Anthropometric characteristics and non-Hodgkin's lymphoma and multiple myeloma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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ABSTRACT

Background

The incidences of non-Hodgkin's lymphoma and multiple myeloma are increasing steadily. It has been hypothesized that this may be due, in part, to the parallel rising prevalence of obesity. It is biologically plausible that anthropometric characteristics can infuence the risk of non-Hodgkin's lymphoma and multiple myeloma.

Design and Methods

In the context of the European Prospective Investigation into Cancer and Nutrition (EPIC), anthropometric characteristics were assessed in 371,983 cancer-free individuals at baseline. During the 8.5 years of follow-up, 1,219 histologically confirmed incident cases of non-Hodgkin's lymphoma and multiple myeloma occurred in 609 men and 610 women. Gender-specific proportional hazards models were used to estimate relative risks and 95% confidence intervals (95% CI) of development of non-Hodgkin's lymphoma and multiple myeloma in relation to the anthropometric characteristics.

Results

Height was associated with overall non-Hodgkin's lymphoma and multiple myeloma in women (RR 1.50, 95% CI 1.14-1.98) for highest versus lowest quartile; p-trend < 0.01) but not in men. Neither obesity (weight and body mass index) nor abdominal fat (waist-to-hip ratio, waist or hip circumference) measures were positively associated with overall non-Hodgkin's lymphoma and multiple myeloma. Relative risks for highest versus lowest body mass index quartile were 1.09 (95% CI 0.85-1.38) and 0.92 (95% CI 0.71-1.19) for men and women, respectively. Women in the upper body mass index quartile were at greater risk of diffuse large B-cell lymphoma (RR 2.18, 95% CI 1.05-4.53) and taller women had an elevated risk of follicular lymphoma (RR 1.25, 95% CI 0.59-2.62). Among men, height and body mass index were non-significantly, positively related to follicular lymphoma. Multiple myeloma risk alone was elevated for taller women (RR 2.34, 95% CI 1.29-4.21) and heavier men (RR 1.77, 95% CI 1.02-3.05).

Conclusions

The EPIC analyses support an association between height and overall non-Hodgkin's lymphoma and multiple myeloma among women and suggest heterogeneous subtype associations. This is one of the first prospective studies focusing on central adiposity and non-Hodgkin's lymphoma subtypes.

Key words: non-Hodgkin's lymphoma, anthropometry, cohort study.

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Introduction

The causes of non-Hodgkin's lymphoma (NHL) are mostly unknown. Exposure to certain infectious organisms such as human T-cell leukemia/lymphoma virus type 1, Epstein-Barr virus, *Helicobacter pylori*, and hepatitis C virus or chemicals (e.g., organic solvents), a family history of NHL, and genetic susceptibility are considered established NHL risk factors along with immuno deficiency, which is the strongest known risk factor.[1,2] Factors that have been associated with multiple myeloma (MM) include high doses of ionizing radiation, and occupational exposure to products used in farming and petrochemical industries.[3]

Human and animal-based evidence links obesity to impaired immune status.[4] It has been hypothesized that the increasing incidence of NHL and MM may be due, in part, to the parallel rising prevalence of obesity. In humans, overweight individuals have weaker antibody responses to vaccinations and they experience a greater incidence and severity of some infectious diseases relative to lean individuals. Obesity also influences hormone levels, e.g., insulin, bioavailable insulin-like growth factor 1, growth hormone, steroid hormones, and leptin, which can activate signaling pathways that can affect tumorigenesis by stimulating cell proliferation or by having inhibitory effects on apoptosis.[5] Likewise, adult height may reflect cumulative exposure to growth hormone and insulin-like growth factor-1[6] or might be an indicator of nutritional status during childhood or adolescence.[7] Thus, it is biologically plausible that anthropometric characteristics indirectly influence NHL risk via the immune system or hormone levels.

Many studies have provided support for an obesity-NHL hypothesis,[8-16] although others have not.[17-26] Results from a meta-analysis by Larsson *et al*. indicate that excess body weight may be a risk factor for NHL and MM,[27,28] whereas a pooled analysis from the InterLymph Consortium found no evidence to support the hypothesis that obesity is a determinant of all types of NHL combined.[29] Of the 19 published reports,[8-26] seven cohort studies focused on incident cases[10,18-22,26] and two cohorts focused on mortality.[8,11] Although sex-specific[8,9,11,14,15,18,19,21,22,26] and NHL histopathologic subtype-specific[14-16,21,23,24] results were available in some studies, only one study reported combined sex- and subtype-specific anthropometric estimates.[14] To date, height[16,19-21,23,30] and central adiposity[21] have received limited attention.

Given the public health importance of identifying an association between modifiable risk factors such as body size characteristics and overall NHL and MM, a test of this hypothesis is warranted. We conducted a prospective study in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort to investigate, separately for men and women, whether NHL and MM risk combined is associated with obesity, central adiposity, and height. Although the statistical power was limited we also explored whether the body size characteristic associations varied for the primary NHL subtypes.

Design and Methods

Population

The EPIC is a multicenter prospective cohort study designed to examine the association between nutrition and cancer. A detailed description of the methods has been previously reported.[31,32] In brief, participants were enrolled from the general population between 1993-1998 at 23 centers in ten European countries: Denmark (Åarhus, Copenhagen), France, Germany (Heidelberg, Potsdam), Greece, Italy (Florence, Varese, Ragusa, Turin, Naples), the Netherlands (Bilthoven, Utrecht), Norway (Lund), Spain (Asturias, Granada, Murcia, Navarra, San Sebastian), Sweden (Malmö, Umea) and the United Kingdom (Cambridge, Oxford). Some of the subcohorts were recruited from special populations, including the French subcohort (women enrolled in a health insurance plan for school employees), the Utrecht cohort in the Netherlands (women attending a mammography screening program), the Ragusa cohort in Italy (blood donors and their spouses) and the Oxford cohort in the United Kingdom (half of the cohort were vegetarian volunteers and healthy eaters, referred to as *health conscious* individuals). France, Norway, Utrecht, and Naples only enrolled women. After exclusion of prevalent cancer cases at baseline, 494,368 participants, primarily 25-70 years of age at recruitment, were eligible. After providing informed consent, participants completed questionnaires about their diet, lifestyle, and medical history. Additionally, participants were invited to donate a blood sample and, at most centers, to allow an anthropometric assessment. The EPIC study was approved by the review boards of the International Agency for Research on Cancer and of all local institutes in which participants were recruited.

Participants were excluded if they did not complete either the diet and/or lifestyle questionnaire, or if they were in the upper or lower 1% with regards to the ratio of energy intake to estimated energy requirement (N=14,514). Participants were also excluded if they were members of the French cohort (no systematic data on lymphoma are available yet in France; N=69,426) or of the Norwegian cohort (only self-reported body size information available; N=35,227), if the diagnosis of lymphoma was uncertain (N=29), or if data on baseline height or weight were unavailable (N=3,120). An additional 64 cases of Hodgkin's lymphoma were excluded. The final analytic cohort comprised 141,425 men and 230,558 women.

