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Body size and risk of non-Hodgkin lymphoma by subtype: a pooled analysis from six prospective cohorts in the United States

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Abstract

In 2021, >100,000 non-Hodgkin lymphoma (NHL) diagnoses are expected, yet few risk factors are confirmed. In this study, data from six US-based cohorts (568,717 individuals) were used to examine body size and risk of NHL. Over >20 years of follow-up, 11,263 NHLs were identified. Hazard ratios (HRs) and 95% confidence intervals (CI) estimated associations with NHLs for

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adult body mass index (BMI), height, weight change, waist circumference, and predicted fat mass. Adult height was broadly associated with NHL, but most strongly B-cell NHLs among non-white participants (e.g., HR_{BLACK}=2.06, 95% CI: 1.62–2.62). However, the strongest association among the anthropometric traits examined was for young-adult body mass index (BMI) and risk of diffuse large B-cell lymphoma (DLBCL), particularly those who maintained a higher BMI into later adulthood. Individuals with BMI>30 kg/m^2 throughout adulthood had more than double the DLBCL risk (HR=2.67, 95% CI: 1.71–4.17) compared to BMI 18.5-<22.9 kg/m^2. Other anthropometric traits were not associated with NHL after controlling for BMI. These results suggest that sustained high BMI is a major driver of DLBCL risk. If confirmed, we estimate that up to 23.5% of all DLBCLs (and 11.1% of all NHLs) may be prevented with avoidance of young adult obesity.

Keywords

non-Hodgkin lymphoma; obesity; body-mass index; population attributable risk; risk factors; epidemiology

Introduction

Collectively, the more than 40 tumors classified as non-Hodgkin lymphoma (NHL) are expected to account for >100,000 new cancer diagnoses and >25,500 cancer deaths in the United States (US) in 2021 (Siegel, *et al* 2021). Incidence and mortality rates for NHL overall increased dramatically from 1950 to the 1990s (Howlader N 2020). Incidence continues to rise for some types of NHL, and survival remains notably poor for many subtypes (Teras, *et al* 2016). Despite the doubling of all NHL incidence rates since the mid-1970 (Howlader N 2020), there are few established risk factors (Cerhan, *et al* 2017) and no screening tools for these cancers. Evidence for modifiable risk factors that could inform prevention strategies is particularly limited, especially from prospective studies. Further complicating the issue is etiologic heterogeneity by NHL subtype, requiring very large studies to adequately assess risk factors for these cancers by subtype.

Since the early 2000s, increases in the prevalence of overweight and obesity in the U.S. have slowed, but excess body weight remains a major public health crisis in this country (Wang, *et al* 2020). Results of studies on the potential impact of body size on NHL risk have been mixed. Adult height has been consistently linked to most types of NHL (Abar, *et al* 2019b), while associations with other body size measures are less clear, possibly due to heterogeneity. The 2019 World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) review concluded that both current and young adult body mass index (BMI) were positively associated with risk of some (diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) but not all (follicular lymphoma (FL)) of the most common types of NHL. To our knowledge, no prospective study has examined anthropometric factors and risk of more rare NHL subtypes; and only a handful have examined metrics of adiposity other than a single measure of adult BMI and height with NHL risk.

Of particular concern, prevalence of overweight and obesity in younger adults is much higher than in previous decades. Among participants in the nationally-representative US National Health and Examination Survey-I (NHANES-I), ~6% of adults age 18–21 had an obese BMI in the early 1970s (CDC), whereas the most recent NHANES survey found that ~28% of young adults were obese (CDC 2017–2018). As sustained weight loss after young adulthood is relatively uncommon, an important unanswered question is how a lifetime of excess body weight may impact NHL risk. In this prospective study we set out to clarify associations between body size and risk of NHL among more than half a million participants collectively enrolled in six US-based prospective studies, and estimate the proportion of NHLs that may be attributed to modifiable body size.

Methods

Study population

Five of the six prospective studies in this pooled analysis were established, large prospective cohort studies with repeated measures of anthropometric traits and follow-up for cancer endpoints: the California Teachers Study (CTS)(Lacey, *et al* 2020), the Cancer Prevention Study-II (CPS-II) Nutrition Cohort (Calle, *et al* 2002), the Health Professionals Follow-up Study (HPFS) (Rimm, *et al* 1991) and the Nurses' Health Studies (NHS and NHSII) (Colditz and Hankinson 2005b). The sixth cohort is a subsample of 32,736 participants from the ~4.6 million racially/ethnically and socioeconomically diverse members of Kaiser Permanente Southern California (KPSC) (Koebnick, *et al* 2012), selected using incidence density sampling (NHLs diagnosed 2007–2012 and 5 controls per case). This study was approved by the Institutional Review Boards (IRBs) for each of the contributing cohorts. See Supplemental Methods more information on the design and data collection methods of the collaborating cohorts.

We excluded individuals with a prior history of cancer (n=30,030), missing/implausible anthropometric information at baseline (n=15,915), or missing/unknown diagnosis information (n=7,062). Implausible values for weight and height were defined as < 0.5 percentile (weight: 41.7 kg, height: 143 cm) or > 99.5th percentile (weight: 139.2 kg, height: 191 cm) of participants in the National Health and Examination Survey (NHANES)-III (1988–1994). The total analytic cohort included 133,237 men and 435,480 women.

Case ascertainment

Incident NHL diagnoses (ICD-8 codes 200, 202 and 204.1; ICD-O-3 9678–9680, 9684, 9690, 9691, 9695,9698, 9670, 9823, 9689, 9699, 9673, 9687, 9826, 9590, 9591, 9596, 9671, 9675, 9727, 9728, 9833, 9835, 9836) were self-reported and verified via medical record or linkage with state cancer registries (CPS-II, CTS, HPFS, NHS, NHSII), or were identified through linkage to a SEER-affiliated cancer registry (KPSC). All cases were classified for histologic subtype according to the World Health Organization classification scheme (Swerdlow, *et al* 2008). NHL subtypes with ≥75 cases in the pooled dataset were analyzed separately. The NHS-II cohort contributed to analyses of all NHL but did not have data to contribute to subtype-specific analyses.

Exposure assessment

Weight, height, and BMI—Study participants in CPS-II, CTS, HPFS, NHS, NHS-2 reported current height, current weight, and young-adult weight (age 18 (CPS-II Nutrition, CTS, NHS and NHS II) or age 21 (HPFS)) on the baseline questionnaire. Current weight was also updated periodically throughout follow-up. Both current and recalled weight have been validated in these or similar studies (Hodge, *et al* 2020, Rimm, *et al* 1990, Troy, *et al* 1995). Measured weight and height information for KPSC was extracted from medical records. Young adult weight was not available for KSPC participants. BMI (weight in kilograms divided by height in meters squared (kg/m^2)) was calculated for every reported/extracted weight. We analyzed young adult BMI and two summary measures of middle/later adult BMI: "recent" BMI (updated current BMI), and "usual adult" BMI (updated cumulative average BMI). To assess the relative impact of early vs. later life body size, we also studied joint associations comparing individuals who were lean (BMI< 25 kg/m^2) at both time points to all other groups.

Other body size measures—Waist circumference (WC) was reported once (CPS-II) or on multiple surveys (CTS, HPFS, NHS, NHS-2) for all cohorts but KSPC. Self-reported waist circumference has been validated against technician measurements (Rimm, *et al* 1990) and found to be associated with other cancers (Genkinger, *et al* 2015, Teras, *et al* 2014, Wang, *et al* 2008). Individuals with implausibly low waist measurement reports (i.e., men: <73.7cm; women: <50.8cm) were excluded from relevant analyses. Adult weight change was calculated as middle/later adult weight (at baseline) minus young-adult weight. Predicted fat mass was calculated using sex-specific formulas derived and validated using NHANES data and described in detail elsewhere (Lee, *et al* 2017). Participants missing data on any of the variables in the formula were not included in the predicted fat mass analyses.

Statistical analyses

Person-time was calculated from the return date of the baseline questionnaire (or 2007 for KPSC) to the date of NHL diagnosis, death, or the end of follow-up, whichever occurred first. Because contributing cohorts utilized differing time intervals between questionnaires, we subdivided follow-up time to one-year intervals to facilitate harmonization across studies. Person-time was classified according to the most recent cohort-specific questionnaire with reporting of a given exposure or covariate. Individuals who reported cancer diagnoses during follow-up were censored at diagnosis date. In cohort- and sex-specific analyses, there was little evidence of statistically significant heterogeneity (Supplementary figures 1 and 2); thus, we pooled directly across cohorts to maximize our sample size for statistical modeling. When updated anthropometric information was available, exposure data was updated in a time-dependent fashion. Information was carried forward if participants missed one follow-up survey, but they were dropped from the model if they missed two or more consecutive surveys, until they subsequently provided updated exposure information. Extended Cox regression (25), fit to the pooled data and stratified by sex and cohort, age (continuous), and calendar year of follow-up, was used to estimate time-dependent hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of NHL associated with each exposure variable.

