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Genetically determined body mass index is associated with diffuse large B-cell lymphoma in polygenic and Mendelian randomization analyses

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Abbreviations: BMI, body mass index; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IARC, International Agency for Research on Cancer; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; OR, odds ratio; PGS, polygenic score; SNP, single nucleotide polymorphism; WHR, waist-to-hip ratio; WHRadjBMI, waist-to-hip ratio adjusted for BMI; 95% CI, 95% confidence interval.

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Abstract

Obesity has been associated with non-Hodgkin lymphoma (NHL), but the evidence is inconclusive. We examined the association between genetically determined adiposity and four common NHL subtypes: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukemia, and marginal zone lymphoma, using eight genome-wide association studies of European ancestry ($N = 10{,}629$ cases, 9505 controls) and constructing polygenic scores for body mass index (BMI), waist-to-hip ratio (WHR), and waist-to-hip ratio adjusted for BMI (WHRadjBMI). Higher genetically determined BMI was associated with an increased risk of DLBCL [odds ratio (OR) per standard deviation (SD) = 1.18, 95% confidence interval (95% CI): 1.05–1.33, $p = .005$]. This finding was consistent with Mendelian randomization analyses, which demonstrated a similar increased risk of DLBCL with higher genetically determined BMI ($OR_{per\ SD} = 1.12$, 95% CI: 1.02–1.23, $p = .03$). No significant associations were observed with other NHL subtypes. Our study demonstrates a positive link between a genetically determined BMI and an increased risk of DLBCL, providing additional support for increased adiposity as a risk factor for DLBCL.

What's New?

Obesity has been linked to the risk of non-Hodgkin lymphoma (NHL), but the evidence remains inconclusive. Here, the authors investigate the possibility of shared genetic risk factors between obesity and four common NHL types. Drawing on data from 8 genome-wide association studies, they found that a higher genetically determined BMI was associated with a higher risk of just one NHL type, diffuse large B cell lymphoma (DLBCL). This positive association was confirmed using Mendelian randomization.

1 | INTRODUCTION

Excess adiposity, possibly through mechanisms involving chronic inflammation, is a suggested risk factor for B-cell lymphomas. Although the findings are not entirely consistent,[1–3] several observational studies of non-Hodgkin lymphoma have shown an association between obesity and lymphoma risk.[4–8] Of more common lymphoma subtypes, the evidence is most convincing for diffuse large B-cell lymphoma (DLBCL), where excess weight-for-height in later adulthood has been found to increase the risk of disease.[2,4–7,9,10] There is also some evidence that being overweight or obese in young adulthood may contribute to DLBCL risk.[10–14] The evidence is less clear for other B-cell lymphomas, such as follicular lymphoma (FL), chronic lymphocytic leukemia (CLL), and marginal zone lymphoma (MZL).[5,6,15] These lymphomas are more indolent in nature, and weight loss in the years leading up to diagnosis could have attenuated any observed association of later adult obesity with disease etiology. Although no associations were observed with body mass index (BMI) and risk of CLL or MZL,[15,16] the InterLymph Consortium reported an association between higher BMI in young adulthood and increased risk of FL in a large pooled analysis.[17]

To date, the majority of epidemiologic studies of lymphoma have used BMI to estimate adiposity, largely due to the ease of obtaining height and weight information, but other measures, such as waist-to-hip ratio (WHR), may provide better indicators of body fat distribution. A larger WHR is indicative of greater abdominal, rather than gluteal, fat deposition, and has been associated with an increased risk of type 2 diabetes, cardiovascular disease, and some cancers.[18–20] The relationship between WHR and NHL has been studied less often. Although most studies have not observed an association with WHR,[2,13,21–24] these studies have generally been small and underpowered to detect associations with specific NHL subtypes. A meta-analysis suggested that higher WHR may be associated with DLBCL, but not FL.[14] Some of the observed discrepancies could be due to the known difficulties in studying anthropometry. These include the reliability of height and weight when self-reported, as is common in studies of lymphoma; the timeframe of anthropometric information relative to lymphoma diagnosis, especially when collected retrospectively; and the different ages, time periods, and places of study where the population prevalence of obesity may vary. Changes in body composition over an individual's lifetime complicate the study of the relationships between obesity and disease risk.

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Although adult adiposity is a marker of multiple biological influences reflecting the interplay of genetics and environment, positive associations between adiposity and NHL risk raise the possibility of shared genetic risk factors. Genetic alleles are randomly allocated at conception, not affected by disease status or environmental exposures, measured reliably, and unchanged over the life course of an individual. Hundreds of genetic variants have been identified to be associated with measures of adiposity, BMI, WHR, and WHR adjusted for BMI (WHRadjBMI); the variants for BMI and WHRadjBMI explain 6.0% and 3.9% of the variance, respectively.[25,26] Many of the loci identified for WHR without adjustment for BMI overlap those loci identified for BMI, making interpretation of the results difficult as associations observed for WHR may be due to correlation with BMI. In contrast, the loci identified for WHRadjBMI are distinct from and independent of those identified for BMI and reflect different biological pathways. By combining SNP-specific associations with adiposity into a single measure, a polygenic score (PGS),[27] one can examine the association between genetically determined adiposity and NHL risk while circumventing some of the aforementioned methodological complexities for characterizing body size. Mendelian randomization, an analytic approach using genetic variation, can be used to investigate potentially causal relationships between risk factors, such as obesity, and disease risk.[28] Indeed, previous Mendelian randomization studies have used adiposity-related polygenic scores as instruments to further elucidate and characterize the etiology of obesity-related diseases.[29,30]

Here, we examined the association between genetically determined adiposity and NHL risk using data from eight GWAS, including 10,629 NHL cases and 9505 controls. As evidence suggests that subtypes of NHL have distinctly different etiologies,[31,32] we focused our analysis on the risk of four major NHL subtypes, DLBCL, FL, CLL, and MZL, and investigated associations with BMI, WHR, and WHRadjBMI.

