Research Article

Cancer Prevention Research

A Prospective Analysis of Body Size during Childhood, Adolescence, and Adulthood and Risk of Non-Hodgkin Lymphoma

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Abstract

The etiology of non-Hodgkin lymphoma (NHL) is poorly understood. Obesity is associated with inflammation, a cytokine milieu conducive to lymphocyte proliferation, and has been associated with NHL risk in some epidemiologic studies. To prospectively examine NHL risk in relation to adult and earlier life obesity, we documented 635 incident NHL diagnoses among 46,390 men in the Health Professionals Follow-up Study and 1,254 diagnoses among 116,794 women in the Nurses' Health Study over 22 to 32 years of follow-up. Using multivariable Cox proportional hazards models, we estimated cohort-specific incidence rate ratios (RR) and 95% confidence intervals (CI) for risk of NHL and major histologic subtypes associated with cumulative average middle and young adult (ages, 18–21 years) body mass index (BMI) and adolescent and childhood somatotype. NHL risk was modestly increased in men (but not women) with a cumulative average middle adult BMI $\geq$ 30 kg/m^2 (vs. 15–22.9 kg/m^2; RR, 1.28; 95% CI, 0.92–1.77; $P_{trend} = 0.05$). In meta-analyses across cohorts, higher young adult BMI was associated with increased risk of all NHL (pooled RR per 5 kg/m^2, 1.19; 95% CI, 1.05–1.37), diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (all $P_{trend} \leq 0.02$). Adolescent somatotype was also positively associated with all NHL, DLBCL, and follicular lymphoma in pooled analyses (all $P_{trend} \leq 0.03$), whereas childhood somatotype was positively associated with NHL overall among women only ($P_{trend} < 0.01$). These findings in two large prospective cohorts provide novel evidence that larger body size in childhood, adolescence, and young adulthood predicts increased risk of NHL, and particularly of DLBCL and follicular lymphoma. *Cancer Prev Res; 6(8); 864–73. ©2013 AACR.*

Introduction

The etiology of non-Hodgkin lymphoma (NHL) is poorly understood, especially about modifiable risk factors that could inform prevention strategies. A significant but largely unexplained increase in NHL incidence rates has been observed for more than 30 years, although rates have leveled off more recently (1, 2). It is well documented that the prevalence of obesity has also increased sharply in the United States over recent decades (3). Body weight and obesity are potentially modifiable risk factors that may contribute to lymphomagenesis by influencing inflammation or immune function (4) and have been associated with NHL risk in several epidemiologic studies (5–7). In 2008, the International Lymphoma Epidemiology Consortium (InterLymph) published a large pooled analysis of 18 case–control studies with more than 10,000 cases and concluded that there was no association between current adult body mass index (BMI) and risk of NHL, with the possible exception of an association for severe obesity (BMI $\geq$ 40 kg/m^2) with risk of diffuse large B-cell lymphoma (DLBCL; ref. 8). In contrast, results from meta-analyses and some cohort studies suggest a weak to moderate positive association (5, 7) and more recent studies have found that the association may be stronger for weight/body size during early adulthood (9–13). We did not find current adult BMI to be a risk factor for NHL in a previous analysis with 14 years of follow-up in the Nurses' Health Study (NHS); however, this analysis was based on only 199 cases (14). Prospective data on obesity and NHL risk are somewhat conflicting and limited (5, 9), however, especially about weight earlier in life and histologic subtypes of NHL.

We conducted the present study to evaluate the association of body size and obesity not only in adulthood but also in childhood, adolescence, and young adulthood, with risk

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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doi: 10.1158/1940-6207.CAPR-13-0132

of NHL and its most common subtypes in the NHS and Health Professionals Follow-up Study (HPFS), two large prospective cohorts of women and men, respectively. The present analysis updates our first analyses after more than twice the follow-up and uses prospectively ascertained, validated anthropometric measures representing body size in adulthood and in earlier decades of life.

Materials and Methods

Study populations

The HPFS is an ongoing cohort study established in 1986 when 51,529 men who were ages 40 to 75 years completed a self-administered questionnaire on risk factors for cancer and other diseases. Every 2 years, questionnaires are sent to cohort members to update information on potential risk factors and to identify newly diagnosed cancers and other diseases. The NHS cohort includes 121,700 female registered nurses ages 30 to 55 years at baseline in 1976. Similar to the HPFS, NHS participants are followed with biennial questionnaires. Vital status is ascertained through next-of-kin and the National Death Index. For this analysis, men and women diagnosed with cancer (except non-melanoma skin cancer) before baseline (1986 for men; 1976 for women) were excluded. The analytic cohort included 46,390 men and 116,794 women representing 4,110,619 person-years of follow-up through 2008.

This study was approved by the Institutional Review Boards of Brigham and Women's Hospital (Boston, MA) and the Harvard School of Public Health (Boston, MA). Informed consent was implied by return of the baseline questionnaire.