All anthropometric factors were modeled as continuous and categorical variables. Individuals missing exposure variables were excluded from continuous variable analyses but were put in a missing category for categorical analyses. BMI was categorized according to WHO cutpoints (WHO 2000) and into finer categories where sample size allowed. Specifically, recent and usual adult BMI categories were BMI < 18.5 kg/m^2, 18.5–22.9 kg/m^2, 23–24.9 kg/m^2 (“lean”), 25–29.9 kg/m^2 (“overweight”), 30–34.9 kg/m^2 (“class 1 obese”), 35–39.9 kg/m^2 (“class 2 obese”) and ≥40 kg/m^2 (“class 3 obese”). Young adult BMI categories were < 18.5 kg/m^2, 18.5–22.9 kg/m^2, 23–24.9 kg/m^2, 25–29.9 kg/m^2, and ≥30 kg/m^2. Joint associations for young and later/middle adult BMI were assessed using collapsed categories for BMI at both time points: 18.5-<25 kg/m^2, 25-<30 kg/m^2, ≥30 kg/m^2. Waist circumference (WC) was categorized using cutpoints summarized in a WHO expert panel report (WHO 2000) (women: <80cm (ref), 80-<88cm, and ≥88cm; men: <94cm (ref), 94-<102cm, and ≥102cm). Quartiles were used for predicted fat mass (Q1:< 19.8kg Q2: 19.8 - < 23.6kg, Q3: 23.6 - < 29.0kg, Q4: ≥29.0kg). Weight change categories were chosen to examine the most extreme amounts of weight change, while maintaining adequate sample size: (weight loss: ≥ 10 kg, 4.5 - < 10 kg, 2 - < 4.5 kg, stable weight (+/− 2 kg), weight gain: 2 - < 4.5 kg, 4.5 - < 10 kg, 10 - < 20 kg, 20 - < 30 kg, and ≥ 30 kg).

Multivariable models initially included sex, age, race, cohort, educational attainment (< high school, high school graduate, college graduate, missing), alcohol consumption (current consumption, no current consumption, missing), and smoking status (never, past, current, missing), and other anthropometric factors. The results were almost identical regardless of covariates, and we therefore present more parsimonious models (controlled only for sex, age, and cohort). Full models are shown in the supplementary material for comparison (Supplementary Table I). Between-study heterogeneity was assessed using a random effects meta-analysis approach, (DerSimonian and Laird 1986, Smith-Warner*, et al* 2006). Effect measure modification by sex and race was evaluated in stratified models (Supplemental Table II) but, with the exception of height, results for the total cohort population were shown in the main manuscript tables due to sample size or lack of heterogeneity. All statistical tests were two-sided, and *P*-values <0.05 were considered statistically significant.

Population attributable risk—Estimates of population attributable risk (AR_P%) were calculated using historical and contemporary NHANES survey data (5, 6) and HRs for modifiable body size factors associated with NHL in the present study:

$$ARP\% = 100\% \left[\frac{\sum_{i=2}^{k} (RR_i - 1) P_i}{1 + \sum_{i=2}^{k} (RR_i - 1) P_i} \right]$$

i = a given non-reference stratum among a total of k strata; RR_i= RR for NHL in stratum i; P_i=prevalence of exposure in stratum i

Results

Among 568,717 individuals in the analytic cohort, 11,263 non-Hodgkin lymphoma cases were identified over an average of 20 (up to 37) years of follow-up. NHL subtypes

with sufficient sample size for analyses were CLL/SLL (n=2,824), DLBCL (n=2,722), FL (n=1,707), marginal zone lymphoma (MZL; n=967), mantle cell leukemia (MCL; n=311), Waldenström macroglobulinemia/lymphoplasmacytic lymphoma (LPL/WM; n=199), Burkitt lymphoma (BL; n=94), peripheral T-cell lymphoma (PTCL; n=312), and mycosis fungoides/Sezary syndrome MF/SS; n=259). On average, participants were age 50 years (IQR: 38 to 62 years) at baseline (Table I). Three-quarters of the analytic cohort identified as female (n=435,480) and 10% percent identified as non-White (n=54,474). The average BMI at baseline was 25 kg/m^2 and ranged from 23.8 kg/m^2 in NHS (study baseline year: 1976) to 28.3 kg/m^2 in KPSC (study baseline year: 2007).

Height

Adult height was associated with NHL overall (HR $_{HEIGHT}$ =1.18, 95% CI: 1.15–1.22 per 10 cm (Table II); and was the only anthropometric factor broadly associated with most NHL subtypes examined. Increased risks of NHL subtypes ranged from 10% (DLBCL) to 33% (MCL) per 10 cm additional height (Table II). Associations with height were similar by sex (all NHL HR: 1.17 for women; 1.20: for men) but varied by race. Positive associations were observed for all race groups but were stronger in non-white participants (Table II). For B-NHL, the association with height was strongest for Black participants HR =2.06, 95% CI: 1.62–2.62, but also stronger for Asian/American Indian/Hawaiian (HR=1.65, 95% CI: 1.30–2.10) compared to White participants (HR=1.13, 95% CI: 1.09–1.18) (Table II; p<0.0001). Associations for T-NHL were similar across sex and race groups with the exception of a suggested inverse association for Asian/American Indian/Hawaiian participants 0.71 (0.28 – 1.76).

Young-Adult BMI

Young-adult BMI was the strongest risk factor for NHL among the anthropometric traits we analyzed (HR =1.14, 95% CI: 1.10–1.20 per 5 kg/m^2; Table III). Hazard ratios for NHL were elevated for individuals with an overweight (HR=1.17, 95% CI: 1.07–1.28) and an obese young-adult BMI (HR =1.29, 95% CI: 1.07–1.56; Table III) compared to the reference category (18.5–22.9 kg/m^2). Associations for both B- and T-NHL were similar to the all NHL results. In subtype-specific results, the association with young-adult BMI appeared limited to DLBCL (HR=1.22, 95% CI: 1.11–1.35 per 5 kg/m^2; p-trend: <0.001; Figure 1), though the differences by subtype were not statistically significant (p-heterogeneity=0.67). In categorical analyses, young-adult BMI≥30 kg/m^2 was associated with approximately double the risk of DLBCL compared to BMI 18.5–22.9 kg/m^2 (HR =1.91, 95% CI: 1.32–2.77; Figure 1). These associations did not vary by sex (Supplementary Table II). Because KPSC - the most diverse cohort - did not have data on young-adult BMI, we did not have adequate sample size to examine young-adult BMI associations separately by race.

BMI across adulthood

We also observed a positive association between usual (cumulative average) adult BMI and overall NHL risk, but it was weaker than the association with young-adult BMI. In categorical analyses, there was no clear trend with increasing usual adult BMI levels, but class 3 obesity (>40kg/m^2) BMI was associated with a 20% (95% CI: 4–37%) higher risk of NHL (Table III). Results for B- and T-NHL were again similar to all NHL. In

subtype analyses, just as with young-adult BMI, DLBCL was the only subtype positively-associated with usual-adult BMI (p-heterogeneity <0.001). For BMI categories above 30 kg/m^2, DLBCL risk increased in a dose-dependent fashion compared to BMI 18.5-<25 kg/m^2 (usual adult BMI 30-<35 kg/m^2: HR=1.17, 95% CI: 1.03–1.34; BMI 35-<40 kg/m^2: HR=1.28, 95% CI: 1.06–1.54; BMI ≥40 kg/m^2: HR= 1.52, 95% CI: 1.18–1.96; p-trend: <0.001; Figure 2). The DLBCL association with usual adult BMI was similar in magnitude across sex and race groups (Supplementary Table II). The only other subtype associated with usual adult BMI was LPL/WM, but in the opposite direction from DLBCL. Both usual (HR=0.75, 95% CI: 0.62–0.90 per 5 kg/m^2 (Figure 2) and recent BMI: HR=0.75, 95% CI: 0.63–0.90) (Supplementary Table I) were inversely associated with LPL/WM risk. Recent BMI was not associated with any other NHL subtype, nor with NHL overall (Supplementary Table II).

In joint association analyses, individuals who were overweight in young adulthood and had a usual adult BMI in the obese range (BMI above 30 kg/m^2) had a 42% higher risk of DLBCL (HR=1.42, 95% CI: 1.05–1.92) compared to stable BMI 18.5-<25 kg/m^2 during adulthood (Figure 3). Individuals who were obese both in young and middle/later adulthood had more than two-fold higher risk of developing subsequent DLBCL (HR=2.67, 95% CI: 1.71–4.17; Figure 3). Although very few participants were overweight/obese in young adulthood and lost enough weight to have a lean BMI in middle/later adulthood, our results suggest that the relative risk of DLBCL for these individuals is not elevated compared to the stable lean BMI group (Table III; figure 3).