Outcome assessment

Incident lymphoma cancer cases were identified by either population cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the UK) or by active follow-up (France, Germany and Greece). Active follow-up included direct contact of participants or next-of-kin, health insurance records, and cancer or pathology registries. The end of follow-up varied by center. Follow-up time was accrued up to the date of last known contact, the date of diagnosis, or the date of death, whichever came first. Lymphoma cases were initially

classified according to the second revision of the International Classification of Disease for Oncology (ICD-O-2). Cases were subsequently recoded according to the WHO classification of tumors of hematopoietic and lymphoid tissues.[33] This conversion was accomplished using a program available on the SEER website (*http://seer.cancer.gov/*) and the expertise of a pathologist. ICD-O-2 codes that could not be unequivocally translated to a lymphoma diagnosis according to the WHO guidelines were categorized as lymphoma unclassified (*NOS*). Thus, the current analysis focuses on 1,219 NHL and MM cases (609 males and 610 females) and 370,764 non-cases (140,816 males and 229,948 females).

Exposure assessment

The anthropometry protocols have been described in detail elsewhere.[34] At baseline, anthropometry was assessed without shoes. Depending on the study center, height was measured to the nearest 0.1, 0.5 or 1.0 cm and weight was assessed to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hip circumference (HC) was measured over the buttocks (UK; Utrecht, the Netherlands; Germany; Denmark) or at the widest circumference (France; Italy; Spain; Bilthoven, the Netherlands; Greece; Malmo, Sweden). Waist circumference (WC) was measured either at the midpoint between the lower ribs and iliac crest (Bilthoven, the Netherlands; Potsdam, Germany; Malmo, Sweden; and Oxford, UK) or at the narrowest torso circumference (France; Italy; Cambridge, UK; Utrecht, the Netherlands). A combination of methods was used in Spain, Greece, Heidelberg Germany, and Denmark; although most participants were measured at the narrowest circumference. WC was divided by HC to compute the waist-to-hip ratio (WHR). Sitting height was measured except at Bilthoven, Sweden, Norway, and the UK study centers as well as only in some of the French cohort. Sitting height was assessed as the length from the seat to the top of the head; leg length was obtained by subtracting sitting height from standing height.

To reduce heterogeneity as a result of protocol differences in clothing worn across sites, anthropometric measurements were corrected.[34] For participants wearing light clothing, weight was adjusted by -1.0 kg and for those normally dressed, correction factors of -1.5 kg for weight and -2.0 cm for circumferences were applied. Many of the Oxford health-conscious volunteers provided self-reported data as well as allowed their anthropometric characteristics to be measured. Prediction equations to correct the self-reported data for possible reporting bias were derived by regressing measured anthropometry onto self-reported anthropometry in age-adjusted, sex-specific models.[35] Participants for whom information on a particular body size measure was lacking were excluded from applicable analyses.

At baseline, information on sociodemographic and lifestyle characteristics and medical history was obtained via questionnaire. The physical activity assessment included current occupation as well as average recreational and household activity during the year prior to baseline. Diet for the 12 months prior to enrollment was assessed using country-specific validated questionnaires[36] and country-specific food composition tables were used to calculate nutrient intakes.[37]

Statistical analyses

Cox proportional hazard models were used to estimate relative risks (RR) as incident rate ratios and 95% confidence intervals (CI) for the association between lymphoma risk and anthropometric characteristics, separately for men and women.[38] Age was the underlying time variable with entry and exit time defined as the participant's age at recruitment and at lymphoma diagnosis or censoring, respectively. Sex-specific quartiles of body size characteristics were based on the frequency distribution of the male or female population. These primary exposures were incorporated into models as indicator variables. Risk estimates are presented for each specific quartile relative to the reference category. Tests of linear trend across categories were conducted by fitting a model treating the different quartile categories as a single ordinal variable. Statistical tests were performed using SAS, version 9.1 (SAS Institute, Cary, NC, USA).

To check the proportional hazards assumption interaction terms of time and age as well as of center and age were added to each model.[39] The proportional hazards varied across center in some of the models among men. Thus, to reduce sensitivity to violations of the proportional hazards assumption and to maintain consistency with previously published EPIC analyses, all models were stratified by recruitment age (in 1-year categories) and study center.

Models were fitted to examine the association between body size characteristics and NHL and MM risk. Overall obesity was examined in three models: models with BMI and weight each as independent predictors and a model with weight adjusted for height. Abdominal fat distribution was explored in three models: models with WC, HC, and WHR each as independent predictors. To examine abdominal fat distribution, independent of overall obesity, abdominal fat distribution models were further adjusted for height and, in additional models, for weight. Effect modification on the multiplicative scale between body size characteristics and study center was evaluated using the log likelihood ratio test to compare the proportional hazards models with and without the cross product terms.[39] First, each study center was considered separately, and then to further explore this issue study center was collapsed into two groups representing the north (UK, the Netherlands, Sweden, Denmark) and the center-south (Germany, Italy, Spain, Greece) of Europe. There was no convincing evidence of heterogeneity of body size estimates across sites; therefore, final models did not include any interaction terms. Finally, predefined well-established definitions of overall obesity and abdominal fat were also examined: BMI [<25.0 (normal), 25.0-29.9 (overweight), ≥30.0 (obese)], waist circumference (<102 or ≥102 cm in men, and <88 or ≥88 cm in women), and WHR (<0.95 or ≥0.95 for men, and <0.80 or ≥0.80 for women).[40,41] Covariates considered as confounders included alcohol consumption at recruitment, smoking status, education, total physical activity, occupational activity, medical history of diabetes, hyperlipidemia and hypertension; as well

as total calorie intake and several food groups.[42] Each co-variate, included as indicator variables, was considered in a separate model. A covariate was considered to be a confounder if at least a 10% change in the body size risk estimates occurred when the covariate was added to the model compared to a model without the covariate. Estimates of the associations remained unchanged in the adjusted models; thus, to create a parsimonious multivariate model only education and smoking, the two most plausible confounders, were included in final models. Participants lacking responses for a particular variable were excluded from a given analyses.

Finally, to explore heterogeneity by NHL and MM subtype, models were fitted for the association between anthropometric variables and the primary NHL subtypes [i.e., B-cell, and among B-cell subtypes: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), chronic lymphocytic leukemia (CLL), and MM)]. Separate T-cell models were not fitted; too few cases were available to obtain stable risk estimates (N=25 and 15 for males and females, respectively). Since there was no convincing evidence of confounding in the NHL and MM models and as a result of limited power, NHL and MM subtype models were not adjusted for education and smoking.

Results

Table 1 shows the cohort characteristics by country, separately for men and women. The 141,425 men and 230,558 women contributed 1,231,985 and 2,018,984 person-years of follow-up, respectively (Table 1). During this time period, incident cases of NHL and MM cases were diagnosed in 609 males and 610 females. Baseline age was similar across countries, though participants from Denmark were slightly older. The overall mean age and standard deviation was similar for the men (51.7±10.1 years) and women (50.2±11.0 years).

Table 2 displays the participants' characteristics by BMI quartile. As expected all body size characteristics other than height increased across BMI categories. Patterns tended to be similar for both sexes. Relative to participants in the lower quartile of BMI, participants in the upper 25th percentile of BMI were older, more likely to have never smoked, were less educated, and more likely to have a history of diabetes, hyperlipidemia, or hypertension. Additionally, men in the upper quartile of BMI drank more alcohol, consumed more calories, and were more likely to have performed heavy manual work or be unemployed. In contrast, women in the upper 25th percentile of BMI reported drinking less alcohol, engaging in more moderate activity, and were more likely to be non-workers. Finally, total physical activity patterns (for men) and average daily energy intake (for women) were similar across BMI quartiles.