Case ascertainment

Cases included new diagnoses of NHL, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Men and women (or their next-of-kin) who reported a new diagnosis of NHL on any biennial questionnaire through 2008 were asked for permission to obtain related medical records and pathology reports. Study investigators blinded to exposure information reviewed available medical records and pathology reports to confirm NHL (ICD-8 codes 200, 202, and 204.1). Histologic subtype was determined according to the World Health Organization classification of lymphomas (15). Specifically, diagnoses were made on the basis of morphology and immunophenotype information available in medical records and pathology reports. Immunophenotype information was not required for diagnoses of CLL/SLL or follicular lymphoma, which can be reliably diagnosed by morphology alone (15). After exclusions, there were 1,889 incident diagnoses of NHL (635 among men and 1,254 among women) over the course of follow-up; of these, 531 were CLL/SLL (207 men; 324 women), 273 were DLBCL (87 men; 185 women) and 291 were follicular lymphoma (72 men; 219 women). The remaining cases included 308 patients with uncommon or unspecified B-cell histology, 88 patients with T-cell lymphoma, and 399 patients who were determined to have NHL on the basis of morphology alone but lacked adequate phenotyping to assign the tumor to the B- or T-cell lineage.

Exposure assessment

Men and women reported their current height and weight on the baseline questionnaire. Men also reported young adult weight (i.e., at age 21 years) on the baseline questionnaire; women reported young adult weight (age 18 years) in 1980. Self-reported and technician-measured weight were highly correlated ($r = 0.97$) in a subsample of HPFS and NHS participants (16) and recalled weight at age 18 years was highly correlated with measured weight in medical records ($r = 0.87$) in the NHS II, a companion cohort of women ages 25 to 42 years (17). Current weight was updated on each biennial questionnaire. BMI was calculated as weight in kg/m^2. Men and women whose calculated BMI was less than 15 or more than 45 kg/m^2 were excluded from analyses of BMI.

In 1988, study participants recalled their body size/fatness at ages 5, 10, and 20 years by selecting one of nine pictograms ("somatotypes") that best represented their body outline (1, most lean to 9, most overweight) at each age (18). The validity of this exposure measure has been shown: among older individuals in another study population, the correlations between recalled somatotype and BMI measured at approximately the same ages generally ranged from 0.53 to 0.75, although a lower correlation (0.36) was noted for males at age 5 years (19).

Waist and hip circumference were ascertained in 1987 (HPFS) and 1986 (NHS) and updated in 1996 (HPFS) and 2000 (NHS). Men and women whose hip or waist measurements were implausibly low (i.e., <29 inches for men; <20 inches for women) were excluded from relevant analyses. Waist and hip circumference measures were validated against technician measurements in a subset of study participants residing in the Boston area (16).

Statistical analyses

Person-time of follow-up was calculated for each participant from the return date of the baseline questionnaire (i.e., 1986 for HPFS and 1976 NHS) to the date of lymphoma diagnosis, death, or the end of follow-up (January 2008, HPFS; June 2008, NHS), whichever occurred first. For analyses of waist and hip circumference, follow-up began in 1986 for both cohorts. Men and women who reported cancer or who died were excluded from subsequent follow-up. Cox proportional hazards models, stratifying by 2-year questionnaire period and treating age in months as the time scale, were used to estimate incidence rate ratios (RR) and 95% confidence intervals (CI). To control for potential confounding, we fit multivariable models that included height (inches), race (White or non-White), smoking status (never, past, or current), and physical activity [quintiles of metabolic equivalent (MET)-hours/week]. These covariates were chosen because of evidence of an association with NHL in previous studies (14, 20, 21). Although there was no evidence of confounding by any of these variables in our study population (compared with age-adjusted models), we

present results from fully adjusted models for completeness and ease of comparison with prior literature.

Cumulative average middle adult BMI was calculated as the mean of all available information on BMI from baseline up to the beginning of each 2-year follow-up cycle to represent "usual" middle adult BMI and was categorized as 15–22.9 (reference), 23–24.9, 25–26.9, 27–29.9, and 30–45 kg/m^2. Young adult BMI was categorized as 15–18.4, 18.5–22.9 (reference), 23–24.9, 25–29.9, and 30–45 kg/m^2. To estimate childhood and adolescent body size/fatness, we averaged reported somatotype at ages 5 and 10 years and ages 10 and 20 years, respectively. Because few individuals reported their body outline at young ages as being greater than level 5, the upper somatotype categories were collapsed. For analysis, we categorized child and adolescent somatotype as <2 (reference), 2–<3, 3–<4, 4–<5, and 5+. We considered sex-specific quartiles of waist circumference and waist-to-hip ratio as categorical exposure variables in main analyses.

To test for linear trend in analyses of BMI, waist circumference, and waist-to-hip ratio, we modeled each exposure as a continuous variable. We also estimated the RR for a 5 kg/m^2 increase in BMI and for a 4 inch increase in waist circumference. (4 inches was close to the SD of waist circumference in both cohorts.) For analyses of childhood and adolescent somatotype, we modeled somatotype as an ordinal score variable to test for linear trend. To assess the relative impact of early versus later life body size, we fit multivariable models that mutually adjusted for adolescent somatotype, young adult BMI, and cumulative average middle adult BMI. Furthermore, we assessed the association between adolescent somatotype within strata of cumulative average (i.e., "usual" middle adult) BMI (<25 kg/m^2 vs. 25+ kg/m^2).