2 | MATERIALS AND METHODS

We used previously genotyped samples of European ancestry and imputed data from eight GWAS of NHL (Supplementary Table 1). Full details of participating studies, including detailed information on quality control and data cleaning, have been previously reported for DLBCL, FL, CLL, and MZL.[33–36] Briefly, the largest GWAS, the InterLymph NHL GWAS, was a pooled study consisting of NHL cases and controls from 22 studies of NHL: nine prospective cohort studies, eight population-based case–control studies, and five hospital or clinic-based case–control or case-series studies. The other seven GWAS were the University of California at San Francisco Molecular Epidemiology of Non-Hodgkin Lymphoma study (UCSF2),[37] University of California at San Francisco Molecular Epidemiology of Non-Hodgkin Lymphoma study (UCSF1)/Nurses' Health Study (NHS),[38] Scandinavian Lymphoma Etiology Study (SCALE),[39] Genetic Epidemiology of CLL Consortium (GEC),[40] Groupe d'Etude des Lymphomes de l'Adulte (GELA)/European Prospective Investigation into Cancer, Chronic Diseases, Nutrition, and Lifestyles (EPIC),[41,42] Mayo Clinic Case–Control Study of Diffuse Large B-cell Lymphoma (Mayo-DLBCL),[43] and the Utah Chronic Lymphocytic Leukemia Study (Utah). Genotyping was performed on commercially available Illumina and Affymetrix platforms (Supplementary Table 1), and standard quality control and filtering metrics (i.e., low SNP and sample call rates, sex discordance, deviation from Hardy–Weinberg proportions) were applied to each GWAS. Imputation was performed separately for each of the eight GWAS using IMPUTE2[44] and the 1000 Genomes Project reference panel.[45] Across the eight GWAS, genotype data were available for a total of 10,629 NHL cases, including 3100 CLL, 3857 DLBCL, 2847 FL, and 825 MZL cases, and up to 9505 controls.

To evaluate the genetically determined adiposity and the risk of NHL, we constructed separate PGS for BMI, WHR, and WHRadjBMI using published genetic loci from the Genetic Investigation of ANthropometric Traits (GIANT) Consortium, which included 941 independent SNPs associated with BMI, 382 independent SNPs associated with WHR, and 463 independent SNPs associated with WHRadjBMI.[25,26] Two SNPs for BMI, 4 SNPs for WHR, and nine SNPs for WHRadjBMI were not available in our GWAS and were excluded. After Steiger filtering,[46] 917 SNPs remained for BMI, 358 SNPs for WHR, and 430 SNPs for WHRadjBMI. The polygenic scores were computed for each individual (i) as the sum of the allelic dosage for each SNP multiplied by the reported weight of the association with BMI, WHR, or WHRadjBMI, as shown below:

$$\mathrm{PGS}_i = \sum_{j=1}^{k} w_j x_{ij}$$

where w_j is the weight or beta coefficient for the jth SNP derived from the literature and x_{ij} is the allelic dosage of the jth SNP. In our study, we used the previously published per-risk-allele β-estimates for the European sex-combined meta-analysis for BMI, WHR, or WHRadjBMI.[25,26]

As previous studies have demonstrated substantial etiologic heterogeneity among NHL subtypes,[31,32] we analyzed each of the four NHL subtypes in this study separately. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CI) for the association with genetically determined BMI, WHR, and WHRadjBMI, separately by GWAS and by subtype. Each PGS was modeled as a continuous variable and categorized into quartiles with quartile cutoffs defined by the distribution among controls. Models were adjusted for sex, age at NHL diagnosis or control selection, and GWAS-specific statistically significant (p <.05) principal components for population stratification. The regression model for the UCSF1/NHS study was not adjusted for sex, as all controls were female. As previous studies have demonstrated sex differences for waist-related traits,[26] as secondary analyses, we also performed sex-stratified analyses using: (1) the same weights for the PGS as the sex-combined analysis, which allowed us to test for differences in the effect size estimates using a Wald test, and (2) sex-specific PGS, which were constructed using the SNPs and weights previously identified for each sex.[25,26] All analyses were adjusted for age and study-specific

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statistically significant principal components. The UCSF1/NHS study was excluded from sex-specific analyses, as all controls were women. Fixed-effects meta-analysis was used to combine association results from the included GWAS for each NHL subtype. Between-study heterogeneity was evaluated by Cochran's *Q* test and was quantified using the I^2 metric. The meta-analysis was conducted using the package *metan* in Stata v16 (StataCorp, College Station, TX). The *p*-values for between-sex heterogeneity were calculated using a Wald test. A *p*-value <.05 was considered nominally statistically significant, and *p*-values of 0.05–0.10 were considered suggestive. To account for multiple testing and control for the false discovery rate, *q*-values were calculated using Benjamini-Hochberg, which is less conservative than Bonferroni.[47]

In addition, we conducted a Mendelian Randomization analysis to assess the potential causal relationship using the inverse-variance weighted (IVW), MR-Egger, weighted median, and weighted mode methods as implemented in the *TwoSampleMR* R package.[48] We focused on the IVW approach as our primary method for analysis. Fixed effects models were used for the IVW analysis. The same SNPs were used for the Mendelian analysis as for the PGS analysis. Using only summary-level data and under certain strict assumptions,[28] the exponentiated coefficient calculated in this manner can be interpreted as the causal OR of a given NHL subtype associated with a one-unit increase in the adiposity trait. The Mendelian randomization analysis requires several assumptions: (1) PGS is related to the exposure, (2) the PGS is not related to other exposures that could be confounders, and (3) the PGS affects the outcome only through the exposure. There should be no directional or horizontal pleiotropy. To assess the potential presence of directional pleiotropic effects, we performed Egger regression and estimated the heterogeneity of SNP association using Cochrane's *Q*-statistic. Scatter plots were used to visualize the associations, and leave-one-out analyses were used to evaluate the impact of outlier SNPs.