The sex-specific associations between quartiles of anthropometric characteristics and NHL and MM risks are presented in Table 3. For women, there was a statistically significant trend of increasing relative risks of NHL and MM risk across height quartiles (p-trend <0.01). Risk was significantly elevated for each height quartile (multivariate RR = 1.35, 1.50, and 1.50 for quartiles 2-4, respectively). Among men, height was not associated with an increased risk of NHL and MM (height ≥179.8 cm versus <170.0 cm, RR = 1.16, 95% CI = 0.89 – 1.51; p-trend = 0.39).

For both sexes, risk did not differ between participants in the upper three quartiles and those in the lowest quartile of BMI (Table 3). The multivariate RR and corresponding 95% CI for the upper versus lower 25th percentile of BMI were 1.09 (0.85-1.38) and 0.92 (0.71-1.19) for men and women, respectively. In addition, there was no relationship between weight and NHL and MM risk (highest versus lowest quartile for men, RR = 1.11, 95% CI = (0.86-1.44); p-trend =0.35; for women, RR = 0.98, 95% CI = (0.76-1.27); p-trend =0.75).

None of the abdominal fat distribution measures, specifically WC, HC, and WHR, was associated with NHL and MM in either sex (Table 3). In analyses that further adjusted for body weight, HC was significantly inversely related to NHL risk in men; men with a HC ≥105.0 cm had a 60% lower risk of NHL and MM relative to men with a HC <96.1 cm (95% CI=0.42-0.91; p-trend=0.03) (Table 4). All other relationships between abdominal fat distribution and NHL and MM risk were similar with and without body weight adjustment (Table

Table 1. Cohort characteristics among 230,558 women and 141,425 men in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Country	Cohort size (n)		Age (mean ±SD, years)		Person-years		Non Hodgkin's lymphoma (n)	
	Men	Women	Men	Women	Men	Women	Men	Women
Denmark	26,259	28,710	56.1±4.4	56.2±4.4	199,057	221,670	141	97
Germany	21,333	27,701	51.9±7.6	48.6±9.0	176,306	230,325	73	42
Greece	10,548	14,948	52.4±12.8	52.8±12.5	73,695	108,953	22	11
Italy	13,870	30,288	49.7±7.5	50.2±8.1	119,273	260,866	52	74
Spain	14,978	24,627	50.2±7.2	47.8±8.4	154,883	243,030	48	50
Sweden	22,209	26,273	51.4±11.1	51.6±10.7	235,675	279,294	154	124
The Netherlands	9,776	26,496	42.7±11.1	50.4±11.6	82,119	234,253	14	74
United Kingdom	22,452	51,515	52.5±13.6	47.2±14.2	190,977	440,593	105	138
Total	141,425	230,558	51.7±10.1	50.2±11.0	1.231,985	2,018,984	609	610

4). In additional analyses examining well-established cut-points of WC and WHR, men with a WC ≥102 cm had a statistically non-significant, higher risk of NHL relative to those with a WC < 102 cm [RR and 95% CI = 1.19 (0.91-1.56)] (Table 5). Compared to men with a WHR < 0.95, men with a WHR ≥0.95 had a relative risk for NHL of 1.12 (95% CI = 0.91-1.36). Among women, risk did not differ between those with a WC ≥88 cm *vs.* < 88 cm [RR and 95% CI = 0.98 (0.74-1.29)] or between those with a WHR ≥0.80 and < 0.80 [RR and 95% CI = 0.93 (0.77-1.13)]. Finally, in analyses with BMI categorized according to well-established definitions, overweight (25 kg/m²≤ BMI ≤ 29.9 kg/m²) and obese (≥30.0 kg/m²) participants were not at greater NHL risk relative to normal weight (<25.0 kg/m²) participants (Table 5).

Given our strong findings with height we conducted exploratory analyses with sitting height and leg length (*data not shown*). There was no evidence of a leg length-NHL/MM relationship. Our results suggested that sitting height may be associated with NHL and MM risk, particularly among women; however there was no evidence of a dose-response relationship. Among women, relative risks and 95% CI for the 2nd, 3th and 4th quartiles were 1.90 (1.35-2.66), 1.84 (1.29-2.64), and 1.89 (1.30-2.77), respectively.

The results of NHL and MM subtype analyses were not consistent between the sexes and the limited number of cases yielded unstable risk estimates (Table 6). Among women, height was positively associated with risk across NHL B-cell subtypes (i.e., DLBCL, FL, CLL, and MM), yet the relationship was only significant for MM risk (RR and 95% CI for the upper two quartiles of

Table 2. Characteristics of study participants divided by body mass index and sex among 230,558 women and 141,425 men in the EPIC Study.

Quartile of BMI (kg/m²)	Men 1	2	3	4	Women 1	2	3	4
Quartile range	<24.0	24.0-26.1	26.2-28.6	≥28.7	<22.3	22.3-24.7	24.8-27.9	≥28.0
Quartile mean*	2.3	25.1	27.3	31.3	20.7	23.6	26.3	31.9
N	35340	35363	35380	35342	57703	57626	57599	57630
Body size characteristics								
Weight, kg, mean*	69.2	77.2	83.1	93.9	55.5	62.5	68.6	81.3
Height, cm, mean*	176.1	175.3	174.4	173.2	163.7	162.8	161.5	159.6
Waist circumference, cm, mean*	84.4	91.1	96.3	105.8	70.1	75.8	81.9	93.8
Hip circumference, cm, mean*	94.6	98.6	101.7	107.7	92.6	97.7	102.4	112.2
Waist-hip-ratio, cm/cm mean*	0.893	0.925	0.949	0.984	0.757	0.777	0.801	0.837
Waist circumference[†], % obese	0.2%	2.0%	15.4%	66.0%	0.4%	2.5%	17.5%	71.1%
Waist-hip-ratio[†], % obese	12.5%	29.6%	47.7%	72.1%	16.2%	31.6%	50.4%	72.2%
Age, years, mean	49.3	51.8	52.6	53.2	45.7	49.6	52.0	53.4
Alcohol, g/day, mean*	18.4	20.6	22.2	24.5	9.2	9.0	8.0	5.9
Smoking status[†], %								
Never smoker	35.8%	31.5%	28.2%	26.1%	48.5%	48.2%	51.9%	60.5%
Current smoker	26.3%	23.3%	23.0%	23.4%	23.4%	21.5%	19.4%	15.1%
Past smoker (<10 years)	9.1%	11.6%	14.5%	17.2%	8.7%	9.5%	8.9%	7.8%
Past smoker (10+ years)	17.2%	22.4%	24.0%	23.4%	12.8%	14.3%	13.6%	11.3%
Other smoking	10.8%	10.2%	9.4%	9.2%	6.1%	5.9%	5.6%	4.6%
Education[†], %								
No school degree or primary school	20.1%	26.4%	33.0%	42.8%	13.6%	23.1%	35.2%	50.2%
Technical or professional school	24.1%	25.1%	25.2%	23.3%	27.5%	28.4%	26.2%	21.2%
Secondary school	18.7%	16.8%	15.1%	12.8%	22.4%	20.6%	17.9%	13.4%
University degree	33.8%	28.7%	23.9%	18.2%	31.9%	23.0%	15.8%	9.8%
Total physical activity[†], %								
Inactive	17.3%	18.6%	18.8%	18.8%	19.0%	16.3%	13.2%	10.0
Moderately inactive	24.9%	25.7%	26.5%	27.9%	28.9%	27.6%	25.8%	24.8%
Moderately active	30.6%	31.9%	33.0%	34.7%	34.4%	39.6%	45.7%	51.6%
Active	11.9%	12.2%	12.4%	12.3%	8.7%	9.2%	8.9%	8.6%
Occupational physical activity[†], %								
Sedentary	35.7%	35.7%	33.9%	31.3%	25.4%	29.2%	23.8%	17.8%
Standing	20.2%	20.7%	21.2%	20.7%	17.0%	21.8%	19.8%	17.8%
Manual work	13.9%	14.5%	15.6%	15.8%	6.3%	8.7%	8.3%	7.8%
Heavy manual work	3.6%	3.9%	4.1%	5.7%	0.9%	1.4%	1.5%	1.4%
Non-worker	22.9%	22.0%	22.3%	23.9%	22.9%	35.6%	43.8%	52.6%
History of[†], %								
Diabetes	2.0%	2.6%	3.6%	6.1%	0.8%	1.2%	2.3%	5.4%
Hyperlipidemia	9.8%	15.9%	20.2%	23.7%	6.4%	9.7%	13.2%	17.9%
Hypertension	9.8%	15.0%	20.3%	29.6%	8.0%	11.9%	17.5%	29.7%
Energy intake, kcal/day, mean*	2434.1	2446.0	2460.4	2508.4	1943.0	1950.7	1949.1	1948.4