We present results for each cohort separately as well as pooled results. We used a random effects meta-analysis approach to derive effect estimates for men and women combined and tested for heterogeneity by cohort/sex (22, 23). We conducted analyses for NHL overall and also conducted separate analyses for the most common NHL subtypes in these cohorts [i.e., CLL/SLL, DLBCL, and follicular lymphoma]. We used a contrast test, which followed an approximate χ^2 distribution, to test whether anthropometric measure associations with major NHL histologic subtypes differed significantly (22, 24). Because of smaller sample sizes for NHL subtypes in men and women, we conducted the tests for heterogeneity by subtype in combined (i.e., pooled) analyses only. Individuals missing primary exposure variables were excluded from relevant analyses. Missing indicator categories were used to account for missing values for categorical covariates. All statistical tests were two-sided and P values less than 0.05 were considered significant.

Results

Among men, the average age at baseline in 1986 was 54 years; among women, the average age at baseline in 1976 was 43 years. Men were less likely to have BMI < 23 kg/m^2 (18%) compared with women (52%), but a similar proportion of men and women were obese (i.e., BMI $\geq$ 30 kg/m^2; 8% of both men and women). After excluding participants with BMI < 15 kg/m^2, less than 1% of men and less than 5% of women had BMI < 18.5 kg/m^2. As shown in Table 1, women who were lean were slightly younger at

Table 1. Baseline characteristics of the study populations by BMI[a]

	HPFS, 1986 (n = 46,390)			NHS, 1976 (n = 116,794)		
Category of baseline BMI, kg/m^2	**15–22.9 (n = 8,439)**	**25–26.9 (n = 12,600)**	**30–45 (n = 3,750)**	**15–22.9 (n = 60,503)**	**25–26.9 (n = 13,628)**	**30–45 (n = 9,721)**
Age, y	53.9 (10.3)	54.7 (9.7)	54.2 (9.0)	41.6 (7.1)	44.4 (7.1)	44.4 (6.9)
Height, inches	70.1 (2.8)	70.1 (2.8)	70.1 (2.8)	64.6 (2.4)	64.5 (2.4)	64.2 (2.4)
Baseline BMI, kg/m^2	21.7 (1.1)	25.9 (0.6)	32.5 (2.5)	20.9 (1.3)	25.9 (0.6)	33.5 (3.2)
Young adult[b] BMI, kg/m^2	21.0 (2.0)	23.2 (2.3)	26.4 (3.4)	20.3 (2.1)	22.2 (2.8)	25.0 (4.1)
Adolescent somatotype[c]	2.6	3.0	3.8	2.4	2.9	3.6
Childhood somatotype[d]	2.3	2.6	3.3	2.1	2.6	3.1
Non-White,%	4	2	2	2	2	2
Smoking history						
Never smoker, %	50	42	40	41	46	50
Past smoker, %	35	44	47	23	23	25
Current smoker, %	11	10	9	36	31	25

NOTE: Values are mean (SD) or percentages.

[a]The lower, middle, and upper categories of baseline BMI are shown.

[b]BMI at age 21 (HPFS) or 18 (NHS) years.

[c]Average of somatotype at ages 10 and 20 years based on 9-level pictogram.

[d]Average of somatotype at ages 5 and 10 years based on 9-level pictogram.

