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Non-Hodgkin lymphoma and Obesity: a pooled analysis from the InterLymph consortium

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Abstract

Nutritional status is known to alter immune function, a suspected risk factor for non-Hodgkin lymphoma (NHL). To investigate whether long-term over, or under, nutrition is associated with

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NHL self-reported anthropometric data on weight and height from over 10000 cases of NHL and 16000 controls were pooled across 18 case-control studies identified through the International Lymphoma Epidemiology Consortium. Study-specific odds ratios (OR) were estimated using logistic regression and combined using a random-effects model. Severe obesity, defined as BMI of 40 kg m^{-2} or more, was not associated with NHL overall (pooled OR=1.00, 95% confidence interval (CI) 0.70–1.41) or the majority of NHL subtypes. An excess was however observed for diffuse large B-cell lymphoma (pooled OR=1.80, 95% CI 1.24–2.62), although not all study-specific ORs were raised. Among the overweight (BMI 25–29.9 kg m^{-2}) and obese (BMI 30–39.9 kg m^{-2}), associations were elevated in some studies and decreased in others, while no association was observed among the underweight (BMI<18.5 kg m^{-2}). There was little suggestion of increasing ORs for NHL or its subtypes with every 5 kg m^{-2} rise in BMI above 18.5 kg m^{-2}. BMI components height and weight were also examined, and the tallest men, but not women, were at marginally increased risk (pooled OR=1.19, 95% CI 1.06–1.34). In summary, whilst we conclude that there is no evidence to support the hypothesis that obesity is a determinant of all types of NHL combined, the association between severe obesity and diffuse large B-cell lymphoma may warrant further investigation.

Keywords

non-Hodgkin lymphoma; lymphoma; body mass index; weight; height; epidemiology

Introduction

Non-Hodgkin lymphomas (NHL) can arise following rare inherited disorders of the immune system, long-term immunosuppressive drug therapy and viral infections such as human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV). In such instances, severe immunosuppression resulting from exposure usually leads to the development of specific NHL subtypes. For the majority of NHL however, the cause remains unknown but it is suspected that factors which affect the immune system are involved. In particular, it has been suggested that the degree of adiposity might be important since over (as well as under) nutrition can alter immune function (1;2). However, while several epidemiological studies have reported associations between excess weight and NHL (3–15) the evidence is far from conclusive (16–28). Here we present a pooled analysis of self-reported height and weight on over 10000 NHL cases and 16000 controls from 18 case-control studies identified through the International Lymphoma Epidemiology Consortium (InterLymph: http://epi.grants.cancer.gov/InterLymph/).

Materials and Methods

Through the InterLymph forum, 18 case-control studies of NHL with anthropometric data collected across 13 countries in parts of North America, Europe, and Japan between 1983 and 2004 were identified. Study designs are briefly outlined in Table 1, and more details are published elsewhere (3;8;14;18;24;29–36). Cases were identified using rapid ascertainment techniques, while controls were randomly selected from population registers (8 studies), outpatient clinics (3 studies) or inpatients (7 studies) hospitalised for a variety of non-neoplastic conditions such as circulatory, digestive or respiratory problems, or with traumatic or non-traumatic orthopaedic conditions. The appropriate ethical committees' approval was granted for each study and informed consent was given by all participants.

NHL diagnoses were pathologically confirmed and subsequently coded to the World Health Organisation (WHO) classification (37) (15 studies), the REAL classification (the 1999–2002 Italian study), or Working Formulation (North Italy and UCSF). Cases with HIV were

excluded. Diagnostic codes from the different studies were combined as previously described (38). The analysis here considers specific B-cell subtypes of NHL (diffuse large B-cell lymphoma: ICDO3 codes 9679/3, 9680/3, 9684/3; follicular lymphoma: 9690/3, 9691/3, 9695/3, 9698/3; chronic lymphocytic leukaemia/small lymphocytic lymphoma: 9670/3, 9823/3; marginal zone lymphoma: 9689/3, 9699/3; mantle cell lymphoma: 9673/3; Burkitt lymphoma: 9687/3, 9826/3; and other unspecified B-cell lymphoma: 9671/3, 9728/3), and T-cell lymphomas as a whole (9700/3, 9701/3, 9702/3, 9705/3, 9708/3, 9709/3, 9714/3, 9716/3, 9717/3, 9718/3, 9719/3, 9729/3, 9827/3) as well as NHL in total (defined by the above ICDO3 codes and 9591/3, 9675/3, and 9727/3).