Other body size measures

Other body size measures were weakly, if at all, associated with NHL or any of the NHL subtypes (Table IV). Waist circumference was positively associated with all NHL (HR=1.05, 95% CI: 1.01–1.09 per 15cm), and associations were at least suggestive for most NHL subtypes, most notably for BL (HR=1.77, 95% CI: 1.05–2.98). However, no clear patterns by waist circumference categories emerged (Table IV). Like BMI, the only NHL subtype associated with predicted fat mass was DLBCL (Q4 v. Q1 HR= 1.30, 95% CI: 1.04–1.62; Table IV). Absolute amount (in kg) of weight change from young to later adulthood did not appear to be associated with NHL or any of the NHL subtypes.

Population Attributable Risk

As adult BMI was the only modifiable risk factor associated with NHL in this study, we estimated the proportion of US NHL cases that could be attributed to having a BMI>25 kg/m^2. In particular we focused on young-adult BMI as this was the BMI measure most strongly related to risk. We first estimated the ARp based on the prevalence of overweight and obesity at the time when the majority of study participants were young adults. Using prevalence data from NHANES I (1971–1975) we estimate that young-adult BMI explained 8.3% (95% CI: 0.0% - 19.1%) of DLBCL cases and 4.2% (95% CI: 0.0% - 8.9%) of NHL cases overall. Because the prevalence of excess body weight has increased so dramatically since that time (Hales*, et al* 2020), we estimate that currently 23.5% (95% CI: 5.4% - 39.3%) of DLBCLs and 11.1% (95% CI: 2.4% - 19.4%) of NHLs can be attributed to young-adult BMI.

Discussion

In this large prospective study, we confirmed—and expanded upon—the findings of previous epidemiologic studies of body size and NHL risk. We confirmed that height was associated with NHL and the more common NHL subtypes (DLBCL, CLL/SLL, FL), and found that it is also associated with rarer subtypes like MCL and MF/SS. We further found that height was associated with NHL across race groups but was strongest for Black study participants and weakest for White participants. BMI was positively associated with the most common NHL subtype (DLBCL) only. Young adult BMI, in particular, was a strong risk factor for DLBCL. Individuals who had an obese young-adult BMI, and remained obese throughout adulthood, had an almost 3-fold higher DLBCL risk compared to maintenance of a lean body mass throughout adulthood. Though adult weight loss is a rare occurrence, our results suggest that DLBCL risk is attenuated in participants who moved to a lower average BMI in middle/later adulthood. We also observed associations between other anthropometric factors and rarer NHL subtypes, including a positive association between waist circumference and BL, and an inverse association between current adult BMI and WM/LPL. Of note, a large case-control study observed a similar inverse association with WM/LPL (Vajdic, *et al* 2014). While intriguing, these results require confirmation from larger prospective studies. Our results underscore the etiologic heterogeneity of these cancers that were once considered a single disease, and posit further questions about the variable biology of lymphomagenesis.

In this study, the only consistent body size association across subtypes was height. This finding agrees with most previous studies on the topic including the recent WCRF/AICR review (Abar, *et al* 2019b). Given that height is also associated with several other cancers in multiple populations (Choi, *et al* 2019, Green, *et al* 2011), the mechanism is likely a global cancer trigger. A recent Mendelian randomization study of height and NHL risk found little evidence of an association (Moore, *et al* 2019), however, suggesting that genetics may not be the major driver of this association. Other hypotheses include the direct effect of a greater number of cells available for replication with taller stature (Giovannucci 2019), growth factors (Giovannucci 2019), and exposure to childhood infections which may simultaneously impact adult height and risk for NHL (Hwang, *et al* 2013). Our finding of a stronger height association for non-white race participants is intriguing. Further exploration of these differences is needed.

BMI was the only remaining factor positively linked to NHL risk, and unlike height, driven by the association with only one subtype (DLBCL). Positive associations between waist circumference and predicted fat mass with DLBCL risk were also suggestive, but neither persisted after mutual control for BMI. We hypothesize that the weaker associations may be due to the smaller available sample size for these analyses (approximately 30% of the total study population had the relevant data). Though the 2016 IARC panel on body size and cancer deemed the evidence for causality between BMI and DLBCL to be limited, (Lauby-Secretan, *et al* 2016) this likely reflected results from small, earlier studies. A recent WCRF/AICR review (Abar, *et al* 2019a), as well as another recent meta-analysis (Hidayat, *et al* 2018) found that BMI, particularly young adult BMI, was associated with DLBCL. Our study expands these findings and shows that that the higher DLBCL risk associated with high early adult BMI is most relevant to those who remain at a high BMI throughout

adulthood, and in a dose dependent fashion. These findings suggest that cumulative exposure to excess adiposity is a major driver of DLBCL risk, perhaps via persistent inflammation, hyperinsulinemia, and/or the influence of adipokines (Hosgood, *et al* 2018, Kolb, *et al* 2016). Future studies assessing the impact of physical activity and/or nutrition-based weight loss interventions on reduction of DLBCL risk are warranted.

Future studies are also needed to expand upon our findings among non-white participants, including the observed differences for height and NHL risk. Though the present study included a substantial number of non-white participants overall, the sample sizes in key groups, such as overweight/obese, Black, Hispanic, or Asian/American Indian/Hawaiian young adults, were too small to study. In part this was due to unavailable data for some of the body size measures (KPSC) or NHL subtypes (NHS-II, NHS, HPFS). Other limitations include self-reported weight and height in all but KPSC. However, validation studies have shown that, overall, the correlation between self-reported and measured weight is very high ($r \geq 0.97$), and the amount of misclassification is small (Lawlor, *et al* 2002, Luo, *et al* 2019, Wright, *et al* 2015). Overweight/obese women may be slightly more likely to underreport weight (Luo, *et al* 2019), but it is unlikely this misclassification would differ by case status. Finally, though we saw no evidence of confounding in our multivariable models, we acknowledge the potential for unmeasured confounding due to missing covariate information for some study participants. However, the data were complete (age and sex) or near complete (race, 4% missing) for the factors previously established as strong NHL risk factors, and we do not think that the missing data is likely to have had a major impact on our results or changed our conclusions. Despite these limitations, this is the most comprehensive prospective study of body size and risk of NHL subtypes in the US to date. Strengths include the prospective assessment of anthropometric traits and their changes during follow-up, long follow-up of a large cohort of individuals across the US, centralized harmonization of the data, and the ability to evaluate potential confounders. Further, the findings appear robust to period and cohort effects, despite the changing prevalence of obesity over time, as results were similar across cohorts, regardless of baseline year and length of follow-up. Future studies should expand upon our findings by race and continue to study associations with rare subtypes like T-NHLs. Further, exploration of other obesity-related factors such as type-II diabetes, and possible risk reduction factors such as physical activity, may offer additional clues as to the mechanisms of this association or possible NHL risk mitigation strategies.

In summary, these results confirm that height is a consistent NHL risk factor, and that excess body weight in young adulthood has a measurable impact on risk of the most common type of NHL, particularly for those who remain heavy throughout their adult life. If this association is confirmed, we estimate that up to a quarter of all DLBCLs (and 11% of all NHLs) may be prevented with avoidance of young adult overweight/obesity. This estimate represents almost triple the fraction of DLBCL cases attributable to excess adiposity in the 1970s when most of these study participants were young adults. Though other factors undoubtedly play an important role in risk of developing this cancer, early intervention to help individuals maintain a healthy bodyweight throughout their adult lives may be a key prevention strategy for a cancer without known modifiable risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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NHS/NHSII/HPFS

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CTS

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All of the data associated with this publication and in the California Teachers Study are available for research use. The California Teachers Study welcomes all such inquiries and encourages individuals to visit https://www.calteachersstudy.org/for-researchers.

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References

Abar L, Sobiecki JG, Cariolou M, Nanu N, Vieira AR, Stevens C, Aune D, Greenwood DC, Chan DS & Norat T (2019a) Body size and obesity during adulthood, and risk of lympho-haematopoietic

cancers: an update of the WCRF-AICR systematic review of published prospective studies. Annals of Oncology, 30, 528–541. [PubMed: 30753270]

Abar L, Sobiecki JG, Cariolou M, Nanu N, Vieira AR, Stevens C, Aune D, Greenwood DC, Chan DS & Norat TJAo.O. (2019b) Body size and obesity during adulthood, and risk of lympho-haematopoietic cancers: an update of the WCRF-AICR systematic review of published prospective studies. 30, 528–541.