3 | RESULTS

Overall, higher genetically determined BMI was associated with an elevated risk of DLBCL ($OR_{per\ SD} = 1.18$, 95% CI = 1.05–1.33, $p = .005$) (Figure 1), which remained significant after adjustment for multiple testing ($q = 0.02$). Compared to the lowest quartile, those in the highest quartile of genetically determined BMI had an 18% increased risk of DLBCL (OR = 1.18, 95% CI:1.04–1.32). After stratifying by sex (Supplementary Table 2), we observed a positive association with increasing BMI PGS and risk of DLBCL for men ($OR_{per\ SD} = 1.23$, 95% CI 1.05–1.44, $p = .01$) with weaker evidence of an association in women ($OR_{per\ SD} = 1.10$, 95% CI 0.92–1.31, $p = .29$); however, the difference was not statistically significant ($p_{heterogeneity} = 0.35$). Further analyses using sex-specific PGS for BMI yielded similar positive associations for both men and women (Supplementary Table 3). Overall, there was no association between genetically predicted BMI and the risk of FL, CLL, or MZL (Figure 1). After stratifying by sex (Supplementary Table 2), higher genetically determined BMI was suggestively associated with an increased risk of CLL among men ($OR_{per\ SD} = 1.17$, 95% CI: 1.00–1.37, $p = .05$) with men in the highest quartile displaying a 15% increased risk of CLL

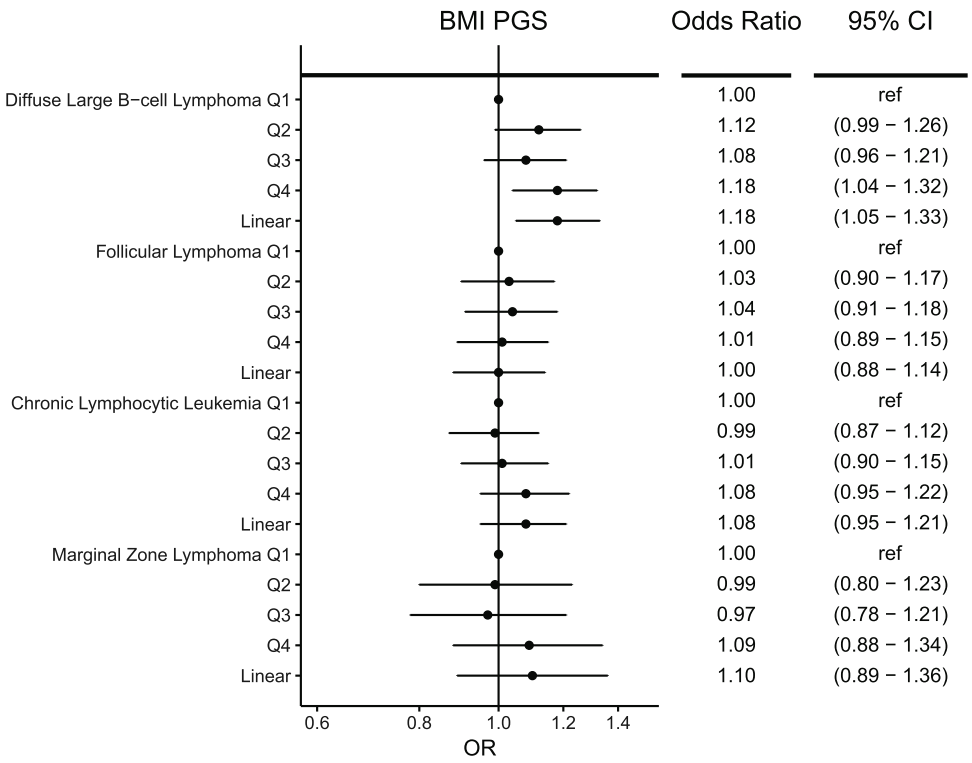

FIGURE 1 Risk of four non-Hodgkin lymphoma subtypes associated with genetically determined body mass index (BMI). Odds ratios (ORs) and 95% confidence intervals (CIs) are shown for quartiles (Q1-Q4) of the BMI polygenic score (PGS) and BMI PGS modeled as a linear term.

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compared to the lowest quartile of BMI PGS (OR = 1.15, 95% CI: 0.98–1.34). No association was observed for women ($OR_{per\ SD}$ = 0.97, 95% CI: 0.79–1.18, p = .73), and there was no significant heterogeneity by sex for CLL risk ($p_{heterogeneity}$ = 0.14). Analyses using sex-specific PGS showed a significant positive association for genetically predicted BMI among men but not women (Supplementary Table 3). Little evidence of heterogeneity among GWAS was observed for the BMI PGS ($P_{heterogeneity}$ >0.05, Supplementary Table 4).