Table 2. RRs and 95% CIs for NHL in relation to BMI in the NHS and HPFS

			All NHL		DLBCL		Follicular lymphoma		CLL/SLL		
		Person-years	Cases	RR (95% CI)[a]	Cases	RR (95% CI)[a]	Cases	RR (95% CI)[a]	Cases	RR (95% CI)[a]	$P_{heterogeneity}$[b]
Cumulative	**Men**										
average	15–22.9	139,494	98	Ref.	11	Ref.	10	Ref.	45	Ref.	
middle adult	23–24.9	233,195	176	1.09 (0.85–1.41)	25	1.57 (0.75–3.28)	25	1.45 (0.69–3.05)	48	0.67 (0.44–1.01)	
BMI, kg/m^2	25–26.9	221,087	164	1.10 (0.85–1.42)	23	1.58 (0.75–3.34)	14	0.87 (0.38–1.98)	59	0.83 (0.56–1.24)	
	27–29.9	167,987	132	1.19 (0.91–1.56)	17	1.65 (0.75–3.64)	15	1.28 (0.57–2.88)	42	0.80 (0.52–1.24)	
	30–45	76,956	65	1.28 (0.92–1.77)	10	2.18 (0.88–5.40)	8	1.65 (0.64–4.27)	13	0.54 (0.28–1.02)	
	RR per 5 kg/m^2			1.13 (1.00–1.29)		1.30 (0.92–1.82)		1.14 (0.78–1.66)		0.87 (0.68–1.10)	
	P_{trend}			*0.05*		*0.14*		*0.49*		*0.24*	
	Women										
	15–22.9	1,344,763	467	Ref.	60	Ref.	78	Ref.	118	Ref.	
	23–24.9	674,793	259	0.90 (0.77–1.05)	38	0.97 (0.64–1.46)	48	1.02 (0.71–1.46)	70	0.94 (0.70–1.27)	
	25–26.9	465,149	186	0.87 (0.73–1.03)	31	1.06 (0.69–1.65)	29	0.84 (0.55–1.29)	53	0.95 (0.69–1.32)	
	27–29.9	405,429	167	0.87 (0.73–1.04)	23	0.85 (0.52–1.38)	28	0.91 (0.59–1.41)	49	1.00 (0.71–1.40)	
	30–45	381,766	175	1.00 (0.84–1.20)	33	1.36 (0.88–2.10)	36	1.34 (0.89–2.01)	34	0.73 (0.49–1.07)	
	RR per 5 kg/m^2			0.99 (0.92–1.05)		1.04 (0.88–1.23)		1.06 (0.91–1.24)		0.93 (0.82–1.07)	
	P_{trend}			*0.68*		*0.65*		*0.46*		*0.32*	
	Pooled										
	RR per 5 kg/m^2			1.05 (0.91–1.20)		1.10 (0.91–1.33)		1.07 (0.93–1.24)		0.92 (0.82–1.03)	
	P_{trend}			*0.52*		*0.31*		*0.35*		*0.15*	***0.14***
Young adult	**Men**										
BMI, kg/m^2											
	15–18.4	27,189	17	0.78 (0.47–1.28)	4	1.36 (0.46–4.02)	1	0.41 (0.05–3.01)	4	0.53 (0.19–1.45)	
	18.5–22.9	378,340	278	Ref.	40	Ref.	35	Ref.	93	Ref.	
	23–24.9	217,439	165	1.19 (0.98–1.44)	19	0.94 (0.54–1.64)	15	0.82 (0.45–1.52)	56	1.19 (0.85–1.66)	
	25–29.9	168,958	136	1.28 (1.04–1.58)	17	1.16 (0.65–2.08)	19	1.40 (0.79–2.48)	34	0.94 (0.63–1.40)	
	30–45	14,530	14	1.56 (0.90–2.69)	4	2.70 (0.93–7.86)	0	—	6	2.17 (0.93–5.04)	
	RR per 5 kg/m^2			1.27 (1.11–1.46)		1.29 (0.89–1.88)		1.17 (0.76–1.80)		1.18 (0.92–1.53)	
	P_{trend}			*<0.01*		*0.18*		*0.47*		*0.20*	

(Continued on the following page)

Table 2. RRs and 95% CIs for NHL in relation to BMI in the NHS and HPFS (Cont'd)

	Person-years	All NHL Cases	All NHL RR (95% CI)[a]	DLBCL Cases	DLBCL RR (95% CI)[a]	Follicular lymphoma Cases	Follicular lymphoma RR (95% CI)[a]	CLL/SLL Cases	CLL/SLL RR (95% CI)[a]	$P_{heterogeneity}$[b]
Women										
15–18.4	317,991	107	0.81 (0.66–0.99)	14	0.71 (0.40–1.24)	17	0.77 (0.46–1.28)	29	0.83 (0.56–1.22)	
18.5–22.9	1,752,680	703	Ref.	104	Ref.	115	Ref.	191	Ref.	
23–24.9	307,521	114	0.92 (0.76–1.13)	18	0.99 (0.60–1.64)	21	1.08 (0.68–1.73)	34	1.04 (0.72–1.50)	
25–29.9	219,570	98	1.11 (0.90–1.37)	17	1.26 (0.75–2.11)	23	1.64 (1.04–2.58)	22	0.98 (0.63–1.53)	
30–45	48,488	19	0.99 (0.63–1.57)	4	1.39 (0.51–3.81)	3	1.05 (0.33–3.32)	4	0.80 (0.29–2.15)	
RR per 5 kg/m2			1.13 (1.02–1.24)		1.28 (1.01–1.63)		1.39 (1.12–1.73)		1.04 (0.85–1.27)	
P_{trend}			*0.02*		*0.04*		*<0.01*		*0.68*	
Pooled										
RR per 5 kg/m^2			1.19 (1.05–1.34)		1.29 (1.05–1.57)		1.34 (1.10–1.63)		1.09 (0.93–1.28)	
P_{trend}			*<0.01*		*0.02*		*<0.01*		*0.26*	***0.22***

[a]RR and CI from multivariable Cox proportional hazards regression models adjusted for age (as the time scale), height (continuous inches), smoking (never, past, and current), physical activity (quintiles), and race (White vs. non-White).
[b]Test for heterogeneity by NHL subtype.

baseline than those who were heavier. Among both men and women, young adult BMI, adolescent somatotype, and childhood somatotype were positively associated with adult BMI. Women were more likely than men to be current smokers at baseline (likely reflecting social norms in 1976 vs. 1986) and smoking was more prevalent among leaner women (Table 1).