Bernstein L, Allen M, Anton-Culver H, Deapen D, Horn-Ross PL, Peel D, Pinder R, Reynolds P, Sullivan-Halley J, West D, Wright W, Ziogas A & Ross RK (2002) High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). Cancer Causes Control, 13, 625–635. [PubMed: 12296510]

Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, Feigelson HS & Thun M.J.J.C.I.I.J.o.t.A.C.S. (2002) The American cancer society cancer prevention study II nutrition cohort: rationale, study design, and baseline characteristics. 94, 2490–2501.

Calle EE, Rodriguez C, Walker-Thurmond K & Thun MJ (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med, 348, 1625–1638. [PubMed: 12711737]

CDC (1971–1974) National Health and Nutrition Examination Survey Data. NHANES I;. In: NHANES I (ed. by NCHS N.C.f.H.S.). U.S. Department of Health and Human Services, Hyattsville, MD.

CDC (2017–2018) National Health and Nutrition Examination Survey Data. In: National Center for Health Statistics (NCHS), Vol. 2021. Department of Health and Human Services, Centers for Disease Control and Prevention.

Cerhan JR, Vajdic CM & Spinelli JJ (2017) The non-hodgkin lymphomas. In: Schottenfeld and Fraumeni Cancer Epidemiology and Prevention, Fourth Edition, pp. 767–796. Oxford University Press.

Choi YJ, Lee DH, Han K-D, Yoon H, Shin CM, Park YS & Kim N (2019) Adult height in relation to risk of cancer in a cohort of 22,809,722 Korean adults. British Journal of Cancer, 120, 668–674. [PubMed: 30778143]

Colditz GA & Hankinson SE (2005a) The Nurses' Health Study: lifestyle and health among women. Nat Rev Cancer, 5, 388–396. [PubMed: 15864280]

Colditz GA & Hankinson SEJNRC (2005b) The Nurses' Health Study: lifestyle and health among women. 5, 388–396.

DerSimonian R & Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials, 7, 177–188. [PubMed: 3802833]

Garfinkel L (1985) Selection, follow-up, and analysis in the American Cancer Society prospective studies. Natl Cancer Inst Monogr, 67, 49–52. [PubMed: 4047150]

Genkinger JM, Kitahara CM, Bernstein L, Berrington de Gonzalez A, Brotzman M, Elena J, Giles G, Hartge P, Singh P & Stolzenberg-Solomon R.Z.J.A.o.O. (2015) Central adiposity, obesity during early adulthood, and pancreatic cancer mortality in a pooled analysis of cohort studies. 26, 2257–2266.

Giovannucci E (2019) A growing link—what is the role of height in cancer risk? British Journal of Cancer, 120, 575–576. [PubMed: 30778142]

Green J, Cairns BJ, Casabonne D, Wright FL, Reeves G, Beral V & oncology M.W.S.c.J.T.l. (2011) Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. 12, 785–794.

Hales CM, Carroll MD, Fryar CD & Ogden CL (2020) Prevalence of obesity and severe obesity among adults: United States, 2017–2018.

Hidayat K, Li H-J & Shi B-M (2018) Anthropometric factors and non-Hodgkin's lymphoma risk: systematic review and meta-analysis of prospective studies. Critical Reviews in Oncology/Hematology, 129, 113–123. [PubMed: 30097229]

Hodge JM, Shah R, McCullough ML, Gapstur SM & Patel A.V.J.P.o. (2020) Validation of self-reported height and weight in a large, nationwide cohort of US adults. 15, e0231229.

Hosgood HD, Gunter MJ, Murphy N, Rohan TE & Strickler HD (2018) The Relation of Obesity-Related Hormonal and Cytokine Levels With Multiple Myeloma and Non-Hodgkin Lymphoma. Frontiers in oncology, 8, 103–103. [PubMed: 29713614]

Howlader N, N.A., Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds.) SEER cancer statistics review, 1975–2017, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission

Hwang AE, Mack TM, Hamilton AS, James Gauderman W, Bernstein L, Cockburn MG, Zadnick J, Rand KA, Hopper JL & Cozen W (2013) Childhood Infections and Adult Height in Monozygotic Twin Pairs. American Journal of Epidemiology, 178, 551–558. [PubMed: 23585330]

Knuth DE (1997) The art of computer programming. Pearson Education.

Koebnick C, Langer-Gould AM, Gould MK, Chao CR, Iyer RL, Smith N, Chen W & Jacobsen SJ (2012) Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. Perm J, 16, 37–41.

Kolb R, Sutterwala FS & Zhang W (2016) Obesity and cancer: inflammation bridges the two. Current opinion in pharmacology, 29, 77–89. [PubMed: 27429211]

Lacey JV, Chung NT, Hughes P, Benbow JL, Duffy C, Savage KE, Spielfogel ES, Wang SS, Martinez ME & Chandra S (2020) Insights from adopting a data commons approach for large-scale observational cohort studies: the California Teachers Study. AACR.

Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F & Straif K (2016) Body fatness and cancer—viewpoint of the IARC Working Group. New England Journal of Medicine, 375, 794–798. [PubMed: 27557308]

Lawlor DA, Bedford C, Taylor M, Ebrahim SJA & Ageing (2002) Agreement between measured and self-reported weight in older women. Results from the British Women's Heart and Health Study. 31, 169–174.

Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Sun Q, Willett WC & Giovannucci E.L.J.B.J.o.N. (2017) Development and validation of anthropometric prediction equations for lean body mass, fat mass and percent fat in adults using the National Health and Nutrition Examination Survey (NHANES) 1999–2006. 118, 858–866.

Luo J, Thomson CA, Hendryx M, Tinker LF, Manson JE, Li Y, Nelson DA, Vitolins MZ, Seguin RA & Eaton C.B.J.P.h.n. (2019) Accuracy of self-reported weight in the Women's Health Initiative. 22, 1019–1028.

Moore A, Kane E, Wang Z, Panagiotou OA, Teras LR, Monnereau A, Wong Doo N, Machiela MJ, Skibola CF, Slager SL, Salles G, Camp NJ, Bracci PM, Nieters A, Vermeulen RCH, Vijai J, Smedby KE, Zhang Y, Vajdic CM, Cozen W, Spinelli JJ, Hjalgrim H, Giles GG, Link BK, Clavel J, Arslan AA, Purdue MP, Tinker LF, Albanes D, Ferri GM, Habermann TM, Adami HO, Becker N, Benavente Y, Bisanzi S, Boffetta P, Brennan P, Brooks-Wilson AR, Canzian F, Conde L, Cox DG, Curtin K, Foretova L, Gapstur SM, Ghesquieres H, Glenn M, Glimelius B, Jackson RD, Lan Q, Liebow M, Maynadie M, McKay J, Melbye M, Miligi L, Milne RL, Molina TJ, Morton LM, North KE, Offit K, Padoan M, Patel AV, Piro S, Ravichandran V, Riboli E, de Sanjose S, Severson RK, Southey MC, Staines A, Stewart C, Travis RC, Weiderpass E, Weinstein S, Zheng T, Chanock SJ, Chatterjee N, Rothman N, Birmann BM, Cerhan JR & Berndt SI (2019) Genetically Determined Height and Risk of Non-hodgkin Lymphoma. Front Oncol, 9, 1539. [PubMed: 32064237]

Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B & Stampfer MJJTL (1991) Prospective study of alcohol consumption and risk of coronary disease in men. 338, 464–468.

Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB & Willett WC (1990) Validity of self-reported waist and hip circumferences in men and women. Epidemiology, 1, 466–473. [PubMed: 2090285]

Siegel RL, Miller KD, Fuchs HE & Jemal AJ (2021) Cancer statistics, 2021. CA: a cancer journal for clinicians, 71, 7–33. [PubMed: 33433946]

Smith-Warner SA, Spiegelman D, Ritz J, Albanes D, Beeson WL, Bernstein L, Berrino F, van den Brandt PA, Buring JE, Cho E, Colditz GA, Folsom AR, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Harnack L, Horn-Ross PL, Krogh V, Leitzmann MF, McCullough

ML, Miller AB, Rodriguez C, Rohan TE, Schatzkin A, Shore R, Virtanen M, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Zhang SM & Hunter DJ (2006) Methods for pooling results of epidemiologic studies: the Pooling Project of Prospective Studies of Diet and Cancer. Am J Epidemiol, 163, 1053–1064. [PubMed: 16624970]

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J & Vardiman JW (eds.) (2008) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. International Agency for Research on Cancer (IARC) Press, Lyon, France.

Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A & Flowers C.R.J.C.a.c.j.f.c. (2016) 2016 US lymphoid malignancy statistics by World Health Organization subtypes. 66, 443–459.