*BMI: body mass index; kg: kilograms; m: meters; cm: centimeters; g: grams; kcal: kilocalories. *All means except the age mean are age-adjusted means. †Numbers do not add to 100% because of missing values.*

height = 1.84 (1.04-3.24) and 2.34 (1.29-4.21), respectively). Among men, the positive height-FL relationship was non-significant and the confidence interval was wide.

Among men, weight was significantly associated with an elevated risk of MM (RR = 1.77 and 95% CI = 1.02-3.05), while among women, there was a non-significant DLBCL-weight association (RR=1.62). BMI was significantly positively related to DLBCL risk among women (RR=2.18 and 95% CI 1.05-4.53) and non-significantly with FL and MM among men. Although the trend was

not significant (p-trend=0.83), among men, an inverse BMI-DLBCL association was observed with a significant RR for 2nd BMI quartile (RR=0.44 and 95% CI= 0.21-0.92). In analyses of well-established BMI cut-points, obese men were at similar risk relative to normal weight men across tumor subtypes. Among women, obesity was non-significantly related to a greater risk of DLBCL tumors (RR=1.54 and 95% CI = 0.92-2.57).

WC, HC, and WHR and well-established definitions of WC and WHR were not significantly, positively, asso-

Table 3. Sex-specific relative risks and 95% confidence intervals for lymphoma risk in relation to anthropometric characteristics (quartiles) among 230,558 women and 141,425 men in the EPIC study.

| | | Men | | | | | | Women | | | |
| | | Crude RR[a] | | Multivariate RR[b] | | | | Crude RR[a] | | Multivariate RR[b] | |
Measure	N		(95% CI)		(95% CI)	Measure	N		(95% CI)		(95% CI)
Height, cm						Height, cm					
<170.0	143	1.00		1.00		<157.1	127	1.00		1.00	
170.0-174.9	157	1.06	(0.84-1.34)	1.04	(0.82-1.32)	157.1-161.9	152	1.30	(1.02-1.66)	1.35	(1.04-1.74)
170.0-179.7	159	1.12	(0.88-1.43)	1.08	(0.84-1.39)	162.0-166.6	178	1.46	(1.14-1.87)	1.50	(1.16-1.94)
≥179.8	150	1.19	(0.93-1.53)	1.16	(0.89-1.51)	≥166.7	153	1.52	(1.17-1.98)	1.50	(1.14-1.98)
p-trend[c]						p-trend[c]					
		0.15		0.39				<0.01		<0.01	
Weight, kg						Weight, kg					
<72.7	142	1.00		1.00		<58.7	125	1.00		1.00	
72.7-79.8	139	0.98	(0.77-1.23)	0.94	(0.73-1.20)	58.7-65.0	137	1.02	(0.80-1.30)	0.91	(0.70-1.18)
79.9-87.7	157	1.09	(0.87-1.38)	1.01	(0.79-1.29)	65.1-73.1	175	1.22	(0.96-1.54)	1.09	(0.85-1.39)
≥87.8	171	1.23	(0.98-1.55)	1.11	(0.86-1.44)	≥73.2	173	1.20	(0.95-1.52)	0.98	(0.76-1.27)
p-trend[c]						p-trend[c]					
		0.04		0.35				0.06		0.75	
Body mass index, kg/m²						Body mass index, kg/m²					
<24.0	139	1.00		1.00		<22.3	124	1.00		1.00	
24.0-26.1	148	0.97	(0.76-1.22)	0.95	(0.75-1.20)	22.3-24.7	160	1.05	(0.83-1.33)	1.01	(0.79-1.29)
26.2-28.6	150	0.97	(0.77-1.23)	0.88	(0.69-1.13)	24.8-27.9	171	1.02	(0.81-1.30)	1.01	(0.79-1.29)
≥28.7	172	1.17	(0.93-1.48)	1.09	(0.85-1.38)	≥28.0	155	0.96	(0.75-1.23)	0.92	(0.71-1.19)
p-trend[c]						p-trend[c]					
		0.18		0.60				0.06		0.50	
Waist circumference, cm[d]						Waist circumference, cm[e]					
<87.9	111	1.00		1.00		<72.0	117	1.00		1.00	
87.9-94.0	139	1.00	(0.78-1.29)	0.94	(0.73-1.22)	72.0-78.9	140	0.87	(0.68-1.12)	0.82	(0.63-1.06)
94.1-100.9	130	1.05	(0.81-1.36)	0.95	(0.73-1.24)	79.0-87.0	160	0.96	(0.75-1.23)	0.89	(0.69-1.16)
≥101.0	164	1.19	(0.92-1.53)	1.06	(0.81-1.38)	≥87.1	155	0.96	(0.74-1.24)	0.89	(0.68-1.17)
p-trend[c]						p-trend[c]					
		0.14		0.59				0.98		0.62	
Hip circumference, cm[d]						Hip circumference, cm[e]					
<96.1	137	1.00		1.00		<95.0	110	1.00		1.00	
96.1-100.1	129	0.93	(0.73-1.19)	0.89	(0.70-1.15)	95.0-99.0	151	1.11	(0.86-1.42)	1.08	(0.84-1.40)
100.2-104.9	140	1.06	(0.84-1.35)	0.97	(0.75-1.25)	100.0-106	157	1.21	(0.94-1.56)	1.07	(0.82-1.39)
≥105.0	136	0.99	(0.77-1.26)	0.85	(0.65-1.11)	≥106.1	154	1.19	(0.92-1.54)	1.10	(0.84-1.44)
p-trend[c]						p-trend[c]					
		0.83		0.36				0.98		0.58	
Waist to hip ratio (WHR)[d]						Waist to hip ratio (WHR)[e]					
<0.90	100	1.00		1.00		<0.74	126	1.00		1.00	
0.90-0.93	126	1.00	(0.77-1.31)	0.95	(0.72-1.25)	0.74-0.78	137	0.91	(0.72-1.17)	0.93	(0.72-1.20)
0.94-0.97	138	1.01	(0.78-1.31)	0.99	(0.76-1.30)	0.79-0.83	163	0.91	(0.71-1.15)	0.89	(0.69-1.15)
≥0.98	178	1.20	(0.93-1.55)	1.12	(0.86-1.46)	≥0.84	146	0.83	(0.64-1.07)	0.84	(0.65-1.10)
p-trend[c]						p-trend[c]					
		0.13		0.30				0.17		0.20	