On the basis of multivariable models that adjusted for age, race, height, smoking history, and physical activity, cumulative average middle adult BMI was weakly associated with increased risk of NHL overall among men but not among women (Table 2). In men, the RR for BMI $\geq$ 30 kg/m^2 compared with BMI 15 to 22.9 kg/m^2 was 1.28 (95% CI, 0.92–1.77) and there was evidence of a borderline statistically significant linear trend ($P_{trend} = 0.05$). Nonsignificantly increased risks were observed for both DLBCL and follicular lymphoma: RRs for BMI $\geq$ 30 kg/m^2 compared with BMI 15 to 22.9 kg/m^2 were 2.18 (95% CI, 0.88–5.40; $P_{trend} = 0.14$) for DLBCL and 1.65 (95% CI, 0.64–4.27; $P_{trend} = 0.49$). In contrast, no association was noted for CLL/SLL. Among women, there was no apparent association between cumulative average middle adult BMI and NHL overall or its common subtypes (Table 2).

Young adult BMI was positively associated with risk of NHL overall in both men and women (RR per 5 kg/m^2, 1.27; 95% CI, 1.11–1.46; $P_{trend} < 0.01$ and 1.13; 95% CI, 1.02–1.24; $P_{trend} = 0.02$ in men and women, respectively) in fully adjusted models (Table 2). Among men, increased risks associated with BMI at age 21 years were most apparent for DLBCL. Among women, there was statistically significant evidence of increased risk of DLBCL (RR per 5 kg/m^2, 1.28; 95% CI, 1.01–1.63; $P_{trend} = 0.04$) and follicular lymphoma (RR per 5 kg/m^2, 1.39; 95% CI, 1.12–1.73; $P_{trend} < 0.01$) associated with BMI at age 18 years. In random effects meta-analysis across men and women, there was statistically significant evidence of a positive association between young adult BMI and all NHL, DLBCL, and follicular lymphoma (all $P_{trend} \leq 0.02$). There was no evidence of heterogeneity in effects by histologic subtype of NHL, however ($P_{heterogeneity} = 0.22$), although statistical power for this test was limited. The associations observed for young adult BMI were not substantially altered upon adjustment for cumulative average BMI (data not shown).

We next considered earlier life body size/fatness as assessed by adolescent and childhood somatotype. Larger adolescent somatotype was significantly associated with all NHL among both men and women (pooled $P_{trend} < 0.01$; Table 3). For men, the RR for the highest category of adolescent somatotype compared with the lowest was 1.36 (95% CI, 0.98–1.89); the corresponding RR for women was 1.40 (95% CI, 1.07–1.83). In general, the strongest associations were noted for the DLBCL subtype, with both men and women of heavier/larger body types during adolescence experiencing almost twice the risk of DLBCL compared with leaner individuals (pooled $P_{trend} = 0.02$). There was also a significant association of adolescent somatotype with follicular lymphoma (pooled $P_{trend} = 0.03$), which was stronger among women ($P_{trend} = 0.03$). In contrast, there was no

Table 3. RRs and 95% CIs for NHL in relation to childhood and adolescent somatotype in the NHS and HPFS