For men and women combined, no significant associations were observed for any NHL subtype with genetically determined body fat distribution as measured by WHR or WHRadjBMI PGS (Figures 2 and 3), although there was a suggestive association with higher WHRadjBMI and increased FL risk (OR = 1.19 [1.00–1.43], p = 0.06). In sex-specific analyses (Supplementary Tables 5), although not significant after adjustment for multiple testing (q = 0.18), higher WHRadjBMI PGS was nominally associated with lower risk of MZL for men ($OR_{per\ SD}$ = 0.60, 95% CI = 0.38–0.94, p = .03) but not women ($OR_{per\ SD}$ = 1.25, 95% CI = 0.84–1.88, p = .28), with evidence of heterogeneity between the sexes ($p_{heterogeneity}$ = 0.02). Men in the highest quartile of WHRadjBMI PGS had a 33% reduction in the risk of MZL compared to the lowest quartile (OR = 0.67, 95% CI: 0.49–0.93). Additional adjustment for genetically determined BMI in the WHRadjBMI analyses did not substantially alter the ORs observed (data not shown). Consistent with the results for WHRadjBMI, a suggestive reduction in MZL risk was also observed for men with higher genetically predicted WHR ($OR_{per\ SD}$ = 0.58 [0.34–1.02], p = .06), but not women ($OR_{per\ SD}$ = 1.13 [0.68–1.86], p = .64) ($P_{heterogeneity}$ = 0.08, Supplementary Table 6). Analyses using sex-specific PGS showed a suggestive reduction in MZL risk for WHRadjBMI among men (Supplementary Tables 7 and 8). No significant linear trends were observed with other subtypes in sex-specific analyses. With the exception of a few individual quartiles, there was little evidence for heterogeneity among the individual GWAS (Supplementary Tables 9 and 10).

To further explore the relationship between adiposity and NHL risk, we conducted Mendelian randomization analyses; we discovered generally high concordance between the associations calculated using individual-level PGS with those estimated using the inverse variance-weighted (IVW), weighted median, and weighted mode methods and summary-level statistics for BMI, WHR, and WHRadjBMI for all NHL subtypes (Figures 4–6, Supplementary Table 11). Similar to what we observed with the individual-level PGS, higher genetically determined BMI was associated with an increased risk of DLBCL using the IVW method ($OR_{per\ SD}$ = 1.12, 95% CI: 1.02–1.23, p = .03) with similar results for the weighted median and weighted mode. No significant associations were observed for the other NHL subtypes. Egger regression did not detect evidence of overall bias in the IVW estimate due to directional pleiotropy in any of the analyses (p >.05 for all, Supplementary Table 11). Scatterplots showing SNP-specific associations for BMI, WHR, and WHRadjBMI with each NHL subtype are shown in

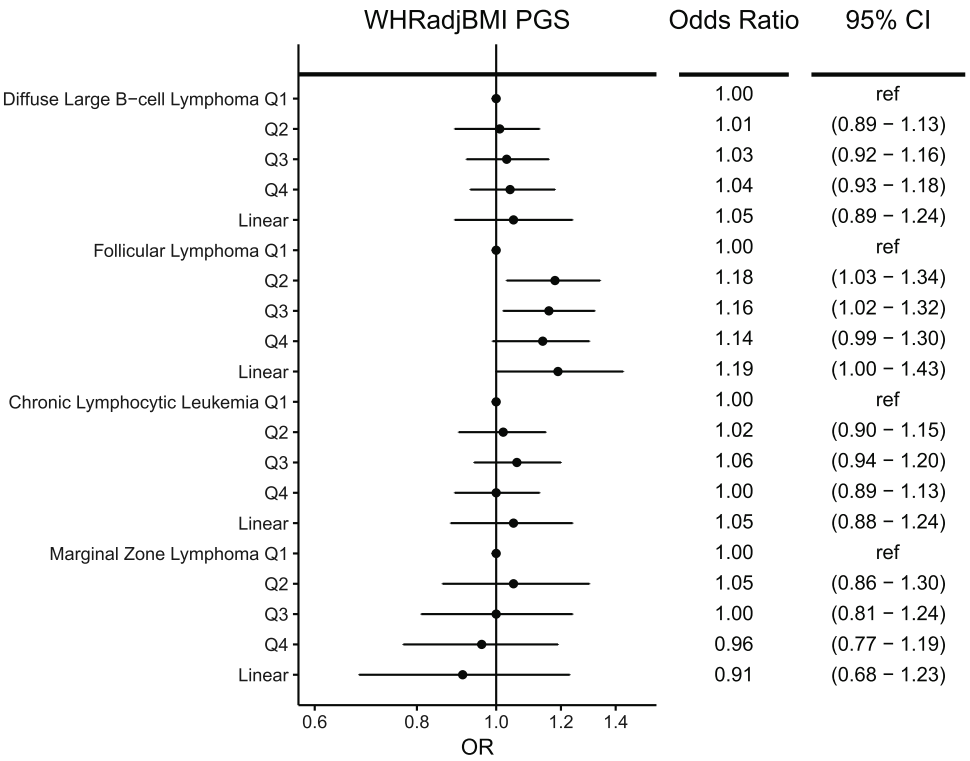

FIGURE 2 Risk of four non-Hodgkin lymphoma subtypes associated with genetically determined waist-to-hip ratio adjusted for BMI (WHRadjBMI). Odds ratios (ORs) and 95% confidence intervals (CIs) are shown for quartiles (Q1-Q4) of the WHRadjBMI polygenic score (PGS) and WHRadjBMI PGS modeled as a linear term.