Teras LR, Kitahara CM, Birmann BM, Hartge PA, Wang SS, Robien K, Patel AV, Adami HO, Weiderpass E & Giles GGJBj.o.h. (2014) Body size and multiple myeloma mortality: a pooled analysis of 20 prospective studies. 166, 667–676.

Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer MJ & Willett WC (1995) The validity of recalled weight among younger women. Int J Obes Relat Metab Disord, 19, 570–572. [PubMed: 7489028]

Vajdic CM, Landgren O, McMaster ML, Slager SL, Brooks-Wilson A, Smith A, Staines A, Dogan A, Ansell SM & Sampson J.N.J.J.o.t.N.C.I.M. (2014) Medical history, lifestyle, family history, and occupational risk factors for lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. 2014, 87–97.

Wang Y, Beydoun MA, Min J, Xue H, Kaminsky LA & Cheskin LJJIj.o.e. (2020) Has the prevalence of overweight, obesity and central obesity levelled off in the United States? Trends, patterns, disparities, and future projections for the obesity epidemic. 49, 810–823.

Wang Y, Jacobs EJ, Patel AV, Rodríguez C, McCullough ML, Thun MJ, Calle EEJCC & Control (2008) A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. 19, 783–792.

WHO (2000) Obesity: Preventing and Managing the Global Epidemic. World Health Organization.

Wright FL, Green J, Reeves G, Beral V & Cairns B.J.J.B.m.r.m. (2015) Validity over time of self-reported anthropometric variables during follow-up of a large cohort of UK women. 15, 81.

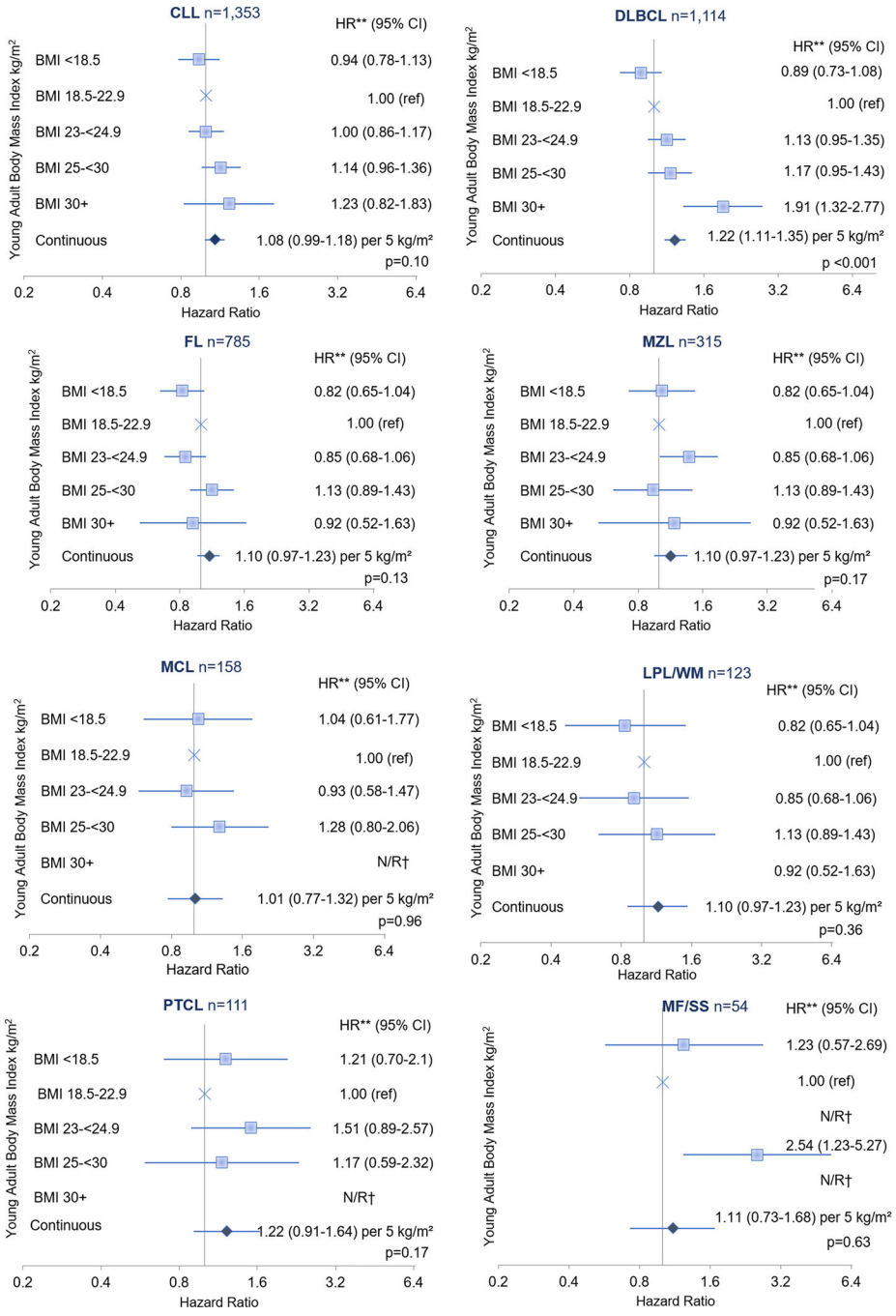

Figure 1. Estimated relative risks for associations of young adult BMI and risk of NHL subtypes in a pooled cohort* of US men and women

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HR, hazard ratio; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM/LPL, Waldenström macroglobulinemia/lymphoplasmacytic lymphoma;

*Analyses include CPS-II, CTS, HPFS, NHS participants; KPSC and NHS-II are not included in these analyses because the relevant data was not available.

**HRs adjusted for age, sex, cohort

p-heterogeneity=0.67

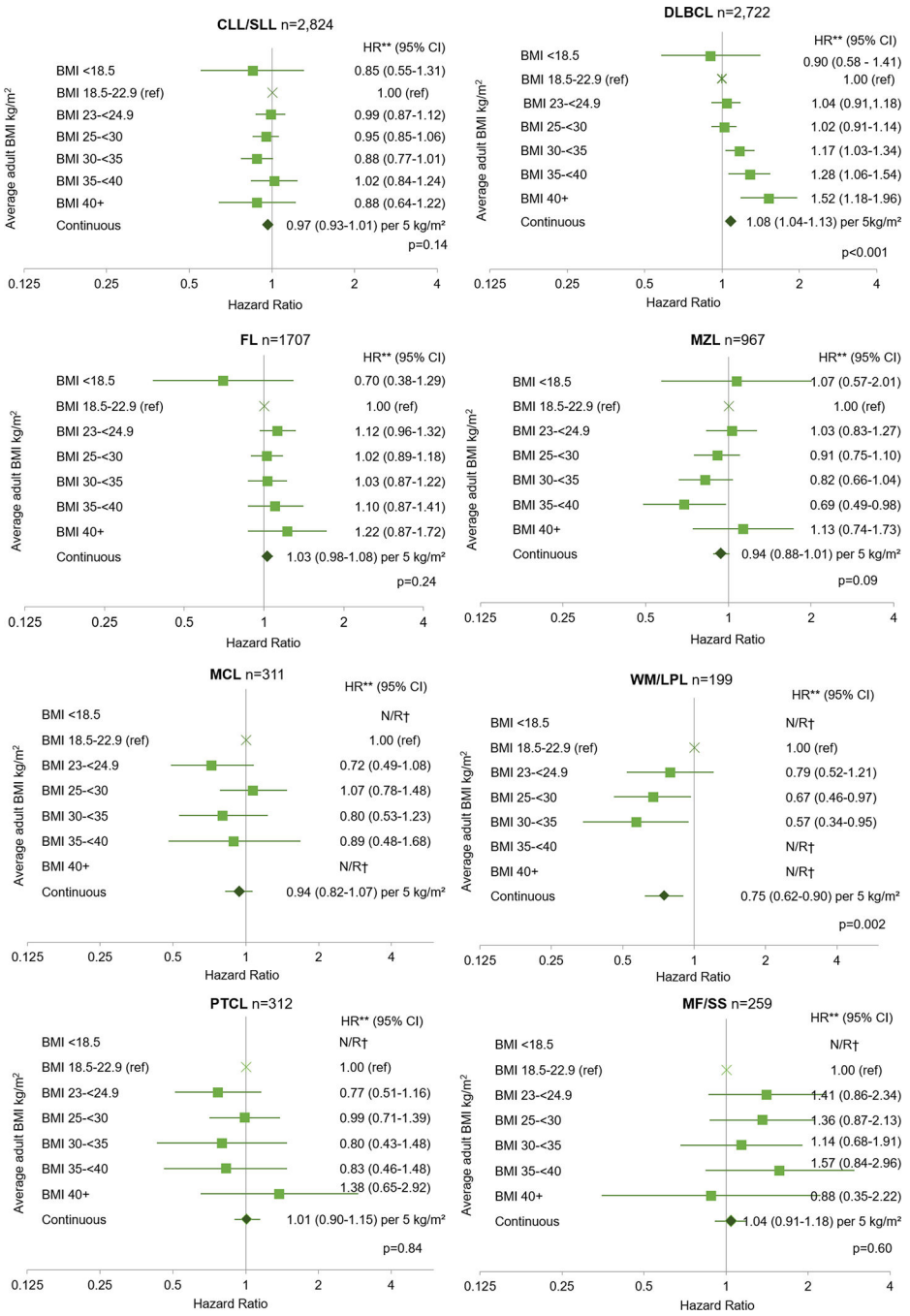

Figure 2. Relative risks and 95% confidence intervals for associations of usual adult BMI and risk of NHL subtypes in the pooled cohort* of US men and women

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HR, hazard ratio; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; LPL/WM, Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia;

*Pooled cohort includes CPS-II, CTS, HPFS, KPSC, NHS; NHS-2 did not have NHL subtype information available.