RR: relative risks; CI: confidence intervals. [a]Cox regression models stratified by recruitment age and study center; [b]Multivariate models were based on the crude model with additional adjustment for smoking status (never, past 10+ years, past < 10 years, current, or other) and education (no school degree or primary school, technical or professional school, secondary school, and university degree). Multivariate models for weight, WC, HC, WHR were further adjusted for height (continuous); [c]p-trends across categories are based on fitting a model treating the different quartile categories as a single ordinal variable; [d]Missing cases among males for waist circumference (N=65), hip circumference (N=67), and for WHR (N=67); [e]Missing cases among females for waist circumference (N=38), hip circumference (N=38), and for WHR (N=38).

ciated with any NHL and MM sub-type in either sex and there was no significant trend of increasing relative risks of NHL sub-type across quartiles of these anthropometric measures. However, positive associations (RR > 1.20 for upper versus lower quartile of anthropometric measures) were observed among men (WC-DLBCL; WC-MM; WHR-DLBCL) and among women (HC-FL; HC-CLL). In analyses of well-established cut-points, men with a WC ≥ 102 cm were at higher risk of DLBCL, and MM tumors relative to men with a WC < 102 cm (RR = 2.03, and 1.50, respectively). WHR ≥ 0.80 was related to a greater risk of MM tumors among women (RR = 1.32).

Finally, several inverse associations were noted between abdominal fat distribution measures and NHL and MM subtypes. For CLL, protective associations were observed for HC among men (*p*-trend=0.02) and for WC, WHR, as well as WHR among women. Trends were not statistically significant for these CLL-body size associations among women but dose-response relationships were suggested by stronger inverse relative risks for increasing categories. Additionally, among men, a significant inverse association was observed between WHR-MM for the 3rd versus 1st quartile; however there was no indication of a trend.

Discussion

Results from this large, prospective, cohort study support the hypothesis that height is related in a dose-response fashion to overall NHL and MM risk in women, but not in men. In contrast, these data do not support the hypotheses that general or abdominal obesity are associated with NHL and MM risk.

The strengths of this study include its prospective design using incident cases and actual measurement rather than self-reporting of body size characteristics.

Table 4. Sex-specific relative risks and 95% confidence intervals for lymphoma risk in relation to waist and hip circumference as well as waist to hip ratio (quartiles) after controlling for body weight among 230,558 women and 141,425 men, in the EPIC study.

Measure	Men Multivariate RR[a] (95% CI)		Measure	Women Multivariate RR[a] (95% CI)	
Waist circumference, cm				*Waist circumference, cm*	
<87.9	1.00			<72.0	1.00	
87.9-94.0	0.92	(0.70-1.22)	72.0-78.9	0.80	(0.61-1.05)
94.1-100.9	0.92	(0.67-1.26)	79.0-87.0	0.84	(0.62-1.14)
≥101.0	0.99	(0.66-1.49)	≥87.1	0.79	(0.52-1.19)
p-trend[b]	0.93		*p*-trend[b]	0.34	
Hip circumference, cm[c]				*Hip circumference, cm*[d]	
<96.1	1.00			<95.0	1.00	
96.1-100.1	0.81	(0.62-1.06)	95.0-99.0	1.10	(0.84-1.44)
100.2-104.9	0.82	(0.61-1.10)	100.0-106	1.10	(0.80-1.50)
≥105.0	0.62	(0.42-0.91)	≥106.1	1.17	(0.77-1.78)
p-trend[b]	0.03		*p*-trend[b]	0.52	
Waist to hip ratio (WHR)[c]				*Waist to hip ratio (WHR)*[d]	
<0.90	1.00			<0.74	1.00	
0.90-0.93	0.95	(0.72-1.25)	0.74-0.78	0.92	(0.72-1.19)
0.94-0.97	0.98	(0.74-1.30)	0.79-0.83	0.87	(0.68-1.13)
≥0.98	1.10	(0.81-1.49)	≥0.84	0.81	(0.61-1.08)
p-trend[b]	0.45		*p*-trend[b]	0.14	

RR: relative risks; CI: confidence intervals. [a]Cox regression models stratified by recruitment age and study center. Multivariate models were adjusted for smoking status (never, past 10+ years, past < 10 years, current, or other) and education (no school degree or primary school, technical or professional school, secondary school, and university degree), height (continuous), and weight (continuous). [b]p-trends across categories are based on fitting a model treating the different quartile categories as a single ordinal variable. [c]Missing cases among males for waist circumference (N=65) and for WHR (N=67). [d]Missing cases among females for waist circumference (N=38) and for WHR (N=38).

Table 5. Sex-specific relative risks and 95% confidence intervals for lymphoma risk in relation to predefined established body mass index, waist circumference, and waist to hip ratio catagories among 230,558 women and 141,425 men in the EPIC study.

Measure	N. of Cases	Men Crude RR (95% CI)[a]		Multivariate RR (95% CI)[b]		Measure	N. of Cases	Women Crude RR (95% CI)[a]		Multivariate RR (95% CI)[b]	
Body mass index, kg/m²						Body mass index, kg/m²					
<25.0 (normal)	205	1.00		1.00		<25.0 (normal)	297	1.00		1.00	
25.0-29.9 (overweight)	296	0.99	(0.83-1.19)	0.93	(0.77-1.12)	25.0-29.9 (overweight)	216	0.97	(0.81-1.17)	0.99	(0.82-1.19)
≥30.0 (obesity)	108	1.22	(0.96-1.56)	1.13	(0.88-1.46)	≥30.0 (obesity)	97	0.94	(0.74-1.20)	0.88	(0.68-1.14)
p-trend[c]				0.54		*p*-trend[c]				0.39	
Waist circumference, cm[d]						Waist circumference, cm[e]					
<102	391	1.00		1.00		<88	420	1.00		1.00	
≥102	153	1.23	(1.02-1.50)	1.19	(0.91-1.56)	≥88	152	1.03	(0.84-1.25)	0.98	(0.74-1.29)
Waist to hip ratio (WHR)[d]						Waist to hip ratio (WHR)[e]					
<0.95	260	1.00		1.00		<0.80	294	1.00		1.00	
≥0.95	282	1.14	(0.96-1.36)	1.12	(0.91-1.36)	≥0.80	278	0.95	(0.80-1.14)	0.93	(0.77-1.13)

RR: relative risks; CI: confidence intervals. [a]Cox regression models stratified by recruitment age and study center. [b]Multivariate models were based on the crude model with additional adjustment for smoking status (never, past 10+ years, past < 10 years, current, or other) and education (no school degree or primary school, technical or professional school, secondary sc. [c]P-trend across categories are based on fitting a model treating the different quartile categories as a single ordinal variable. [d]Missing cases among males for waist circumference (N=65) and for WHR (N=67). [e]Missing cases among females for waist circumference (N=38) and for WHR (N=38).