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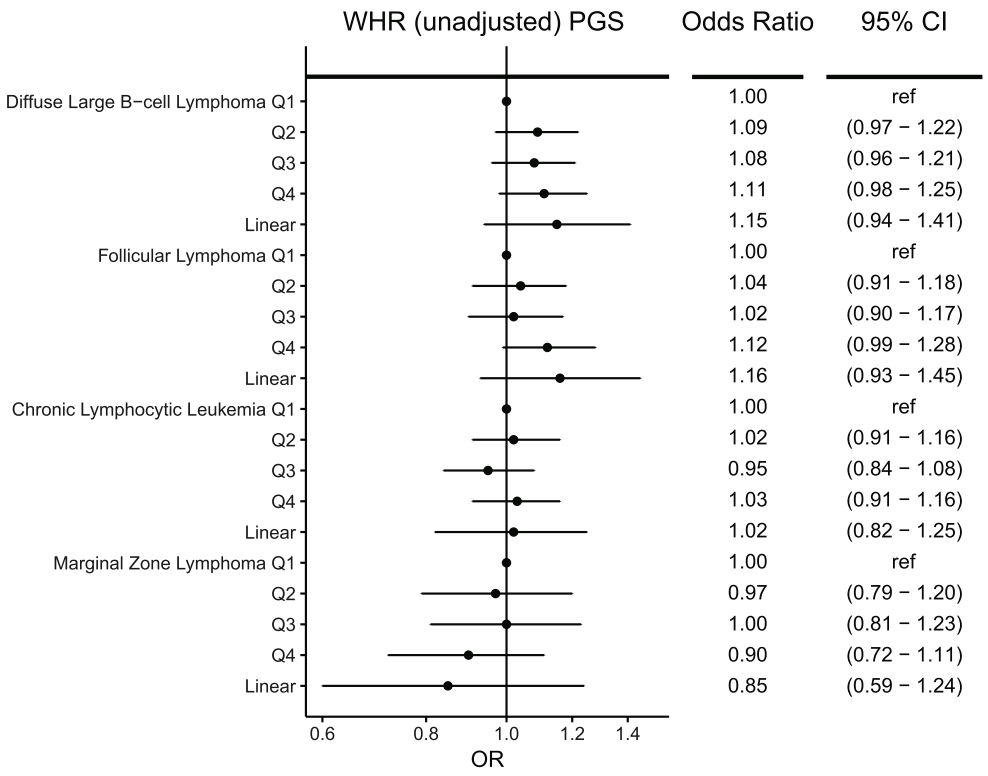

FIGURE 3 Risk of four non-Hodgkin lymphoma subtypes associated with genetically determined waist-to-hip ratio (WHR). Odds ratios (ORs) and 95% confidence intervals (CIs) are shown for quartiles (Q1-Q4) of the WHR polygenic score (PGS) and WHR PGS modeled as a linear term.

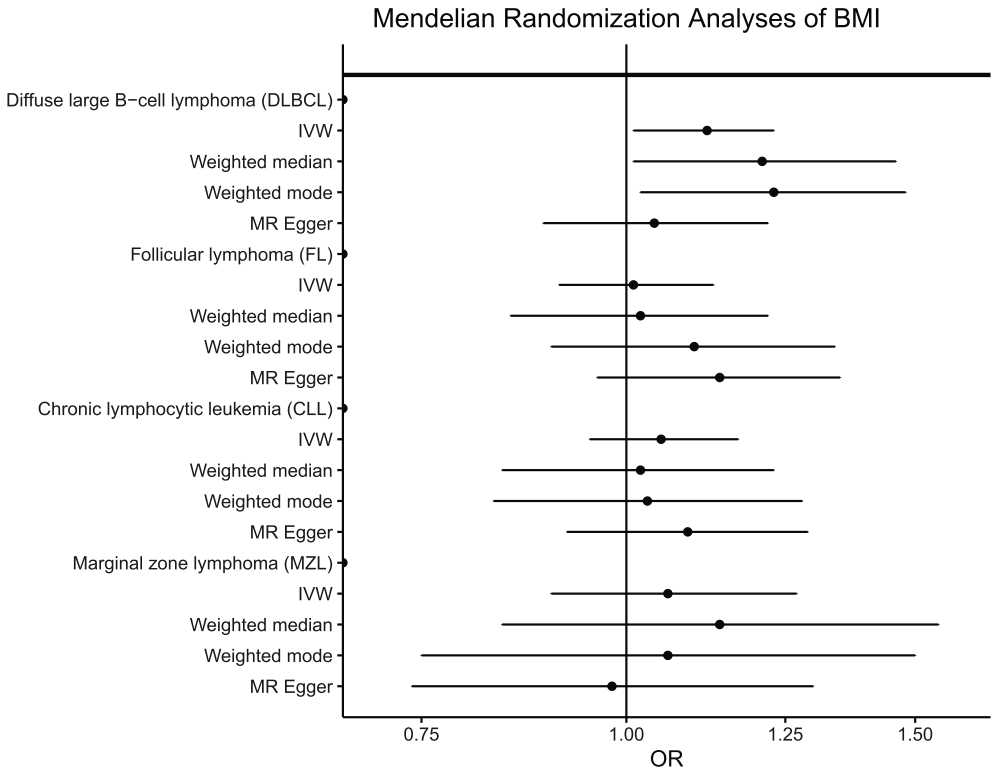

FIGURE 4 Mendelian randomization analyses of body mass index (BMI) and the risk of four non-Hodgkin lymphoma subtypes. Odds ratios (ORs) and 95% confidence intervals (CIs) are shown for each subtype using the inverse variance weighted (IVW), weighted median, weighted mode, and MR Egger methods.