**HRs adjusted for age, sex, cohort

p-heterogeneity for subtype results: $p<0.0001$

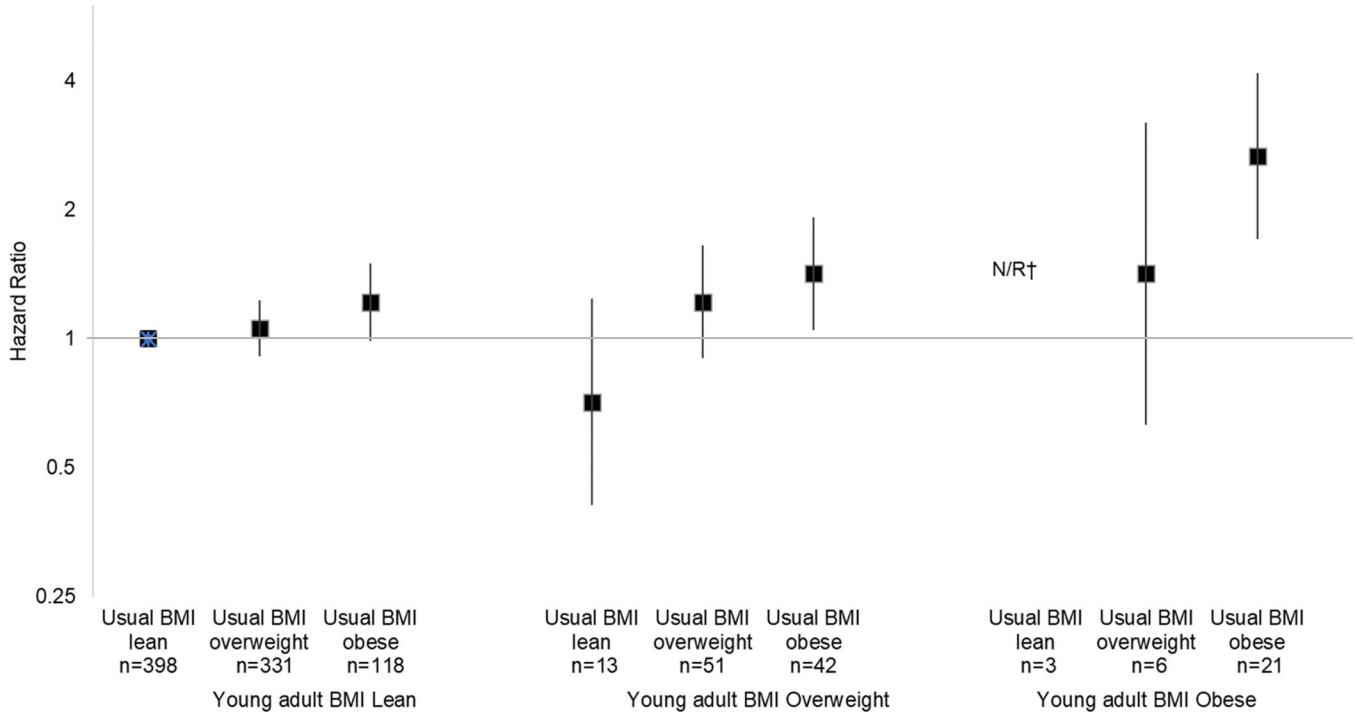

Figure 3. Joint association of young and usual adult BMI with risk of diffuse large B-cell lymphoma (DLBCL) in the pooled cohort*

*Pooled cohort includes CPS-II, CTS, HPFS, KPSC, NHS; NHS-2 did not have NHL subtype information available

HRs adjusted for age, sex, cohort

BMI category labels: "lean" = BMI 18.5-<25 kg/m^2, "overweight" = BMI 25-<30 kg/m^2, "obese" = BMI ≥30 kg/m^2

†N/R= not reported due to small sample size (n<5)

Table I.

Selected characteristics of the six US-based prospective studies included in a pooled analysis of body size and risk of non-Hodgkin lymphoma

Characteristic	Total	NHS	NHS-II	HPFS	CPS-II	CTS	KPSC
Study size	568,717	116,784	114,080	44,471	150,706	109,940	32,736
Baseline year		1976	1989	1986	1992/1993	1995	2007–2014
Mean (range) follow-up time (years)	20.8 (0–37)	30.5 (0–37)	23.6 (0–25)	19.0 (0–25)	16.8 (0 –23)	18.5 (0–20)	5.2 (0–7)
NHL cases	11,263	1,427	408	721	2,338	902	5,467
DLBCL	2,722	221	N/A	100	618	220	1,563
FL	1,707	238	N/A	71	365	167	866
CLL/SLL	2,824	309	N/A	254	640	210	1,411
MZL	967	71	N/A	28	138	92	638
MCL	311	23	N/A	27	94	22	145
LPL/WM	199	19	N/A	15	92	4	69
BL	94	6	N/A	5	18	3	62
T-cell	796	60	N/A	34	168	65	469
MF/SS	259	0	N/A	0	33	21	205
PTCL	312	0	N/A	0	72	40	200
Mean (range) baseline age (years)	50 (18–>90)	43 (30–56)	35 (25–44)	54 (39–79)	63 (40–>90)	52 (21–>90)	62 (18–>90)
Mean (sd) baseline BMI (kg/m^2)	25.0 (4.6)	23.8 (4.1)	24.1 (4.9)	25.5 (3.1)	26.0 (4.2)	24.8 (5.0)	28.3 (5.4)
Mean (sd) baseline height (cm)	167.3 (8.6)	163.8 (6.1)	164.8 (6.5)	177.8 (6.3)	170.5 (9.4)	164.6 (6.5)	168.4 (10.1)
Mean (sd) baseline weight (kg)	70.4 (15.3)	63.9 (11.8)	65.5 (14.2)	80.8 (11.2)	76.0 (15.0)	67.1 (14.2)	80.7 (18.1)
n (%) non-white	54,474 (10%)	7,262 (6%)	8,589 (8%)	4,199 (9%)	3,985 (3%)	14,707 (13%)	15,732 (48%)
% Female	77%	100%	100%	0%	53%	100%	45%
% Never smoker at baseline	50%	43%	65%	45%	44%	66%	N/A
% College educated	68%	100%	100%	100%	38%	50%	N/A

Abbreviations: BL, Burkitt lymphoma; BMI, body mass index; CLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; cm, centimeters; CPS-II, Cancer Prevention Study-II Nutrition Cohort; CTS, California Teachers' Study; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HPFS, Health Professionals Follow-up Study; kg, kilograms; KPSC, Kaiser Permanente Southern California; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MCL, mantle cell lymphoma; MF/SS, mycosis fungoides/Sezary syndrome; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma, NHS, Nurses' Health Study; NHS-II, Nurses' Health Study II; PTCL, peripheral T-cell lymphoma; sd, standard deviation

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Table II.