The large study population (n=371,983) and number of cases (n=1,219) allowed us to estimate sex-specific risks and to evaluate confounding. In addition, though the statistical power was limited, we were able to estimate sex- and histological-specific estimates. The two previous cohort studies with large numbers of incident cases focused on men.[22,26] In our study, the prospective design and the direct assessment of anthropometry at baseline minimized exposure misclassification. Some previous studies used direct assessment,[8,19,26,30] although, to date,

Table 6A. Relative risks and 95% confidence intervals for lymphoma subtype risk in relation to anthropometric characteristics among 141,425 men in the EPIC study.

| | | | | | **B-NHL subtypes** | | | | | | | | |
| | **B-NHL** | | | **DLBCL** | | | **FL** | | | **CLL** | | | **MM** | |
Measure	N (513)	RR[a] (95% CI)	N (71)	RR[a] (95% CI)		N (53)	RR[a] (95% CI)	N (126)	RR[a] (95% CI)		N (139)	RR[a] (95% CI)	
Height, cm													
<170.0	125	1.00	20	1.00		11	1.00	32	1.00		35	1.00	
170.0-147.9	134	1.27 (0.82-1.99)	14	0.65 (0.32-1.32)		16	1.60 (0.72-3.58)	31	0.95 (0.57-1.60)		9	0.99 (0.61-1.59)	
170.0-179.7	130	1.11 (0.71-1.72)	19	0.93 (0.48-1.83)		11	1.25 (0.51-3.08)	33	1.08 (0.64-1.83)		34	0.85 (0.51-1.40)	
≥179.8	123	0.95 (0.59-1.52)	18	0.94 (0.46-1.90)		15	1.92 (0.80-4.61)	30	1.12 (0.65-1.95)		31	0.87 (0.51-1.47)	
p-trend[b]		0.24		0.59			0.48		0.41			0.54	
Weight, kg													
<72.7	121	1.00	19	1.00		12	1.00	34	1.00		26	1.00	
72.7-79.8	117	0.81 (0.52-1.27)	13	0.59 (0.29-1.20)		11	0.84 (0.36-1.94)	24	0.74 (0.43-1.26)		37	1.49 (0.89-2.48)	
79.9-87.7	137	1.05 (0.68-1.63)	20	0.90 (0.46-1.74)		17	1.15 (0.52-2.52)	32	0.93 (0.56-1.57)		36	1.49 (0.88-2.53)	
≥87.8	137	0.83 (0.54-1.27)	19	0.86 (0.42-1.77)		13	0.82 (0.34-1.98)	36	1.08 (0.63-1.84)		40	1.77 (1.02-3.05)	
p-trend[b]		0.64		1.00			0.85		0.59			0.06	
Body mass index, kg/m²													
<24.0	119	1.00	21	1.00		8	1.00	28	1.00		27	1.00	
24.0-26.1	129	0.91 (0.61-1.36)	11	0.44 (0.21-0.92)		21	2.26 (1.00-5.13)	33	1.14 (0.68-1.90)		37	1.21 (0.74-2.00)	
26.2-28.6	122	0.88 (0.57-1.36)	17	0.62 (0.32-1.19)		10	1.02 (0.40-2.61)	33	1.09 (0.65-1.83)		33	1.13 (0.68-1.89)	
≥28.7	142	0.94 (0.63-1.40)	22	0.84 (0.45-1.56)		14	1.43 (0.58-3.52)	32	1.06 (0.62-1.80)		42	1.52 (0.92-2.51)	
p-trend[b]		0.76		0.83			0.94		0.90			0.13	
Waist circumference, cm													
<87.9	96	1.00	13	1.00		9	1.00	24	1.00		26	1.00	
87.9-94.0	120	0.85 (0.51-1.42)	16	1.03 (0.47-2.26)		16	1.19 (0.49-2.89)	34	1.02 (0.58-1.80)		24	0.71 (0.39-1.30)	
94.1-100.9	103	0.98 (0.53-1.84)	14	1.05 (0.42-2.62)		12	0.83 (0.29-2.39)	27	0.81 (0.42-1.59)		24	0.86 (0.44-1.69)	
≥101.0	136	0.89 (0.38-2.05)	22	1.74 (0.56-5.45)		10	0.51 (0.12-2.10)	31	0.68 (0.29-1.64)		39	1.23 (0.53-2.83)	
p-trend[b]		0.91		0.39			0.30		0.32			0.56	
Hip circumference, cm													
<96.1	121	1.00	18	1.00		11	1.00	31	1.00		33	1.00	
96.1-100.1	113	0.77 (0.47-1.26)	18	0.81 (0.40-1.64)		10	0.79 (0.32-1.98)	34	0.88 (0.52-1.50)		23	0.63 (0.36-1.11)	
100.2-104.9	108	0.71 (0.39-1.28)	15	0.62 (0.27-1.42)		16	1.16 (0.45-2.99)	26	0.61 (0.32-1.14)		27	0.75 (0.41-1.39)	
≥105.0	112	0.73 (0.33-1.64)	14	0.44 (0.15-1.32)		10	0.52 (0.14-2.02)	25	0.39 (0.17-0.91)		30	0.66 (0.29-1.47)	
p-trend[b]		0.37		0.13			0.64		0.02			0.40	
Waist to hip ratio (WHR)													
<0.90	85	1.00	11	1.00		11	1.00	20	1.00		27	1.00	
0.90-0.93	102	1.25 (0.72-2.17)	16	1.14 (0.52-2.51)		10	0.75 (0.31-1.84)	31	1.23 (0.68-2.22)		22	0.61 (0.34-1.09)	
0.94-0.97	123	0.77 (0.45-1.32)	13	0.84 (0.36-1.97)		16	1.12 (0.48-2.62)	32	1.09 (0.59-2.01)		21	0.51 (0.28-0.95)	
≥0.98	144	0.93 (0.51-1.70)	25	1.47 (0.63-3.43)		10	0.67 (0.24-1.89)	33	1.01 (0.52-1.96)		43	0.88 (0.48-1.60)	
p-trend[b]		0.45		0.44			0.69		0.82			0.82	
Body mass index, kg/m²													
<25.0 (normal)	173	1.00	24	1.00		16	1.00	43	1.00		43	1.00	
25.0-29.9 (overweight)	251	0.84 (0.54-1.29)	37	0.83 (0.39-1.76)		30	0.89 (0.36-2.24)	59	1.26 (0.75-2.13)		72	1.33 (0.79-2.23)	
≥30.0 (obesity)	88	0.89 (0.64-1.22)	10	0.94 (0.56-1.59)		7	1.17 (0.63-2.18)	24	0.95 (0.63-1.42)		24	1.17 (0.80-1.72)	
p-trend[b]		0.37		0.63			0.96		0.50			0.26	
Waist circumference, cm													
<102	330	1.00	44	1.00		37	1.00	88	1.00		78	1.00	
≥102	125	0.98 (0.58-1.65)	21	2.03 (0.96-4.28)		10	0.76 (0.30-1.95)	28	0.81 (0.45-1.46)		35	1.50 (0.85-2.65)	
Waist to hip ratio (WHR)													
<0.95	218	1.00	32	1.00		24	1.00	56	1.00		53	1.00	
≥0.95	236	0.82 (0.56-1.19)	33	0.97 (0.56-1.69)		23	1.17 (0.60-2.26)	60	1.07 (0.70-1.62)		60	1.08 (0.70-1.65)	

RR: relative risks; CI: confidence intervals. B-NHL: B-cell non-Hodgkin's lymphoma; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; CLL: chronic lympocytic leukemia; MM: multiple myeloma. Other abbreviations are explained in Table 2. ªCox regression models stratified by recruitment age and study center. Models for weight were further adjusted for height (continuous). Models for WC, HC, WHR were further adjusted for height (continuous) as well as weight (continuous). ᵇp-trend across categories are based on fitting a model treating the different quartile categories as a single ordinal variable.