			All NHL		DLBCL		Follicular lymphoma		CLL/SLL		
		Person-years	Cases	RR (95% CI)[a]	Cases	RR (95% CI)[a]	Cases	RR (95% CI)[a]	Cases	RR (95% CI)[a]	$P_{heterogeneity}$[b]
Adolescent somatotype[d]	**Men**										
	<2	112,178	88	Ref.	9	Ref.	10	Ref.	30	Ref.	
	2–<3	203,448	151	1.01 (0.77–1.32)	20	1.24 (0.56–2.75)	23	1.38 (0.65–2.94)	48	0.88 (0.55–1.40)	
	3–<4	142,022	120	1.25 (0.94–1.66)	21	2.10 (0.94–4.69)	13	1.23 (0.53–2.84)	36	1.07 (0.65–1.76)	
	4–<5	95,997	71	1.13 (0.82–1.56)	10	1.29 (0.51–3.26)	8	1.10 (0.43–2.82)	29	1.35 (0.80–2.27)	
	5+	76,593	65	1.36 (0.98–1.89)	9	1.82 (0.70–4.72)	9	1.74 (0.69–4.38)	13	0.76 (0.39–1.47)	
	P_{trend}[c]			*0.04*		*0.20*		*0.48*		*0.73*	
	Women										
	<2	606,901	239	Ref.	36	Ref.	45	Ref.	56	Ref.	
	2–<3	727,298	272	1.01 (0.84–1.20)	42	1.06 (0.68–1.66)	49	0.96 (0.64–1.43)	79	1.25 (0.89–1.76)	
	3–<4	536,565	227	1.17 (0.98–1.41)	37	1.27 (0.80–2.02)	41	1.15 (0.75–1.76)	69	1.50 (1.05–2.14)	
	4–<5	326,453	135	1.17 (0.94–1.44)	21	1.28 (0.74–2.20)	27	1.25 (0.77–2.01)	39	1.43 (0.94–2.15)	
	5+	136,611	71	1.40 (1.07–1.83)	14	1.92 (1.03–3.58)	18	1.90 (1.09–3.29)	12	1.03 (0.55–1.92)	
	P_{trend}[c]			*<0.01*		*0.05*		*0.03*		*0.15*	
	Pooled										
	P_{trend}[c]			*<0.01*		*0.02*		*0.03*		*0.18*	***0.45***
Childhood somatotype[e]	**Men**										
	<2	221,000	180	Ref.	25	Ref.	22	Ref.	58	Ref.	
	2–<3	147,134	116	1.09 (0.86–1.38)	17	1.19 (0.63–2.25)	16	1.26 (0.65–2.42)	35	0.92 (0.60–1.42)	
	3–<4	103,043	71	1.00 (0.75–1.32)	11	0.94 (0.43–2.04)	9	1.11 (0.50–2.44)	22	0.97 (0.59–1.60)	
	4–<5	73,501	62	1.21 (0.90–1.62)	8	1.10 (0.49–2.48)	8	1.17 (0.51–2.67)	22	1.43 (0.86–2.36)	
	5+	80,290	63	1.18 (0.88–1.58)	7	0.94 (0.40–2.22)	7	1.06 (0.45–2.54)	19	1.03 (0.60–1.74)	
	P_{trend}[c]			*0.20*		*0.91*		*0.83*		*0.47*	
	Women										
	<2	907,862	355	Ref.	57	Ref.	72	Ref.	87	Ref.	
	2–<3	554,054	221	1.10 (0.93–1.30)	35	1.11 (0.73–1.70)	35	0.86 (0.57–1.29)	71	1.41 (1.03–1.93)	
	3–<4	423,382	164	1.08 (0.89–1.30)	26	1.10 (0.69–1.76)	32	1.05 (0.69–1.59)	42	1.09 (0.75–1.58)	
	4–<5	261,991	118	1.25 (1.01–1.54)	19	1.29 (0.76–2.17)	23	1.26 (0.78–2.02)	36	1.51 (1.02–2.24)	
	5+	162,284	78	1.33 (1.04–1.70)	13	1.48 (0.80–2.71)	17	1.39 (0.82–2.37)	17	1.20 (0.71–2.02)	
	P_{trend}[c]			*<0.01*		*0.18*		*0.16*		*0.16*	
	Pooled										
	P_{trend}[c]			*<0.01*		*0.29*		*0.19*		*0.12*	***0.99***

[a]RR and CI from multivariable Cox proportional hazards regression models adjusted for age (as the time scale), height (continuous inches), smoking (never, past, and current), physical activity (quintiles), and race (White vs. non-White).
[b]Test for heterogeneity by NHL subtype.
[c]Trend test based on ordinal score.
[d]Average of somatotype at ages 10 and 20 years based on 9-level pictogram.
[e]Average of somatotype at ages 5 and 10 years based on 9-level pictogram.

clear association with CLL/SLL. Again, there was no evidence of statistical heterogeneity by NHL subtype (Table 3). These results were not materially changed upon adjustment for young adult BMI, cumulative average BMI, or both variables together. For example, for DLBCL, the RRs comparing the heaviest adolescent somatotype to the leanest were 1.64 (95% CI, 0.62–4.37) and 1.90 (95% CI, 0.99–3.62) for men and women, respectively, after adjusting for cumulative average middle adult BMI. The corresponding RRs were 1.70 (95% CI, 0.59–4.91) and 1.62 (95% CI, 0.73–3.57) after adjusting for young adult BMI. Furthermore, similar positive associations of adolescent somatotype with all NHL and DLBCL were noted within strata of cumulative average BMI (data not shown). Regarding childhood somatotype, a nonsignificant positive association with NHL was noted among men, whereas larger childhood somatotype was significantly associated with risk of all NHL among women ($P_{trend} < 0.01$; Table 3).

We also examined adult waist circumference and waist-to-hip ratio as proxy measures of central adiposity. In general, results were similar to those from analyses of cumulative average BMI. For example, men in the top quintile of waist circumference versus the bottom quintile had an elevated risk of NHL overall (RR, 1.26; 95% CI,

0.94–1.71; $P_{trend} = 0.05$) and of DLBCL in particular (RR, 2.25; 95% CI, 0.91–5.58; $P_{trend} = 0.44$), whereas there was no clear association between waist circumference and NHL or its common subtypes among women. Similar patterns were observed for waist-to-hip ratio (Supplementary Table). As noted earlier, observed associations of cumulative average middle adult BMI and waist circumference in relation to all NHL were restricted to men ($P_{heterogeneity} = 0.06$ and 0.05, respectively); however, there was no evidence of statistically significant between-study heterogeneity (i.e., heterogeneity by sex) in analyses of young adult BMI or younger age somatotype.