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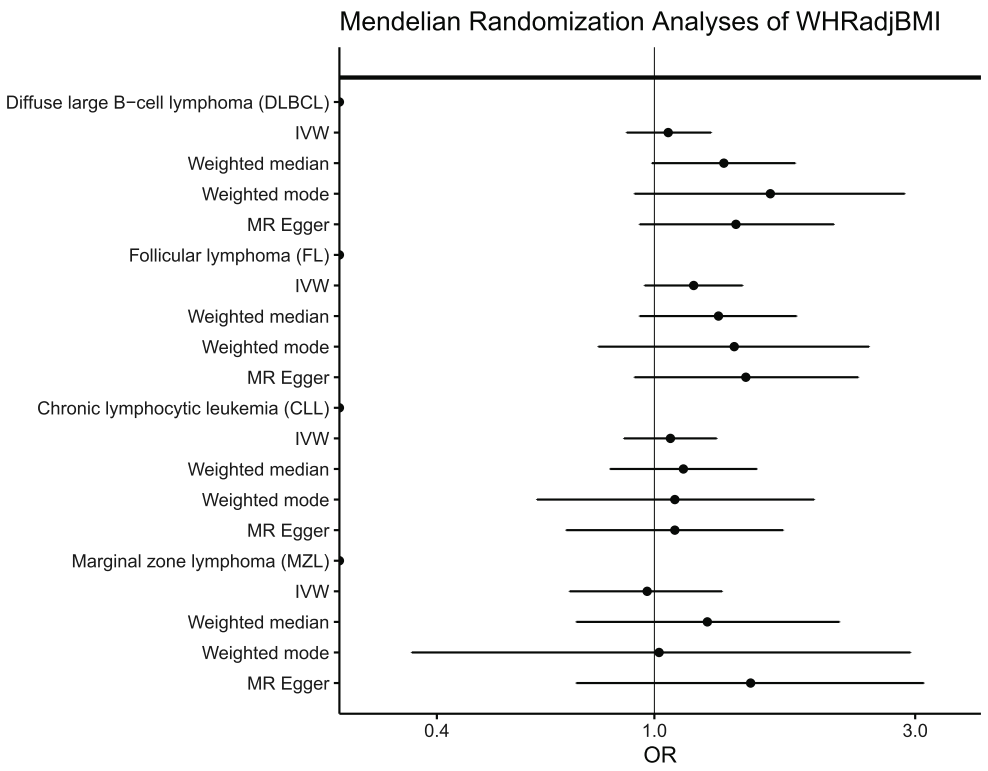

FIGURE 5 Mendelian randomization analyses of waist-to-hip ratio adjusted for body mass index (WHRadjBMI) and the risk of four non-Hodgkin lymphoma subtypes. Odds ratios (ORs) and 95% confidence intervals (CIs) are shown for each subtype using the inverse variance weighted (IVW), weighted median, weighted mode, and MR Egger methods.

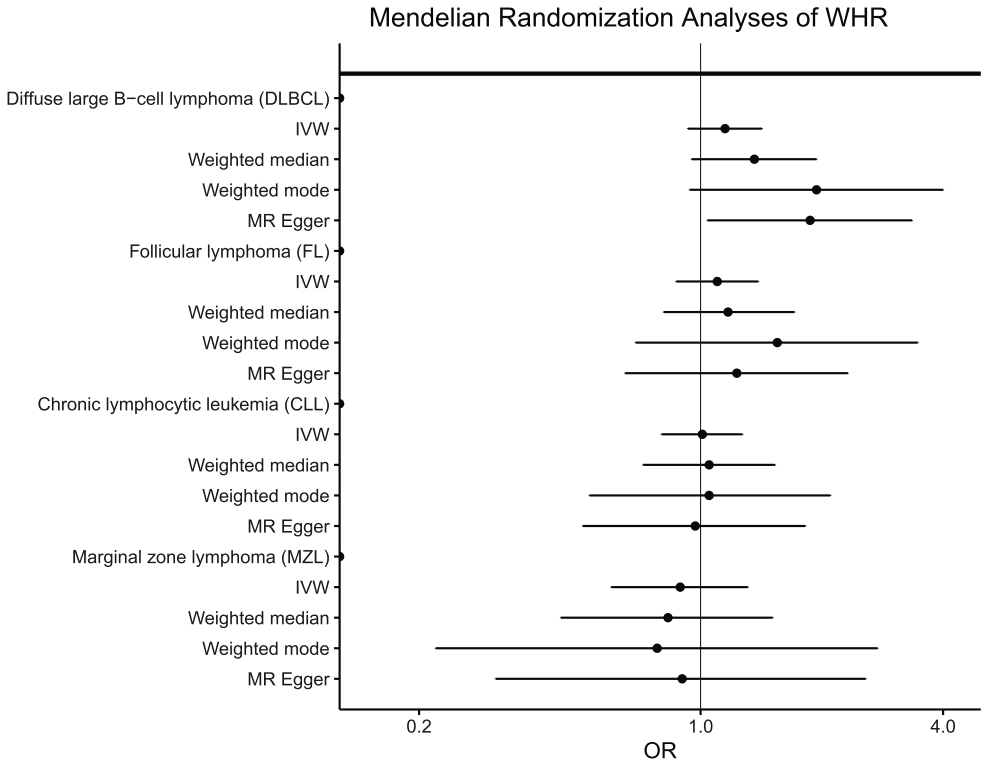

FIGURE 6 Mendelian randomization analyses of waist-to-hip ratio (WHR) and the risk of four non-Hodgkin lymphoma subtypes. Odds ratios (ORs) and 95% confidence intervals (CIs) are shown for each subtype using the inverse variance weighted (IVW), weighted median, weighted mode, and MR Egger methods.

