartile 3	20.4–22.33	126	33	1.78	0.97–3.25	26	2.11	1.04–4.31		
	Quartile 4	>22.33	132	30	1.52	0.82–2.80	27	2.16	1.06–4.38		
	P-trend				0.093			0.017		3	0.72
	P-interaction+				0.48			0.4			

* All models adjusted for age at enrollment, gender, and county of residence.

^ DF for the test of heterogeneity across the subtypes; note that these associated p-values are testing whether the trend differs across the three main subtypes and "other" subtypes.

+ p-value for the test of statistical interaction between gender and physical activity.

Table 3

Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (95% CI) for NHL risk according to Physical Activity level at different life stages; Mayo Case-Control Study of NHL, 2002–2008

				ALL NHL			FL		
Variable	**Level**	**Cut Point Value**	**Controls**	**Cases**	**Odds Ratio***	**95% CI**	**Cases**	**Odds Ratio***	**95% CI**
Recent Adult Physical Activity (2 Years Prior to enrollment)									
Total Met-minutes/week at diagnosis	Quartile 1	<615 Mets/wk	268	218	1	*Reference*	55	1	*Reference*
	Quartile 2	616–1470 Mets/wk	270	237	1.09	0.85– 1.40	59	1.07	0.72–1.61
	Quartile 3	1471–2700 Mets/wk	267	200	0.92	0.71– 1.19	55	1.01	0.67–1.52
	Quartile 4	2701+ Mets/wk	266	219	1.03	0.80– 1.33	53	0.98	0.65–1.48
	P-trend				0.85			0.86	
males	Quartile 1		172	142	1	*Reference*	34	1	*Reference*
	Quartile 2		144	129	1.09	0.79– 1.52	30	1.05	0.61–1.80
	Quartile 3		141	114	0.95	0.68– 1.33	27	0.95	0.55–1.65
	Quartile 4		117	131	1.37	0.98– 1.92	22	0.96	0.53–1.72
	P-trend				0.15			0.82	
females	Quartile 1		96	76	1	*Reference*	21	1	*Reference*
	Quartile 2		126	108	1.06	0.71– 1.58	29	1.03	0.55–1.92
	Quartile 3		126	86	0.84	0.55– 1.26	28	0.97	0.52–1.83
	Quartile 4		149	88	0.71	0.47– 1.07	31	0.9	0.49–1.67
	P-trend				0.039			0.70	
	p-interaction†				0.059			0.99	
Early Adult Physical Activity									
Strenuous activity at age 18	Never		316	274	1	*Reference*	73	1	*Reference*
	Ever		708	578	0.88	0.72– 1.07	153	0.91	0.67–1.24
males	Never		97	85	1	*Reference*	17	1	*Reference*
	Ever		465	414	1.00	0.73– 1.39	96	1.17	0.67–2.05
females	Never		219	189	1	*Reference*	56	1	*Reference*
	Ever		243	164	0.81	0.61– 1.07	57	0.96	0.64–1.46
	p-interaction†				0.30			0.52	