Finally, we confirmed our previous report of a significant positive association between height and NHL risk among women in the NHS (14) in this updated analysis. Specifically, the multivariable RR per 2-inch increment of height for NHL overall was 1.08 (95% CI, 1.03–1.13; $P_{trend} < 0.01$). For DLBCL, follicular lymphoma, and CLL/SLL, the corresponding RRs were 1.11 (95% CI, 0.98–1.25; $P_{trend} = 0.10$), 1.18 (95% CI, 1.06–1.32; $P_{trend} < 0.01$), and 1.06 (95% CI, 0.96–1.16; $P_{trend} = 0.23$), respectively. In contrast, height was not associated with NHL risk in men (Supplementary Table; $P_{heterogeneity} < 0.01$).

Discussion

The present study extended our previous investigation of anthropometric risk factors for NHL through twice as many years of follow-up in the NHS and to men in the HPFS. Furthermore, we incorporated novel data on young adult, adolescent, and childhood body size. We observed statistically significant associations between BMI in young adulthood (i.e., ages 18 and 21 years) and risk of NHL, with somewhat stronger associations apparent for men and particularly for the DLBCL and follicular lymphoma subtypes of NHL. The findings for early life somatotype and NHL risk were consistent with results from our analysis of young adult BMI, with increased risks of NHL and particularly DLBCL and follicular lymphoma associated with larger body sizes during adolescence among both men and women, whereas associations with childhood somatotype were evident among women only. Usual middle-adult BMI, as assessed by cumulative average BMI, was also weakly associated with NHL risk in men but not in women, whereas height predicted risk in women but not in men.

Although not all previous studies (9–11) have reported positive associations between BMI in adulthood and risk of NHL, the bulk of the more recent epidemiologic literature supports a weak positive association between obesity and NHL overall, with the most consistent evidence apparent for the DLBCL subtype (5, 8). Several prior studies have evaluated central adiposity as measured by waist circumference and waist-to-hip ratio (9, 11, 25–27); most have found no association.

Fewer studies have evaluated measures of body size earlier in life (9–13, 27, 28). Regarding BMI in young adulthood (i.e., age 18–21 years), the positive associations with NHL overall observed in the NHS and HPFS are consistent with the majority of these prior reports (9–13). Together, these results suggest that weight and body size during early adulthood may be more relevant for NHL etiology than body size later in life. An alternative explanation is that BMI between ages 18 and 21 years better represents body fatness over a lifetime (10); however, we observed that associations between young adult BMI and NHL were stronger and more consistent than associations between a composite measure of usual middle adult BMI (i.e., cumulative average BMI) and NHL. We found the strongest associations for young-adult BMI with the DLBCL and follicular lymphoma subtypes, particularly among women; however, subtype-specific associations have differed in published studies, which have been limited by smaller sample sizes for analyses by histologic subtype.

Our findings of significantly increased NHL risk associated with larger body outlines in childhood and adolescence suggest that the role of obesity and body size in NHL may begin even earlier in life than ages 18 to 21 years. Again, this association was most apparent for DLBCL, but a positive association was also evident for adolescent body size and follicular lymphoma, which was stronger and statistically significant for women. Because body size in early and later life is strongly correlated, it is difficult to disentangle the effects on NHL risk. In these analyses, however, the positive association between adolescent somatotype and NHL persisted even after adjustment for young adult BMI and usual adult BMI, suggesting that early life body size plays a role in the development of NHL beyond its effect on later-life body size. Furthermore, the positive associations between adolescent body size and NHL risk were evident among individuals who were lean or heavy in adulthood. Statistical power to detect interaction in stratified analyses was limited, however. To our knowledge, only one prior study has evaluated a measure of body size in childhood or adolescence as a possible risk factor for NHL: Cerhan and colleagues (27) reported a positive association for "above average" relative weight at age of 12 years with risk of CLL and SLL, but no association for NHL overall, DLBCL, or follicular lymphoma. Positive associations with height in this and other studies (8, 9, 11, 28–31) further support the hypothesis that early life influences are relevant to NHL etiology, as attained height reflects in part nutritional influences and circulating levels of growth factors and insulin-like growth factor-1 (IGF-1) early in life (32, 33). Although previous studies including men have reported positive associations between height and NHL (8, 29), in our analyses, this association was observed only among women, consistent with gender-restricted findings reported by the Netherlands Cohort Study (28).

Although some differences in risk estimates were noted for men and women, there was no clear pattern of differences in associations and no statistical evidence of heterogeneity in effects by sex, with the exception of cumulative average middle adult BMI and waist circumference in relation to risk of all NHL. For example, associations between young adult BMI and NHL risk appeared stronger among men, whereas associations between childhood and adolescent somatotype and NHL risk appeared stronger among

women. Observations of sex-specific associations may reflect differences between men and women in their recall of early life body size (19) or the distribution of unmeasured confounders or may be chance findings.