Estimated relative risks of non-Hodgkin lymphoma per 10 cm increase in height among Asian, Black, White, and participants from mixed or other race groups in a pooled cohort[*] of US men and women

	All Participants		Women		Men		Sex Het	White		Black		Asian/Pacific Islander/American Indian		Other/ Mixed Race		Race Het
	n	HR[**] (95% CI)	n	HR[**] (95% CI)	n	HR[**] (95% CI)	p-value	n	HR[**] (95% CI)	n	HR[**] (95% CI)	n	HR[**] (95% CI)	n	HR[**] (95% CI)	p-value
all NHL	11,263	**1.18 (1.15–1.22)**	6,295	**1.17 (1.13–1.22)**	4,968	**1.20 (1.15–1.25)**	0.43	8,537	**1.12 (1.08–1.16)**	577	**1.95 (1.57–2.42)**	537	**1.50 (1.20–1.86)**	1,612	**1.32 (1.21–1.45)**	<.0001
any B-cell NHL[†]	9,235	**1.19 (1.16–1.23)**	4,959	**1.18 (1.13–1.24)**	4,276	**1.20 (1.15–1.26)**	0.61	6,978	**1.13 (1.09–1.18)**	450	**2.06 (1.62–2.62)**	451	**1.65 (1.30–2.10)**	1,356	**1.30 (1.18–1.44)**	<.0001
CLL[†]	2,824	**1.31 (1.23–1.38)**	1,369	**1.26 (1.16–1.37)**	1,455	**1.35 (1.24–1.46)**	0.28	2,324	**1.11 (1.04–1.19)**	148	**1.95 (1.36–2.82)**	70	**1.87 (1.05–3.32)**	282	**1.69 (1.36–2.10)**	<.0001
DLBCL[†]	2,722	**1.10 (1.04–1.17)**	1,465	1.08 (0.99–1.17)	1,257	**1.13 (1.04–1.23)**	0.42	1,854	**1.12 (1.04–1.21)**	141	**3.00 (1.76–5.08)**	212	**1.83 (1.27–2.63)**	515	1.17 (0.99–1.38)	0.0003
FL[†]	1,707	**1.22 (1.13–1.31)**	1,044	**1.26 (1.14–1.38)**	663	**1.16 (1.04–1.30)**	0.30	1,286	**1.21 (1.10–1.32)**	64	**2.55 (1.33–4.88)**	73	1.74 (0.95–3.18)	284	1.14 (0.93–1.40)	0.08
MZL[†]	967	1.08 (0.98–1.19)	569	1.12 (0.99–1.28)	398	1.03 (0.89–1.19)	0.38	642	0.98 (0.86–1.12)	75	1.60 (0.84–3.05)	69	1.78 (0.94–3.37)	181	**1.43 (1.10–1.87)**	0.02
MCL[†]	311	**1.33 (1.12–1.58)**	113	**1.47 (1.10–1.96)**	198	**1.26 (1.02–1.56)**	0.41	249	**1.39 (1.13–1.72)**	6	1.99 (0.26–15.25)	9	0.34 (0.08–1.41)	47	1.01 (0.61–1.66)	0.17
LPL/WM[†]	199	1.14 (0.92–1.42)	92	1.13 (0.82–1.58)	107	1.15 (0.86–1.54)	0.94	167	1.12 (0.87–1.44)	6	0.98 (0.13–7.64)	11	2.90 (0.65–13.01)	15	2.08 (0.80–5.36)	0.41
BL[†‡]	94	1.24 (0.89–1.72)	29	1.42 (0.76–2.66)	65	1.17 (0.79–1.73)	0.61	67	1.22 (0.77–1.93)	4	NR[§]	4	NR[§]	19	1.17 (0.52–2.63)	0.02
Other & unknown B-cell[†]	823	**1.16 (1.04–1.30)**	524	**1.19 (1.04–1.37)**	299	1.12 (0.94–1.34)	0.60	662	1.12 (0.99–1.27)	38	**2.60 (1.08–6.21)**	34	0.77 (0.32–1.81)	89	1.43 (0.97–2.08)	0.13
Any T-cell NHL[†]	796	**1.14 (1.02–1.27)**	404	1.06 (0.90–1.24)	392	**1.22 (1.05–1.43)**	0.19	516	1.01 (0.88–1.17)	83	1.31 (0.66–2.59)	45	0.71 (0.28–1.76)	152	**1.43 (1.02–2.02)**	0.21

	All Participants		Women		Men		Sex Het	White		Black		Asian/Pacific Islander/American Indian		Other/ Mixed Race		Race Het
	n	HR** (95% CI)	n	HR** (95% CI)	n	HR** (95% CI)	p-value	n	HR** (95% CI)	n	HR** (95% CI)	n	HR** (95% CI)	n	HR** (95% CI)	p-value
PTCL †‡	312	1.04 (0.88–1.23)	149	1.00 (0.78–1.29)	163	1.07 (0.85–1.35)	0.70	216	0.92 (0.73–1.16)	21	4.93 (0.95–25.64)	18	0.32 (0.08–1.22)	57	1.03 (0.56–1.88)	0.09
MF/SS †‡	259	**1.30 (1.07–1.57)**	133	1.13 (0.86–1.49)	126	**1.48 (1.12–1.95)**	0.18	117	1.20 (0.89–1.62)	55	1.10 (0.48–2.50)	20	1.44 (0.30–6.98)	67	1.53 (0.91–2.56)	0.86

Abbreviations: BL, Burkitt lymphoma; CI, confidence interval; CLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CPS-II, Cancer Prevention Study-II Nutrition Cohort; CTS, California Teachers' Study; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; Het, heterogeneity; HR, hazard ratio; HPFS, Health Professionals Follow-up Study; KPSC, Kaiser Permanente Southern California; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; MCL, mantle cell lymphoma; MF/SS, mycosis fungoides/Sezary syndrome; MZL, marginal zone lymphoma; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; PTCL, peripheral T-cell lymphoma

*Analyses include participants from CPS-II, CTS, HPFS, KPSC, NHS, and NHS-2 unless otherwise specified.

**HRs adjusted for age, sex (where applicable), cohort

†NHS-2 participants were not included in NHL subtype analyses because the relevant data was not available from this cohort.

‡HPFS and NHS were not included in analyses of BL, PTCL, MF/SS because specification of these subtypes was not available for these cohorts.

§HRs based on fewer than 5 cases are not reported in tables.

Table III.

Estimated relative risks of non-Hodgkin lymphoma (NHL), B-cell NHL, and T-cell NHL by adult body mass index in a pooled cohort[*] of US men and women

	all NHL		B-cell NHL[‡]		T-cell NHL[‡]	
	n	HR[**] (95% CI)	n	HR[**] (95% CI)	n	HR[**] (95% CI)
Young adult BMI [†]						
<18.5 kg/m^2	561	0.90 (0.82–0.98)	438	0.89 (0.81–0.99)	36	1.00 (0.69–1.43)
18.5–22.9 kg/m^2	3,387	1.00 (ref)	2,657	1.00 (ref)	187	1.00 (ref)
23–24.9 kg/m^2	806	1.06 (0.98–1.14)	623	1.03 (0.94–1.12)	50	1.17 (0.85–1.61)
25–<29.9 kg/m^2	606	**1.17 (1.07–1.28)**	469	**1.15 (1.04–1.27)**	34	1.18 (0.81–1.72)
≥30 kg/m^2	111	**1.29 (1.07–1.56)**	81	**1.26 (1.00–1.57)**	6	1.20 (0.53–2.73)
per 5 kg/m ^{2}	5,471	**1.14 (1.10–1.20)**	4,268	**1.13 (1.07–1.19)**	313	1.15 (0.96–1.38)
Usual adult BMI						
<18.5 kg/m^2	112	1.06 (0.87–1.29)	80	0.92 (0.73–1.16)	6	0.84 (0.35–1.99)
18.5–22.9 kg/m^2	2,298	1.00 (ref)	1,802	1.00 (ref)	139	1.00 (ref)
23–24.9 kg/m^2	2,054	1.02 (0.96–1.08)	1,657	1.01 (0.94–1.08)	145	1.13 (0.88–1.45)
25–29.9 kg/m^2	4,205	0.98 (0.93–1.04)	3,533	0.98 (0.93–1.05)	310	1.11 (0.89–1.38)
30–<35 kg/m^2	1,750	0.99 (0.92–1.06)	1,463	0.98 (0.91–1.06)	129	0.99 (0.76–1.30)
35–<40 kg/m^2	588	1.04 (0.95–1.15)	493	1.06 (0.95–1.18)	47	1.06 (0.72–1.54)
≥40 kg/m^2	256	**1.20 (1.04–1.37)**	207	**1.17 (1.00–1.36)**	20	1.18 (0.71–1.98)
per 5 kg/m ^{2}	11,263	1.01 (0.99–1.03)	9,235	1.01 (0.99–1.04)	796	1.01 (0.94–1.09)
Young adult[†], usual adult BMI (joint association) [§]						
Lean, lean	2,118	1.00 (ref)	1,616	1.00 (ref)	120	1.00 (ref)
Lean, overweight	1,525	0.96 (0.90–1.03)	1,253	0.99 (0.92–1.07)	80	0.82 (0.62–1.10)
Lean, obese	523	1.06 (0.96–1.17)	389	1.02 (0.91–1.14)	36	1.26 (0.86–1.84)
Overweight, lean	108	1.10 (0.90–1.34)	81	1.05 (0.84–1.32)	9	1.55 (0.78–3.07)
Overweight, overweight	**284**	**1.21 (1.06–1.37)**	224	**1.19 (1.03–1.38)**	17	1.19 (0.70–2.00)
Overweight, obese	212	1.10 (0.96–1.27)	162	1.12 (0.95–1.32)	8	0.70 (0.33–1.45)
Obese, lean	15	1.08 (0.64–1.79)	11	0.95 (0.53–1.73)	3	N/A[∞]
Obese, overweight	31	1.29 (0.90–1.84)	26	1.35 (0.91–2.00)	0	N/A[∞]
Obese, obese	**65**	**1.32 (1.03–1.70)**	44	1.30 (0.96–1.75)	3	N/A[∞]

Abbreviations: BMI, body mass index; CI, confidence interval; CPS-II, Cancer Prevention Study-II Nutrition Cohort; CTS, California Teachers' Study; HR, hazard ratio; HPFS, Health Professionals Follow-up Study; KPSC, Kaiser Permanente Southern California; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II

[*] Analyses included participants from all six cohorts: CPS-II, CTS, HPFS, KPSC, NHS, NHS-2 unless otherwise specified.