In all studies, information on anthropometrics, demographics, lifestyle, occupations and medical histories were collected by in-person or telephone interviews. For the purposes of the present analyses, anonymised data were provided and checked for inconsistencies before coding uniformly. Within each study, height in metres was categorised using sex-specific quintiles of the height distribution among controls, and data were then combined across studies to reflect the relative position, rather than the absolute value, of this variable. In the statistical analysis, the referent category for height was taken as the 3rd quintile, since this central group contains the median and has the narrowest range. Usual adult weight was requested in 10 studies (Nebraska, UCSF, SCALE and EpiLymph studies). Elsewhere different questions were used (weight at diagnosis/interview (HERPACC1, HERPACC2); one year (NCI-SEER, British Columbia, North Italy, Italy); two years (Mayo Phase 1); or five years (UK) prior to diagnosis/interview).

For the pooled analysis, body mass index (BMI) was computed by dividing weight in kilograms by the square of height in metres where each study's weight variable was considered at the closest time point prior to diagnosis/interview, or else the usual adult weight. BMI was grouped using the World Health Organisation categories of underweight (<18.5 kg m^{-2}), normal (18.5–24.99 kg m^{-2}), grade 1 overweight (25–29.99 kg m^{-2}), grade 2 obese (30–39.99 kg m^{-2}) and grade 3 obese (40 kg m^{-2} or more) (39). For a person 1.7 m (5′ 7″) tall, these cut-off points relate to weights of 53 kg (118 lb), 72 kg (159 lb), 87 kg (191 lb), and 116 kg (255 lb) respectively. Socioeconomic status was defined by the level of education attained, except in British Columbia and the UK where self-reported household income and a census-based household deprivation indicator were used respectively; and no socioeconomic status information was collected in the Japanese studies (HERPACC1 and 2).

Statistical analysis followed similar methods to those employed in previous InterLymph pooling projects (40–44). Firstly, individual data were combined in an unconditional logistic regression model adjusting for study, age, sex, and race. To test for between-study heterogeneity, this model was compared using the likelihood ratio test with the model that included an additional term for interaction between the anthropometric variable and a variable indexing the studies. Heterogeneity was assumed to be present when the likelihood ratio test yielded a p-value<0.05. This flexible approach utilises all data and provides one statistic to test for heterogeneity. Where the likelihood ratio test was not statistically significant, the pooled adjusted OR and 95% CI computed from all individual data in an unconditional logistic regression model are presented.

Between-study heterogeneity was further examined among risk estimates at each category of the anthropometric variables. Study-specific odds ratios (OR) and 95% confidence intervals (CI) adjusted for sex, age, and race were computed using unconditional logistic regression (45). For each category of height or BMI, the study-specific ORs were combined using a random effects meta-analysis to produce a combined OR and corresponding 95% CI. The extent of heterogeneity for each category was indicated by Cochran's *Q*-statistic which was

considered statistically significant when $p<0.10$. The I^2-statistic was also reported to describe the percentage of total variation in the study-specific ORs which was due to heterogeneity (46).

Since the ORs were diverse across studies, a variety of approaches were applied to explore heterogeneity (47). To assess relative obesity within study populations rather than the absolute value, BMI was grouped into quintiles based on the control distributions within each study before combining the relative quintile groupings across studies; these analyses are not presented here since their findings were similar to those reported. Sensitivity analyses using various stratifications and subsets of data were also conducted (48). Study-specific ORs were combined by continent, study design and time period (corresponding to the original lymphoma classification used) as well as by level of participation. Given that the study-specific associations with BMI were heterogeneous in all analyses, forest plots with ORs pooled by continent were judged to be the most informative. Pooled ORs stratified by study design are also presented.