Table 6B. Relative risks and 95% confidence intervals for lymphoma subtype risk in relation to anthropometric characteristics among 230,558 women in the EPIC study.

	B-NHL		DLBCL		FL		CLL		MM	
Measure	N (515)	RR[a] (95% CI)	N (73)	RR[a] (95% CI)	N (78)	RR[a] (95% CI)	N (92)	RR[a] (95% CI)	N (129)	RR[a] (95% CI)
Height, cm										
<170.0	107	1.00	18	1.00	18	1.00	20	1.00	23	1.00
170.0-174.9	127	0.85 (0.52-1.41)	16	0.91 (0.45-1.82)	18	1.13 (0.57-2.23)	20	0.98 (0.51-1.86)	32	1.66 (0.95-2.90)
170.0-179.7	150	1.03 (0.64-1.65)	19	1.01 (0.50-2.03)	25	1.59 (0.82-3.08)	28	1.20 (0.65-2.24)	37	1.84 (1.04-3.24)
≥179.8	131	0.86 (0.51-1.44)	20	1.15 (0.56-2.36)	17	1.25 (0.59-2.62)	24	1.27 (0.66-2.46)	37	2.34 (1.29-4.21)
p-trend[b]		0.38		0.37		0.01		0.62		0.78
Weight, kg										
<72.7	110	1.00	14	1.00	16	1.00	18	1.00	25	1.00
72.7-79.8	108	0.83 (0.51-1.34)	12	0.78 (0.35-1.69)	25	1.33 (0.70-2.52)	20	0.92 (0.48-1.76)	22	0.69 (0.39-1.23)
79.9-87.7	151	0.74 (0.47-1.17)	21	1.32 (0.66-2.68)	15	0.69 (0.33-1.43)	25	1.01 (0.54-1.89)	44	1.19 (0.71-1.99)
?87.8	146	0.76 (0.47-1.22)	26	1.62 (0.81-3.25)	22	0.98 (0.49-1.98)	29	1.10 (0.59-2.06)	38	0.95 (0.55-1.63)
p-trend[b]		0.24		0.06		0.49		0.24		0.62
Body mass index, kg/m²										
<24.0	104	1.00	11	1.00	17	1.00	14	1.00	26	1.00
24.0-26.1	138	1.10 (0.69-1.74)	17	1.27 (0.59-2.72)	21	0.95 (0.50-1.81)	31	1.73 (0.92-3.26)	28	0.84 (0.49-1.44)
26.2-28.6	145	0.79 (0.49-1.25)	18	1.36 (0.63-2.91)	23	0.92 (0.48-1.76)	23	1.18 (0.60-2.31)	41	1.10 (0.66-1.82)
≥28.7	128	0.79 (0.49-1.28)	27	2.18 (1.05-4.53)	17	0.70 (0.34-1.41)	24	1.24 (0.63-2.45)	34	0.91 (0.53-1.56)
p-trend[b]		0.16		0.03		0.32		0.16		0.99
Waist circumference, cm										
<87.9	99	1.00	11	1.00	13	1.00	21	1.00	24	1.00
87.9-94.0	123	1.08 (0.65-1.80)	13	0.78 (0.34-1.82)	25	1.29 (0.63-2.64)	21	0.51 (0.27-0.97)	25	0.71 (0.39-1.28)
94.1-100.9	132	0.82 (0.47-1.43)	22	1.20 (0.51-2.83)	17	0.81 (0.34-1.90)	20	0.36 (0.18-0.74)	33	0.84 (0.44-1.59)
≥101.0	135	0.79 (0.37-1.69)	22	1.05 (0.34-3.22)	22	1.06 (0.35-3.18)	25	0.30 (0.11-0.77)	36	0.86 (0.37-2.02)
p-trend[b]		0.40		0.67		0.72		0.40		0.85
Hip circumference, cm										
<96.1	94	1.00	12	1.00	9	1.00	12	1.00	23	1.00
96.1-100.1	135	0.96 (0.58-1.59)	15	0.79 (0.36-1.75)	30	2.47 (1.11-5.46)	25	1.66 (0.80-3.45)	26	0.81 (0.44-1.47)
100.2-104.9	126	0.66 (0.36-1.21)	17	0.84 (0.36-1.96)	19	1.68 (0.66-4.28)	20	1.47 (0.63-3.41)	37	1.17 (0.61-2.24)
≥105.0	134	0.84 (0.36-1.94)	24	0.97 (0.33-2.88)	19	1.64 (0.49-5.48)	30	2.55 (0.91-7.19)	32	0.94 (0.38-2.32)
p-trend[b]		0.38		0.98		0.74		0.38		0.75
Waist to hip ratio (WHR)										
<0.90	109	1.00	15	1.00	17	1.00	23	1.00	24	1.00
0.90-0.93	117	0.85 (0.51-1.43)	16	0.97 (0.48-1.98)	20	1.02 (0.53-1.98)	27	0.86 (0.49-1.52)	22	0.76 (0.42-1.37)
0.94-0.97	140	0.67 (0.41-1.10)	16	0.78 (0.37-1.63)	19	0.81 (0.40-1.61)	19	0.45 (0.24-0.85)	41	1.11 (0.65-1.91)
≥0.98	123	0.75 (0.43-1.31)	21	0.93 (0.43-2.01)	21	0.86 (0.41-1.81)	18	0.35 (0.17-0.71)	31	0.84 (0.45-1.56)
p-trend[b]		0.21		0.75		0.57		0.21		0.93
Body mass index, kg/m²										
<25.0 (normal)	253	1.00	30	1.00	40	1.00	46	1.00	59	1.00
25.0-29.9 (overweight)	186	0.81 (0.50-1.32)	31	1.27 (0.63-2.55)	28	0.68 (0.33-1.40)	32	0.84 (0.45-1.56)	49	0.93 (0.55-1.56)
≥30.0 (obesity)	76	0.72 (0.50-1.03)	12	1.54 (0.92-2.57)	10	0.89 (0.54-1.46)	14	0.91 (0.57-1.44)	21	1.06 (0.72-1.58)
p-trend[b]		0.17		0.28		0.30		0.17		0.89
Waist circumference, cm										
<88	356	1.00	47	1.00	56	1.00	62	1.00	82	1.00
≥88	133	1.02 (0.60-1.72)	21	0.88 (0.42-1.85)	21	1.07 (0.52-2.20)	25	0.84 (0.43-1.61)	36	1.17 (0.66-2.06)
Waist to hip ratio (WHR)										
<0.80	250	1.00	33	1.00	39	1.00	57	1.00	51	1.00
≥0.80	239	0.76 (0.52-1.12)	35	0.99 (0.57-1.70)	38	0.97 (0.59-1.61)	30	0.39 (0.24-0.64)	67	1.32 (0.88-1.99)

RR: relative risks; CI: confidence intervals. [a]Cox regression models stratified by recruitment age and study center. Models for weight were further adjusted for height (continuous). Models for WC, HC, WHR were further adjusted for height (continuous) as well as weight (continuous). [b]p-trend across categories are based on fitting a model treating the different quartile categories as a single ordinal variable.

the assessment in EPIC is the most comprehensive as it includes waist and hip circumference. Most studies have relied on self-reported anthropometric data[11-17,20,21,23,25] or on obesity hospital discharge codes,[10,18,22] while the methods of others are vague.[9,24] Individuals generally underreport weight and overreport height. Non-differential exposure misclassification in cohort studies results in attenuated estimates. In contrast, case control studies are subject to differential reporting by cases versus healthy participants, which would yield overestimated

weight and BMI associations, but underestimated height estimates.