Variable	Level	Cut Point Value	Controls	CLL/SLL Cases	CLL/SLL Odds Ratio*	CLL/SLL 95% CI	DLBCL Cases	DLBCL Odds Ratio*	DLBCL 95% CI	DF^	p-value^
Recent Adult Physical Activity (2 Years Prior to enrollment)											
Total Met-minutes/week at diagnosis	Quartile 1	<615 Mets/wk	268	69	1	*Reference*	40	1	*Reference*		
	Quartile 2	616–1470 Mets/wk	270	66	0.96	0.66–1.40	49	1.22	0.78–1.91		
	Quartile 3	1471–2700 Mets/wk	267	70	1.01	0.70–1.47	39	0.98	0.61–1.57		
	Quartile 4	2701+ Mets/wk	266	73	1.09	0.75–1.58	39	0.99	0.62–1.59		
	P-trend				0.60			0.72		3	0.82
males	Quartile 1		172	48	1	*Reference*	26	1	*Reference*		
	Quartile 2		144	40	1.01	0.62–1.62	21	0.96	0.52–1.78		
	Quartile 3		141	41	1.01	0.62–1.62	20	0.94	0.50–1.75		
	Quartile 4		117	55	1.71	1.08–2.70	21	1.19	0.64–2.21		
	P-trend				0.032			0.67		3	0.36
females	Quartile 1		96	21	1	*Reference*	14	1	*Reference*		
	Quartile 2		126	26	0.93	0.49–1.76	28	1.5	0.75–3.01		
	Quartile 3		126	29	1.06	0.57–1.98	19	1	0.48–2.10		
	Quartile 4		149	18	0.53	0.27–1.06	18	0.8	0.38–1.69		
	P-trend				0.10			0.2442		3	0.59
	p-interaction+				0.01			0.37			
Early Adult Physical Activity											
Strenuous activity at age 18	Never		316	86	1	*Reference*	54	1	*Reference*		
	Ever		708	186	0.87	0.65–1.17	99	0.8	0.55–1.14	3	0.93
males	Never		97	32	1	*Reference*	15	1	*Reference*		
	Ever		465	145	0.92	0.59–1.44	65	0.9	0.49–1.65	3	0.87
females	Never		219	54	1	*Reference*	39	1	*Reference*		
	Ever		243	41	0.70	0.44–1.09	34	0.81	0.50–1.34	3	0.69
	p-interaction+				0.37			0.76			

*All models adjusted for age at enrollment, gender, and county of residence.

^DF for the test of heterogeneity across the subtypes; note that these associated p-values are testing whether the trend differs across the three main subtypes and "other" subtypes.

+p-value for the test of statistical interaction between gender and physical activity.

Table 4

Multivariate Model Results, all NHL subtypes combined; Mayo Case-Control Study of NHL, 2002–2008

Variables		NHL Overall					NHL Overall, Males only					NHL Overall, Females Only				
		Cases	**Controls**	**OR**	**95% CI**	**p-value**	**Cases**	**Controls**	**OR**	**95% CI**	**p-value**	**Cases**	**Controls**	**OR**	**95% CI**	**p-value**
Model 1: Early Adult BMI and Physical Activity																
BMI at age 18	Quartile 1	188	265	1	*Reference*	0.00053	130	149	1	*Reference*	0.25	58	116	1	*Reference*	0.00016
	Quartile 2	169	250	0.94	0.72–1.24		92	131	0.74	0.51–1.06		77	119	1.33	0.86–2.04	
	Quartile 3	226	244	1.32	1.01–1.71		124	136	0.98	0.69–1.38		102	108	1.97	1.29–3.01	
	Quartile 4	262	256	1.45	1.12–1.87		150	141	1.13	0.81–1.58		112	115	2.06	1.36–3.11	
Strenuous PA at age 18	Never	273	310	1	*Reference*	0.151	85	94	1	*Reference*	0.91	188	216	1	*Reference*	0.13
	Ever	572	705	0.86	0.71–1.06		411	463	0.98	0.71–1.36		161	242	0.8	0.60–1.07	
Model 2: Recent Adult BMI and Physical Activity																
Adult BMI	<18.5	7	12	0.83	0.32–2.16	0.3	0	0	NA	NA	0.94	7	12	0.88	0.33–2.32	0.3
	18.5–24.9	257	333	1	*Reference*		113	115	1	*Reference*		144	218	1	*Reference*	
	25.0–29.9	346	435	0.94	0.75–1.17		238	281	0.86	0.62–1.17		108	154	0.97	0.69–1.35	
	30.0+	249	265	1.13	0.89–1.44		158	162	0.99	0.70–1.39		91	103	1.23	0.85–1.77	
Adult PA	Quartile 1	213	259	1	*Reference*	0.93	140	166	1	*Reference*	0.14	73	93	1	*Reference*	0.062
	Quartile 2	232	263	1.09	0.84–1.41		127	141	1.08	0.77–1.50		105	122	1.11	0.73–1.67	
	Quartile 3	199	263	0.93	0.72–1.21		113	138	0.95	0.68–1.33		86	125	0.89	0.58–1.35	
	Quartile 4	215	260	1.04	0.80–1.35		129	113	1.39	0.99–1.95		86	147	0.74	0.48–1.12	
Model 3: Early Adult and Recent Adult BMI																
Adult BMI	<18.5	8	13	0.87	0.35–2.16	0.86	0	0	NA	NA	0.69	8	13	1.05	0.42–2.67	0.86
	18.5–24.9	274	350	1	*Reference*		114	117	1	*Reference*		160	233	1	*Reference*	
	25.0–29.9	376	463	0.9	0.72–1.12		253	300	0.84	0.61–1.16		123	163	0.97	0.70–1.33	
	30.0+	270	285	0.98	0.76–1.25		171	174	0.91	0.63–1.31		99	111	1.06	0.73–1.54	
BMI at age 18	Quartile 1	213	286	1	*Reference*	0.0019	144	157	1	*Reference*	0.18	69	129	1	*Reference*	0.0014
	Quartile 2	188	280	0.88	0.68–1.14		100	144	0.72	0.51–1.01		88	136	1.21	0.81–1.81	
	Quartile 3	243	272	1.21	0.94–1.56		132	146	0.96	0.68–1.34		111	126	1.69	1.13–2.52	
	Quartile 4	284	273	1.41	1.08–1.83		162	144	1.19	0.84–1.69		122	129	1.82	1.20–2.77	
Model 4: Early Adult and Recent Adult Physical Activity																
Adult PA	Quartile 1	188	234	1	*Reference*	0.68	122	155	1	*Reference*	0.10	66	79	1	*Reference*	0.15
	Quartile 2	210	239	1.14	0.87–1.49		119	130	1.21	0.85–1.73		91	109	1.01	0.65–1.56	