Within studies, analyses were performed separately for men, women, Caucasian subjects and persons aged 18 to 65. The resulting study-specific ORs were combined in a random-effects meta-analysis to examine heterogeneity. Potential confounding factors, such as smoking, alcohol and socioeconomic status, were assessed by comparing study-specific regression models with and without the confounding factor using the likelihood ratio test. A factor was considered a confounder when the likelihood ratio test was significant and the adjusted OR changed by more than 10%. Continuous variables corresponding to 10 cm increases in height and 5 kg m^{-2} increases in BMI were created to assess trends. All analyses were conducted using Stata (49).

Results

The pooled dataset from the 18 case-control studies comprised anthropometric information from 10453 cases of NHL and 16507 controls. Most cases (85%) were diagnosed with a B-cell lymphoma, 5% with a T-cell lymphoma and for 11%, immunophenotype was not known. The three most common NHL subtypes were diffuse large B-cell lymphoma (DLBCL) (32%), follicular lymphoma (FL) (22%) and chronic lymphocytic lymphoma/small lymphocytic lymphoma (CLL/SLL) (16%). A slightly higher proportion of cases were men (57%), 90% of all cases were Caucasian and the median age was 60 years. Cases tended to be older in age, of white race and of lower socioeconomic status than controls (data not shown).

Height distributions among male and female controls varied by study; for both sexes, the median height was highest in the American studies, generally decreased from Northern to Southern Europe, and was lowest in the two Japanese studies (data not shown). Among men, compared to the third quintile the odds ratio was increased in the highest quintile (OR=1.19, 95% CI 1.06–1.34), but was close to one in the lowest two quintiles (Supplementary Table 1). When examining trend within studies, no consistent population pattern emerged; most studies showed no evidence of a trend with 10 cm increases in height, six a significant positive trend, and two a significant negative trend (data not shown). Similar patterns were observed for the majority of NHL subtypes. Little association between height and NHL, or its subtypes, was observed among women (Supplementary Table 1).

Figure 1 gives the distribution of BMI among controls by study. Like height, studies conducted in the US had the greatest median BMI, and Japan the lowest. When BMI was classified using WHO categories, associations between BMI and NHL were heterogeneous between studies (likelihood ratio test: $\chi^2=139.1$, $p<0.0001$). Study-specific ORs showed that

the heterogeneity was most marked in Grade 1 overweight, where ORs ranged from 0.50 (95% CI 0.34–0.74) in EpiLymph Italy to 1.70 (95% CI 1.02–2.84) in EpiLymph Ireland and Grade 2 obese (ranging from OR=0.42, 95% CI 0.24–0.74 in EpiLymph Italy to OR=1.78, 95% CI 1.36–2.32 in UCSF) (Figures 2(b) and (c)). In the underweight and Grade 3 obese categories, where the numbers of subjects were small, ORs were also diverse (ranging from OR=0.27, 95% CI 0.03–2.34 in EpiLymph Ireland to OR=3.14, 95% CI 0.41–23.9 in EpiLymph Finland; and from OR=0.19, 95% CI 0.02–1.58 in EpiLymph Germany to OR=4.23, 95% CI 1.51–11.9 in UK, respectively) (Figures 2(a) and (d)). Trends with a 5 kg m^{-2} increase in BMI above 18.5 kg m^{-2} were significantly increased in two studies, significantly decreased in four studies and showed little effect in the remaining studies (Figure 3). ORs were pooled across North America, Northern Europe, Southern Europe and Japan. In North America, a homogeneous increased OR was suggested for Grade 1 overweight (Figure 2(b)) but no effect was found among Grade 3 obese (Figure 2(d)), and with the exception of the Californian study (UCSF), no significant positive trends were observed (Figure 3). Heterogeneity was still evident when the analyses were restricted to population-based studies conducted in the period 1998–2005; to those designed to code to the WHO classification; or to those where control participation rates were 70% or more. Similarly study-specific ORs were heterogeneous among men or women; subjects aged 18 to 65; or Caucasian subjects (data not shown).