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Supplementary Figures 1–3; no individual SNPs were associated with any NHL subtype at a Bonferroni significance level of 5.5×10^{-5} for BMI, 1.4×10^{-4} for WHR, and 1.2×10^{-4} for WHRadjBMI. There was little evidence of heterogeneity in SNP effects (p>.01 for all, Supplementary Table 11) Leave-one-SNP-out analyses yielded similar results and did not provide evidence of any SNP unduly influencing the results (data not shown).

4 | DISCUSSION

In this large study of genetically determined adiposity and NHL risk, we observed a positive association between genetically determined BMI and risk of DLBCL. The International Agency for Research on Cancer (IARC) previously concluded that there was limited, but insufficient, evidence for an association between excess body fatness and DLBCL.[49] Our study provides additional evidence for a role of adiposity in DLBCL risk. Our results are consistent with epidemiologic studies of measured or self-reported BMI, including a pooled analysis of prospective cohorts that reported a statistically significant positive association between BMI and risk of DLBCL[10] and a pooled analysis based on case–control data from the InterLymph Consortium that discovered elevated risks for DLBCL with increasing young adult BMI.[50] Prospective data from the Nurses' Health Study and Health Professionals Follow-up Study and other studies further support a role for BMI throughout the life course.[11–14]

A positive association between BMI and DLBCL risk was further supported by our Mendelian randomization analysis, suggesting a potential causal relationship between BMI and DLBCL risk. Obesity has been linked to many altered metabolic processes, including alterations in the insulin-like growth factor pathway, sex hormones, and adipokines as well as chronic low-grade inflammation,[51] which may promote lymphomagenesis. However, some caution should be exercised in inferring causality from this analysis. Although the intercept term calculated using Egger regression for DLBCL was not significantly different from zero, this statistical test does not rule out the existence of directional pleiotropy. BMI is a polygenic trait, and the etiology of DLBCL has yet to be fully elucidated. The existence of biological pleiotropy at one or more loci has the potential to violate the Instrument Strength Independent of Direct Effect (InSIDE) assumption of Mendelian randomization if those variants are related to an unmeasured confounder or act by the same pleiotropic mechanism (e.g., innate immunity).

Given the epidemiologic associations between measured or reported adult BMI and risk of DLBCL in both men and women, it is intriguing that our study found a positive association between the genetically determined BMI and DLBCL risk in men, but less evidence for women. There is ample evidence for sex-specific aspects of adiposity. For instance, women are relatively protected from certain obesity-related diseases, such as cardiovascular disease, until menopause when the resulting hormonal changes result in a shift in fat distribution.[52] Twin studies suggest that the genetic influence on BMI may differ between men and women,[53] and, across multiple populations, that sex-specific genetic influences on BMI are strongest after puberty.[54] It is possible that overall adiposity plays a stronger role in the risk of DLBCL for men. However, it is important to note that the difference in risk between men and women was not statistically significant in our study, and the elevated risk observed for men could be a chance finding.

For genetically inferred WHRadjBMI, we discovered a nominally lower risk of MZL with higher WHRadjBMI PGS among men but not women. Although collider bias is possible, additional adjustment for genetically determined BMI in the WHRadjBMI analyses did not substantially alter the associations observed, and results were similar for WHR analyses. Although the difference between sexes was significant, some caution should be exercised in drawing inferences as this was a subgroup finding. The result was not statistically significant after adjustment for multiple testing ($q = 0.18$), and heritability of WHRadjBMI and variance explained by the reported loci is less for men compared to women.[26] Although not statistically significant, we also observed a borderline increased risk of FL in the PGS analysis with similar, albeit weaker, evidence in the Mendelian randomization analyses. Although we used over 400 genetic variants to construct the PGS and Mendelian randomization instrument for WHRadjBMI, these variants combined explain only 1.0%–3.9% of the variation.[26] As such, there is likely misclassification in the ranking of individuals for these traits based on their PGS. Assuming that the misclassification is non-differential, this could have biased our observed results toward the null. Other studies have reported positive associations between increasing genetically inferred BMI and WHRadjBMI with risk of colorectal cancer using a similar approach,[29,55] indicating that it is possible to uncover associations with cancer risk with only a small percentage of the variation captured by the score. However, these studies had a larger sample size, and we may have been underpowered to detect a modest association with risk in our study. Burgess et al. reported that a sample size of ~10,000 cases is required to detect a modest association in Mendelian randomization analyses using an instrumental variable explaining 5% of the variance.[56]

Although the literature on WHR and cancer risk is limited compared with that on BMI and cancer, previous work that examined WHR as a risk factor, most of which has been conducted in women, has not found associations with NHL risk.[2,21–24,57] WHR represents a different measure of adiposity that incorporates the observed protective effects of an increased femoral-gluteal muscle,[58] and studies of cardiovascular disease have shown associations with WHR independent of BMI.[19] WHRadjBMI loci have been shown to be enriched for genes expressed in adipose tissue itself, and pathway analyses implicated genes involved in angiogenesis, transcriptional regulation, and insulin resistance,[59] the latter of which are also established pathways for carcinogenesis. However, we only found limited evidence for a role of WHR and WHRadjBMI in NHL risk in subgroup analyses in our study.