[**] HRs adjusted for age, sex, and cohort.

[†] KPSC was not included in analyses of young adult BMI because the relevant information was not available from this cohort.

[‡] NHS-II was not included in analyses specifying NHL subtypes because the relevant information was not available from this cohort.

[§] BMI category labels: “lean” = BMI 18.5–<25 kg/m^2, “overweight” = BMI 25–<30 kg/m^2, “obese” = BMI ≥30 kg/m^2

[∞] HRs based on fewer than 5 cases are not reported in tables

Table IV.

Estimated relative risks of the association between adult waist circumference, weight change from young adulthood, predicted percent fat mass and risk of NHL and the most common NHL subtypes in the pooled cohort*

	NHL		B-cell NHL†		T-cell NHL†		CLL/SLL†		DLBCL†		FL†	
Variable∞	**Case**	**HR** (95% CI)**	**Case**	**HR** (95% CI)**	**Case**	**HR** (95% CI)**	**Case**	**HR** (95% CI)**	**Case**	**HR** (95% CI)**	**Case**	**HR** (95% CI)**
Waist circumference (cm)												
W: <80 cm; M: <94 cm (ref)	1,459	1.00 (ref)	1,181	1.00 (ref)	87	1.00 (ref)	399	1.00 (ref)	302	1.00 (ref)	221	1.00 (ref)
W: 80–88cm; M: 94-<102cm	1,060	1.02 (0.94–1.10)	883	1.01 (0.93–1.11)	55	0.84 (0.60–1.18)	297	1.01 (0.87–1.18)	216	0.95 (0.79–1.13)	148	0.95 (0.77–1.17)
W: ≥94cm; M >=102cm	1,411	1.08 (1.00–1.16)	1,141	1.06 (0.97–1.15)	85	1.08 (0.80–1.46)	353	1.00 (0.86–1.15)	317	1.11 (0.95–1.30)	195	0.98 (0.81–1.20)
Waist circumference per 15cm	3,930	**1.05 (1.01–1.09)**	3,205	1.03 (0.98–1.07)	227	1.13 (0.96–1.34)	1,049	0.97 (0.89–1.05)	835	1.08 (0.99–1.18)	564	1.01 (0.90–1.12)
Predicted fat mass												
Q1	753	1.00 (ref)	607	1.00 (ref)	51	1.00 (ref)	220	1.00 (ref)	143	1.00 (ref)	104	1.00 (ref)
Q2	855	1.08 (0.98–1.19)	709	1.10 (0.99–1.23)	40	0.72 (0.47–1.09)	236	1.07 (0.89–1.29)	187	1.22 (0.98–1.52)	129	1.12 (0.86–1.45)
Q3	882	1.07 (0.97–1.18)	734	1.08 (0.96–1.20)	46	0.80 (0.53–1.20)	232	1.01 (0.83–1.22)	196	1.17 (0.94–1.46)	127	1.05 (0.81–1.36)
Q4	838	1.10 (0.99–1.22)	684	1.08 (0.97–1.21)	42	0.79 (0.51–1.20)	188	0.93 (0.76–1.14)	209	**1.30 (1.04–1.62)**	125	1.07 (0.82–1.40)
Predicted fat mass per kg	3,328	1.01 (1.00–1.01)	2,734	1.00 (1.00–1.01)	179	1.01 (0.99–1.03)	876	1.00 (0.99–1.01)	735	1.01 (1.00–1.02)	485	1.01 (0.99–1.02)
Adult weight change (kg; young adult to study baseline)												
Weight loss: >= 10 kg	121	1.13 (0.93–1.38)	90	1.09 (0.86–1.37)	5	0.88 (0.33–2.34)	28	1.10 (0.73–1.67)	22	1.12 (0.69–1.80)	21	1.32 (0.81–2.16)
Weight loss: 4.5 – < 10 kg	231	1.03 (0.88–1.20)	167	1.00 (0.83–1.20)	14	1.31 (0.67–2.58)	51	0.97 (0.70–1.35)	37	0.95 (0.64–1.41)	27	0.86 (0.55–1.34)
Weight loss: 2 – < 4.5 kg	182	0.98 (0.82–1.16)	132	0.97 (0.80–1.19)	12	1.49 (0.73–3.02)	44	1.01 (0.71–1.43)	34	1.07 (0.72–1.60)	24	0.93 (0.58–1.48)
Stable weight: +/− 2 kg	495	1.00 (ref)	361	1.00 (ref)	22	1.00 (ref)	117	1.00 (ref)	83	1.00 (ref)	69	1.00 (ref)
Weight gain: 2 – < 4.5 kg	490	1.04 (0.92–1.18)	358	1.04 (0.90–1.21)	22	1.01 (0.56–1.84)	125	1.12 (0.87–1.44)	93	1.15 (0.85–1.55)	74	1.18 (0.84–1.64)
Weight gain: 4.5 – < 10 kg	1,349	0.97 (0.88–1.08)	1,019	0.96 (0.85–1.09)	76	1.12 (0.69–1.81)	344	0.99 (0.80–1.23)	250	0.99 (0.77–1.27)	180	0.94 (0.71–1.25)

	NHL		B-cell NHL†		T-cell NHL†		CLL/SLL†		DLBCL†		FL†	
Variable∞	**Case**	**HR**	**(95% CI)**	**Case**	**HR**	**(95% CI)**	**Case**	**HR**	**(95% CI)**	**Case**	**HR**	**(95% CI)**	**Case**	**HR**	**(95% CI)**
Weight gain: 10 – < 20 kg	1,418	0.91	(0.82–1.01)	1,161	0.93	(0.82–1.05)	75	0.89	(0.55–1.45)	360	0.89	(0.72–1.10)	302	0.97	(0.75–1.24)	213	0.98	(0.75–1.30)
Weight gain: 20 – < 30 kg	670	0.94	(0.83–1.06)	553	0.92	(0.81–1.06)	41	1.01	(0.60–1.72)	167	0.88	(0.69–1.12)	167	1.10	(0.84–1.44)	101	0.99	(0.72–1.35)
Weight gain: >= 30 kg	283	1.01	(0.87–1.17)	227	0.97	(0.82–1.15)	21	1.35	(0.73–2.49)	53	0.73	(0.53–1.02)	77	1.28	(0.93–1.76)	38	0.93	(0.62–1.39)
Weight change per 2 kg	5,239	1.00	(0.99–1.00)	4,068	1.00	(0.99–1.00)	288	1.00	(0.98–1.02)	1,289	0.99	(0.98–1.00)	1,065	1.01	(1.00–1.02)	747	1.00	(0.98–1.01)

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CPS-II, Cancer Prevention Study-II Nutrition Cohort; CTS, California Teachers' Study; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HR, hazard ratio; HPFS, Health Professionals Follow-up Study; KPSC, Kaiser Permanente Southern California; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II

*Analyses included participants from five of the cohorts: CPS-II, CTS, HPFS, NHS, NHS-2 unless otherwise specified. KPSC was not included because waist circumference and young adult BMI data was not available.

**HRs adjusted for age, sex, and cohort.

†NHS-II was not included in analyses specifying NHL subtypes because the relevant data was not available.

‡HPFS and NHS were not included in analyses of BL, PTCL, MF/SS because specification of these subtypes was not available for these cohorts.

§HRs based on fewer than 5 cases (in either the referent or exposed categories) are not reported in tables.

∞Participants with missing information for one of the body size measures were not included in models for that factor but were included in analyses for the other anthropometric measures.