Statistically significant between-study heterogeneity was also present for the three most common NHL subtypes (likelihood ratio tests for WHO BMI and DLBCL: χ^2=104.2, p=0.002; FL: χ^2=82.7, p=0.003; CLL/SLL: χ^2=58.7, p=0.04). For these three subtypes, as for NHL as a whole, study-specific ORs varied around one in all WHO BMI groups, with tests for heterogeneity in the two-stage random effects model being significant among Grade 1 overweight and Grade 2 obese (DLBCL: Supplementary Figures 1(a)–(d); FL: Supplementary Figures 3(a)–(d); CLL/SLL: Supplementary Figures 4(a)–(d)). In the underweight and Grade 3 obese groups, the meta-analyses generally suggested that ORs were more homogeneous and the combined risk estimates were not significantly different from one. The pooled OR for DLBCL among Grade 3 obese was increased (OR=1.80, 95% CI 1.24–2.62, Q=16.7, p=0.40, I^2=4.4%), being elevated in North America and Northern Europe, but as with all analyses in this BMI group, study-specific risk estimates were diverse, based on small numbers of subjects, and with wide and overlapping confidence intervals (Supplementary Figure 1(d)). Like NHL as a whole, a 5 kg m^{-2} increase in BMI did not consistently increase the risk of DLBCL (Supplementary Figure 2) or the other subtypes (data not shown). ORs for the rarer B-cell lymphomas and T-cell lymphoma were mostly not significantly different between studies, probably due to the small number of cases, and there was little suggestion of associations between these NHL subtypes and BMI (Supplementary Table 2).

Pooling data from studies with the highest WHO BMI prevalences of overweight/obese controls (EpiLymph Czech Republic, Nebraska, Mayo Phase 1, EpiLymph Italy, EpiLymph Germany, Italy-Aviano and Naples, and EpiLymph Finland) gave more homogeneous ORs (likelihood ratio test: χ^2=32.3, p=0.12). Within this subset of seven studies, there was still little evidence that higher than average BMI increases the risk of NHL and its subtypes (Table 2). These findings were consistent when data were stratified by sex, age, or race.

Discussion

The present InterLymph analysis, which is based on 18 studies from 13 countries, found little evidence to support the hypothesis that excess weight-for-height is associated with NHL. A slightly increased OR amongst the tallest men was observed compared to those who were of mid-range height but no association was found among women. The large number of

subjects included in this analysis enabled examination of risks for subtypes of NHL. While findings for most were consistent with total NHL, an increased risk for DLBCL among persons with a BMI of 40 kg m^{-2} or more was observed in a meta-analysis of study-specific ORs. For DLBCL, ORs were elevated with overweight/obesity in North America and amongst the most obese in Northern Europe, yet studies in either region did not show an increasing trend with a 5 kg m^{-2} rise in BMI. Marked heterogeneity between studies was present for all categories of BMI, which remained when studies were combined by continent, study design, time period, WHO lymphoma classification used; and when data were restricted to men or women, persons aged 18 to 65, Caucasians alone or studies with participation rates of 70% or more. ORs were less heterogeneous amongst studies with the greatest proportions of controls with a BMI of 25 kg m^{-2} or more. Of the seven studies in this subset, no effect of BMI on NHL risk was observed, and the lack of association with obesity was consistent across NHL subtypes, amongst men and women, and at age ≤45, 46–55, 56–65, and ≥66 years.

Six of the case-control studies included in this pooled analysis have previously published data on NHL and obesity (3;8;11;14;23;24;50) and a further 12 are included here for the first time. Apart from case-control studies, adiposity has been investigated in cohorts where height and weight were measured (9;10;12;13;25–27) or self-reported (5;15;20;21), and among persons with a hospital discharge for obesity (4;19;22). Cohort studies have the advantage of prospectively collected information, although not necessarily at a relevant time point. Positive associations with obesity have been reported for some cohorts (5;9;10;12;13;15), but not for others (4;19–22;25–27); and a further case-control investigation nested within a cohort reported a reduced risk based on measured height and weight (16). Only one additional study of case-control design- which is not part of the InterLymph consortium- has published its findings, observing an excess risk of NHL with obesity (6).