Study limitations that deserve consideration include differences in anthropometric assessment methods across EPIC centers as well as the relatively short duration of follow-up. To account for the variability in anthropometric assessments among centers and improve comparability among centers, the type of clothing that was worn at the time of measurement was adjusted for; however, it is likely that some residual variability existed. We cannot exclude the possibility that some participants were enrolled with undiagnosed NHL and MM and that those individuals might have experienced weight loss, which is an early symptom of NHL. In analyses excluding cases diagnosed within the first 2 years of follow-up (~18% of male and female cases), the height relationship among women became weaker; relative risks and 95% CI for the 2nd, 3rd and 4th quartiles were 1.19 (0.90-1.58), 1.39 (1.05-1.84), and 1.37 (1.02-1.85), respectively. However, height is clearly not expected to change for early disease manifestations. All other risk estimates were not materially different indicating that inclusion of cases with underlying disease (who might have experienced disease-related weight loss) did not bias our study findings. We have no rational explanation for the height estimates becoming marginally weaker, suggesting that the change in risk estimates might be due to chance.

Previous studies have primarily reported on BMI as a measure of obesity. We observed no relationship between BMI and the risk of NHL and MM for either sex. The null findings observed in EPIC when examining BMI-quartiles were confirmed in the analysis of BMI classified according to WHO categories. Previously published studies[9,11-13,15-17,19-21,23-26] are about evenly divided, with half supportive of a positive association.[9,11-13,15,16,26] Of the positive studies, five were population-based case control studies[9,12,13,15,16] and two were cohort studies.[11,26] One of the prospective cohort studies focused on mortality[11] and the other study population was 97% male.[26] The negative studies included two population-based case control studies,[23,25] one with a sample size in excess of 3,000 cases,[25] as well as three prospective cohort studies all with a limited number of cases (<275 cases).[19-21] Among the studies that presented results separately for the sexes,[9,11,12,15,26] all but one,[15] found a stronger positive association among women. Despite the stronger findings for females, the results were still strongly supportive of a positive association for men; three observed statistically significant elevated risks[9,12,15] and one observed a borderline significant elevated risk.[11] Interestingly, there was no evidence of a BMI-NHL and MM relationship (RR=1.0) in either of the two cohort studies restricted to females.[20,21]

Of the three previous studies examining weight, one large population-based case-control study observed a borderline significant, elevated NHL and MM risk of 1.38 for men and women combined.[23] The negative studies, the Iowa women's cohort (women only)[21] and the Icelandic cohort (analyses for men and women separately)[19] had limited numbers of cases. The lack of a weight-NHL and MM association in these cohort studies as well

as within the EPIC cohort suggests that recall bias may account for the discrepancy in results between the previously published case-control[23] and cohort findings.[19,21] Our findings of no WHR-NHL and MM risk are in agreement with the results of the Iowa women's cohort study, the only other study that has explored this hypothesis.[21] To our knowledge, no previous studies have investigated waist and hip circumference or well-established WC and WHR definitions in relation to NHL and MM risk among either of the sexes.

Our finding that tall stature was associated with elevated NHL and MM risk in women is in agreement with three previous studies, including the Nurses' Health Study[20] and a large population-based U.S. case-control study of 1,321 male and female cases.[23] The lack of a height-NHL and MM relationship among men is supported by the reports of three other studies: a cohort of Icelanders,[19] as well as two large European population-based case-control studies.[16,25] Yet, our finding for men contradicts the positive height association noted in the Whitehall mortality study of men.[30] Exposure misclassification could have occurred due to the reliance on self-reported height information in previously published studies and might explain the failure to observe a height-NHL and MM association in the Iowa women's cohort study[21] as well as in the case-control studies.[16,25] Four studies reported sex-specific findings.[16,20,21,30] For the highest versus lowest category of height, strong, significant relative risks of 2.4 and 1.89 were observed for women[20] and men,[30] respectively. However, the results of the other two studies were not supportive of sex-specific associations.[16,21]

In EPIC, there was a suggestion that sitting height, but not leg length, was positively associated with the risk of NHL and MM. No previous study has reported on sitting height or leg length in relation to NHL and MM risk. It is not surprising that discrepant results were observed for the two height components. Due to their weak correlation, the growth of leg and trunk length have been hypothesized to be independently influenced by different exposures.[43,44] Findings of the 1946 British National birth cohort indicated that despite the common predictors (i.e., birthweight and parental height) of the height components, breastfeeding and dietary intake were uniquely, positively associated with leg length, while serious illness in childhood and parental divorce were inversely related to trunk length, probably as indicators of lower childhood social class.[44] Childhood social class can be linked to NHL and MM risk factors. It has been suggested repeatedly[45] that delayed infection could be a NHL risk factor through the stimulation of cytokine production and B-cell proliferation, and delayed exposure to common infectious agents is itself strongly associated with higher social class. Thus, no or delayed infectious diseases in childhood would be associated with longer trunk and the latter associated indirectly with NHL.

Most previous studies reporting on subtypes have focused on heterogeneity between DLBCL and FL. In one study, DLBCL were more strongly associated with general obesity as measured by weight or BMI and FL were more strongly related to height.[23] Three additional studies confirmed the stronger obesity-DLBCL associa-

tion,[14,16,25] although the association was observed for men, but not women, in the study by Willett *et al.*[16] Our findings among women agree with the hypothesis of a general obesity-DLBCL relationship and of a height-FL association. In the male EPIC population, associations with body size characteristics differed between DLBCL and FL. However our results suggested that height and BMI were related to FL, rather than DLBCL tumors. Our findings are in contrast with those of other studies reporting no heterogeneity for DLBCL versus FL subtypes for weight[21] or for height.[16,21,25] MM has also been examined in a number of studies.[8,10-12,19,22,46] In contrast to our finding of an elevated risk of MM among taller women, the Iowa women's cohort study observed no association.[46] Among men, the most prominent MM risk factors were weight, BMI and WC as categorized according to well-established definitions. In support of these findings several studies have observed strong associations for BMI[11,12,46] or obesity based on medical records[22] in both men[11,12,22] and women.[11,12,46] Yet, a few studies, all with limited numbers of cases, found no association.[8,10,19] Finally, given the lack of biological plausibility and the number of comparisons made in this investigation, the inverse subtype associations observed in EPIC are likely due to chance.

In conclusion, we found that height was a strong risk factor for NHL and MM risk in women. Potential residual confounding accounting for this association was addressed by stratification by center; however, neither confounding by an unknown risk factor nor a chance finding can be ruled out as a possible explanation. No other anthropometric characteristic was positively associated, in a dose-response fashion, with NHL and MM risk. Also, our study suggests that relationships between anthropometric characteristics and NHL and MM risk may vary for NHL and MM subtypes (e.g., DLBCL versus FL subtypes). The potential mechanisms explaining such differences need to be elucidated in further studies.

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Authorship and Disclosures

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