Variables		NHL Overall					NHL Overall, Males only					NHL Overall, Females Only				
		Cases	Controls	OR	95% CI	p-value	Cases	Controls	OR	95% CI	p-value	Cases	Controls	OR	95% CI	p-value
	Quartile 3	186	253	0.94	0.72–1.24		105	136	0.98	0.68–1.41		81	117	0.83	0.53–1.29	
	Quartile 4	205	238	1.13	0.86–1.49		123	110	1.48	1.03–2.13		82	128	0.77	0.49–1.20	
Strenuous PA at age 18	Never	247	291	1	*Reference*	0.20	81	91	1	*Reference*	0.64	166	200	1	*Reference*	0.34
	Ever	542	673	0.87	0.70–1.08		388	440	0.92	0.65–1.30		154	233	0.86	0.64–1.17	
Model 5: Early Adult BMI and Recent Adult Physical Activity																
BMI at age 18	Quartile 1	191	263	1	*Reference*	0.0016	134	144	1	*Reference*	0.40	57	119	1	*Reference*	0.0003
	Quartile 2	174	263	0.89	0.68–1.16		95	135	0.69	0.48–0.99		79	128	1.31	0.85–2.01	
	Quartile 3	224	261	1.17	0.90–1.52		125	142	0.88	0.63–1.24		99	119	1.77	1.16–2.69	
	Quartile 4	271	267	1.4	1.08–1.80		153	143	1.08	0.77–1.51		118	124	2.02	1.34–3.05	
Adult PA	Quartile 1	214	260	1	*Reference*	0.81	140	166	1	*Reference*	0.26	74	94	1	*Reference*	0.10
	Quartile 2	235	267	1.1	0.85–1.42		128	142	1.09	0.78–1.53		107	125	1.09	0.72–1.64	
	Quartile 3	197	264	0.92	0.71–1.20		112	139	0.92	0.66–1.30		85	125	0.89	0.58–1.37	
	Quartile 4	214	263	1.03	0.79–1.33		127	117	1.31	0.93–1.85		87	146	0.76	0.50–1.16	

N.B. Variable sizes differ by model due to missing values in the varying model covariates; all models adjusted for age at enrollment, gender, and county of residence; PA, physical activity.