Hitherto only a few individual case-control studies and two cohort studies have considered lymphoma subtypes, proposing an association with excess adiposity for DLBCL, but less so for FL and CLL/SLL (8;11;14;15;21;22;24;50). A recent meta-analysis of published risk estimates suggested a slight increased risk of NHL, particularly DLBCL based upon data from both case-control and cohort studies (51). The pooled analysis presented here has the advantage of being less susceptible to positive publication bias since it is based on all studies within the InterLymph consortium that collected anthropometric information - around 40% of the data have not been presented before. Another advantage of pooling individual records is that it permits uniform categorization of data, as well as the assessment of the effects of potentially confounding factors. In this regard, adjustment for smoking and alcohol consumption did not greatly alter the risk estimates.

With respect to potential biases, participation rates were generally lower in controls than cases, and a particular concern is whether controls are representative of the populations from which cases were drawn. It is reassuring to note that pooling data from studies with control participation rates of 70% or more gave findings similar to those reported overall. Nonetheless, it is still possible that poor control participation could have influenced our findings since we cannot rule out the possibility that those with obesity-related health problems (e.g. type 2 diabetes, cardiovascular disease, respiratory difficulties, chronic musculoskeletal problems) may have been (more or) less likely to participate. If the latter applied, the increased risks in the highest BMI category could be an artefact of differential case-control participation.

The rapidly changing prevalence of obesity is a growing public health problem, and to further investigate the issue, age-standardised data calculated from height and weight

measurements were sourced from the World Health Organisation Global Database on Body Mass Index (http://www.who.int/bmi/). Interestingly, the relative order of the overweight (25–29.99 kg m^{-2}) /obesity (≥30 kg m^{-2}) prevalence across studies among our controls and that of the corresponding country-specific WHO BMI prevalence from around the year 2000 are not strongly correlated (Spearman's ρ=0.41, p=0.08) (Figure 4). WHO data place the USA, Germany and the UK at the top while our self-reported information rate the Czech Republic, USA and Italy as having the highest overweight/obesity prevalence. Whilst differences between our data and WHO are likely to be related to factors such as age, sex and time period, they serve to illustrate the rapidly changing patterns and wide variations that exist around the world.

Self-reports of anthropometric information is known to be inexact, with height tending to be overestimated and weight underestimated (52). The nature of individual misreporting is likely to be complex, being related not only to their actual size but also to other factors such as age and sex. In a cohort of British adults, for instance, where self-reported and measured data were compared, height was overestimated most by older people, shorter men and heavier women, while the greatest underestimation of weight was amongst heavier men and women (53). This tendency for people to report BMI closer to 'normal' may have diluted our odds ratios. It is also possible that weight loss associated with lymphoma may have influenced the recall of cases differently to that of controls. Because of this, at interview subjects were either asked to recall their usual weight or their weight at a specified times before diagnosis/interview, and restricting the analyses to the six studies (NCI-SEER, Mayo Phase 1, British Columbia, UK, North Italy and Italy) where data were requested at 1 or 5 years prior to diagnosis yielded similar results to the findings overall.

Whilst BMI derived from height and weight acts as an easily obtained estimate of adiposity, its use as a marker of obesity has several potential weaknesses. Across different ethnic groups, for example, a given BMI may not correspond to the same proportions of body fat (54). Moreover since the index was originally devised as a means of assessing average body composition among sedentary individuals of working age it may not truly reflect the degree of adiposity across the population as a whole. For instance, among the elderly where muscle mass may have started to decline, body fat mass may be underestimated by BMI whereas amongst athletes it may be overestimated. To account for the potential variation in BMI as a marker of body fat across different populations, we grouped our data according to study-specific control distributions as well as WHO BMI categories. We also repeated the analyses restricting data to Caucasians, and to North American and Northern European studies combined. Sensitivity analyses were conducted too among persons aged 65 or less (71% of our subjects), and among those who were not regular heavy exercisers where this information was requested (NCI-SEER, British Columbia and HERPACC2). These additional investigations gave similar findings to the presented results. More specific estimates of adiposity may be derived from total body fat mass and, as a marker for abdominal fat distribution, waist-to-hip ratios, but such data were not obtained in the studies included here and have only rarely been investigated with respect to NHL elsewhere, showing little effect (15;21;26).