Our study has limitations that are important to consider. Our participants were sampled from populations of European descent, limiting the generalizability of results to other ethnic groups, but this also has the benefit of reducing bias from population stratification. As many of

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our subjects came from retrospective case–control studies, there is the possibility of participation bias, as obese subjects may be less likely to be controls; however, genotypes, distributed at birth, are unlikely to be related to study participation. We did not have individual-level data on BMI or WHR from all studies and could not evaluate the variance explained by the PGS in our study. Although we were able to combine multiple studies of NHL together in one analysis and achieve sample sizes of several thousand cases for three out of the four subtypes, our study had limited power to detect modest associations between these anthropometric traits and specific NHL subtypes. Larger studies are needed to further explore the suggestive findings in this study. Previous studies of measured or self-reported adiposity and cancer risk have been susceptible to recall bias, reverse causation, residual confounding, and misclassification. By utilizing genetically determined measures of adiposity, our results are less sensitive to these concerns and provide additional insight into the role of adiposity on NHL risk, though at the expense of the non-genetic contribution.

In conclusion, our study provides evidence supporting a positive association between BMI and DLBCL risk, consistent with the previously reported epidemiologic studies of measured or self-reported adult BMI and risk of DLBCL. Future exploration of biological pathways that underlie the association with BMI and DLBCL is warranted as well as the evaluation of BMI with DLBCL subtypes, as these may provide more insight into the etiology of NHL.

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authors, and endorsement by the State of California, the California Department of Health Services, the National Cancer Institute, or the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred. *UTAH/Sheffield*—National Institutes of Health CA134674. Partial support for data collection at the Utah site was made possible by the Utah Population Database (UPDB) and the Utah Cancer Registry (UCR). Partial support for all datasets within the UPDB is provided by the Huntsman Cancer Institute (HCI) and the HCI Cancer Center Support grant, P30 CA42014. The UCR is funded by the NCI's SEER Program, Contract No. HHSN261201800016I, the US Centers for Disease Control and Prevention's National Program of Cancer Registries, Cooperative Agreement No. NU58DP007131, with additional support from the University of Utah and Huntsman Cancer Foundation. Partial support for data collection in Sheffield, UK was made possible by funds from Yorkshire Cancer Research and the Sheffield Experimental Cancer Medicine Centre. We thank the NCRI Haemato-oncology Clinical Studies Group, colleagues in the North Trent Cancer Network, and the North Trent Haemato-oncology Database. WHI—WHI investigators are: *Program Office*—(National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller; *Clinical Coordinating Center*—(Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg; *Investigators and Academic Centers*—(Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; *Women's Health Initiative Memory Study*—(Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. *YALE*—National Cancer Institute (CA62006); National Cancer Institute (CA165923).

CONFLICT OF INTEREST STATEMENT

G. Salles is on the advisory board for Abbvie, Beigene, BMS, Genentech/Roche, Genmab, Incyte, Ipsen, Janssen, Kite/Gilead, Loxo/Lilly, Merck, Novartis, and Nurix; consults for Abbvie, Atbtherapeutics, Beigene, BMS, Debiopharm, Genentech/Roche, Genmab, Innate Pharma, Incyte, Ipsen, Kite/Gilead, Modex, Molecular Partners, Nordic, Nanovector, Orna Therapeutics, and Treeline; receives research support from Abbvie, Genentech, Genmab, Janssen, Ipsen, and Nurix; and is a shareholder of Owkin. T.M. Habermann is on the data monitoring committee for Seagen and Eli Lilly and receives research program support from Roche/Genentech, BMS, and Genmab. The remaining authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Genotype data from the NCI NHL GWAS is available on dbGaP (phs000801.v2.p1) for research purposes in accordance with dbGaP data access policies. Other data that support the findings of this study are available for research purposes through the InterLymph Consortium upon approval in accordance with institutional review boards and general data protection regulations.

ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the following Institutional Review Boards: ATBC:(NCI Special Studies Institutional Review Board), BCCA: UBC BC Cancer Research Ethics Board, CPS-II: American Cancer Society, ELCCS: Northern and Yorkshire Research Ethics Committee, ENGELA: IRB00003888—Comite d' Evaluation Ethique de l'Inserm IRB # 1, EPIC: Imperial College London, EpiLymph: International Agency for Research on Cancer, HPFS: Harvard School of Public Health (HSPH) Institutional Review Board, Iowa-Mayo SPORE: University of Iowa Institutional Review Board, Italian GxE: Comitato Etico Azienda Ospedaliero Universitaria di Cagliari, Mayo Clinic Case–Control: Mayo Clinic Institutional Review Board, MCCS: Cancer Council Victoria's Human Research Ethics Committee, MD Anderson: University of Texas MD Anderson Cancer Center Institutional Review Board, MSKCC: Memorial Sloan-Kettering Cancer Center Institutional Review Board, NCI-SEER (NCI Special Studies Institutional Review Board), NHS: Partners Human Research Committee, Brigham and Women's Hospital, NSW: NSW Cancer Council Ethics Committee, NYU-WHS: New York University School of Medicine Institutional Review Board, PLCO: (NCI Special Studies Institutional Review Board), SCALE: Scientific Ethics Committee for the Capital Region of Denmark, SCALE: Regional Ethical Review Board in Stockholm (Section 4) IRB#5, UCSF2: University of California San Francisco Committee on Human Research, WHI: Fred Hutchinson Cancer Research Center, Yale: Human Investigation Committee, Yale University School of Medicine. Informed consent was obtained from all subjects involved in the study.

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