Various mechanisms may mediate the association between overweight/obesity and cancer (34). In particular, pathways that involve B-cell proliferation or immunomodulation are biologically plausible with respect to NHL development. Obesity is known to be a proinflammatory state in which circulating levels of B-cell stimulatory cytokines, growth factors, and adipokines such as adiponectin and leptin are altered and immune function is impaired (34–37). Increased weight and height during childhood are also associated with IGF-1 measured concurrently (38); IGF-1, in turn, promotes B-cell proliferation and inhibits apoptosis (34, 39, 40) and could contribute to lymphomagenesis through these effects. In the NHS, however, early life body size was inversely correlated with IGF-1 levels measured later in adulthood (41), suggesting that any mechanism potentially mediated by IGF-1 is complex. In addition, obesity is associated with increased levels of circulating insulin, insulin resistance, and chronic hyperinsulinemia, factors that favor cell growth and proliferation (34). Recent epidemiologic evidence suggests that polymorphisms in the obesity-related genes leptin and leptin receptor, which are important for energy homeostasis and immune function, may be associated with NHL risk (42, 43). Finally, excess body size could be a marker of diet or physical activity, factors that have been suggested as possible NHL risk factors in recent studies (21, 44, 45).

NHL is a heterogeneous group of diseases, with more than 35 recognized histologic subtypes (15). Increasing evidence points to both common and distinct etiologies among subtypes (46). Our findings suggest that body size at different times in life may be associated with both DLBCL and follicular lymphoma. Although the subtype analyses should be interpreted with caution because of smaller case counts and imprecise estimates, it is plausible that these subtypes may share common pathways of lymphomagenesis. For example, a recent genome-wide association study identified a marker in the human leukocyte antigen (HLA) class II region, which comprises immune-related genes, that was associated with both DLBCL and follicular lymphoma, indicating possible shared genetic etiology (47). Wang and colleagues (48) observed similarly increased risks of DLBCL and follicular lymphoma among individuals with both an autoimmune condition and a polymorphism in either of the immunoregulatory genes TNF or interleukin-10 (IL-10). This finding again suggests possible shared disease mechanisms for these NHL subtypes; however, in this study, the joint effect of genetic polymorphisms and obesity was only observed for DLBCL. Finally, the t(14;18) chromosomal translocation occurs in 70% to 90% of follicular lymphomas and 20% to 30% of DLBCL (15). Chang and colleagues (49) recently reported common risk factors, including height but not BMI, for t(14;18)-positive DLBCL and follicular lymphoma. Risk factor associations have differed according to the t(14;18) status of NHL in several studies (50). It is unknown, however, whether these genetic and molecular markers mediate the association between obesity and NHL risk.

Some limitations to our analyses are worth noting. First, our assessments of weight and height rely on self-reported data. Similarly, assessment of childhood and adolescent body size and BMI at ages 18 to 21 years was based on participants' recall. Although these measures have been validated and correlate well with actual measurements (12, 16, 19), there is likely to be some measurement error. This error would be expected to be nondifferential with respect to disease; therefore, any errors in exposure assessment would be likely to lead to attenuated effect estimates. Second, the majority of our study population is Caucasian. Although we adjusted for potential confounding by race and we are not aware of biologic mechanisms that would operate differently to influence obesity-related NHL risk in Caucasians versus non-Caucasians, our results may not be generalizeable to other racial/ethnic groups, for which the distribution of BMI may be different. Third, although we considered potential confounding by suspected NHL risk factors, confounding by unmeasured factors (e.g., by diet or infections), cannot be ruled out.

Despite these limitations, our study has several important strengths, including its prospective design, detailed information on covariates, and large sample size, allowing for separate analyses of common histologic subtypes of NHL, which may be etiologically distinct (46). In addition, we had considerably longer follow-up (22–32 years) over which to assess risk compared with other prospective cohort studies (9–11, 25, 28), and we updated information on BMI every 2 years. Finally, to our knowledge, this is the first study to evaluate adolescent and childhood somatotype as risk factors for NHL. These analyses in two large prospective cohorts support the hypothesis that larger body size in childhood, adolescence, and young adulthood predicts an increased risk of NHL in both men and women, particularly for DLBCL and follicular lymphoma. Future research, particularly biomarker-based studies, will help elucidate the possible biologic mechanisms involved in these associations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.A. Bertrand, E. Giovannucci
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.A. Bertrand, S.M. Zhang, B. Rosner, B.M. Birmann
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): B.M. Birmann
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Acknowledgments

The authors thank the participants and staff of the NHS and the HPFS for their valuable contributions as well as the following state cancer registries for

their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, and WY.

Grant Support

This work was supported by the NIH (CA87969, CA098122, CA055075, and K07 CA115687; to B.M. Birmann) and the American Cancer Society (RSG-11-020-01-CNE). K.A. Bertrand was supported by the Nutritional Epidemiology of Cancer Education and Career Development Program (R25 CA098566).

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Received April 11, 2013; revised May 31, 2013; accepted June 17, 2013; published OnlineFirst June 26, 2013.

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