In conclusion, this pooled analysis of case-control studies from 13 countries, crossing 3 continents, did not find an association between NHL and increased BMI. ORs were raised in studies from some countries, namely the US, Canada and Northern European nations, but even within this group, heterogeneity was observed, questioning the validity of a combined odds ratio. The findings presented here were based on individual data from a large number of subjects enrolled in 18 studies, pooling of which were accomplished through the InterLymph consortium. Some of the advantages of this pooled analysis include information on confounders and NHL subtypes as well as data on height and weight, the constituent

components of BMI. One potential confounding factor not assessed here is diet but dietary data will be examined, in conjunction with BMI, in a future InterLymph pooled analysis. Such investigations may further elucidate whether NHL or its subtypes are associated with obesity per se.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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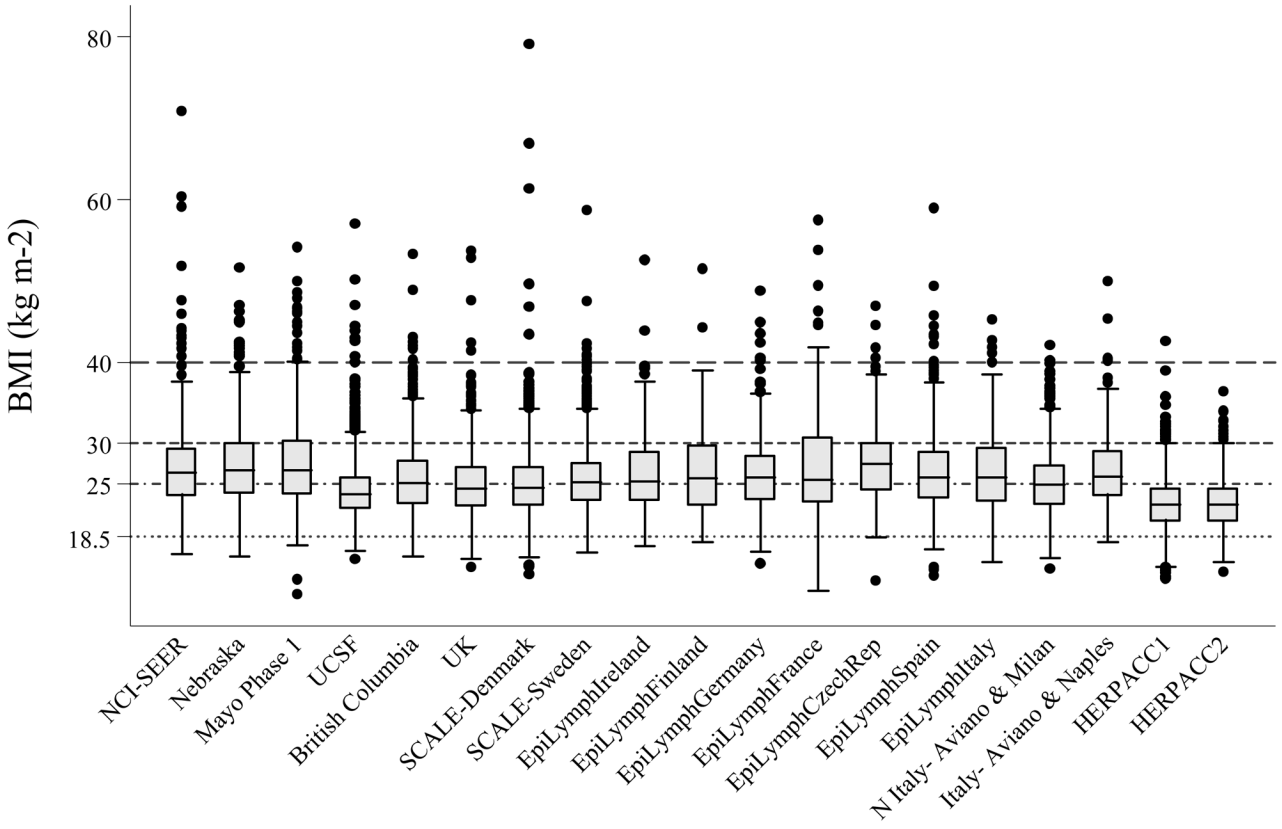
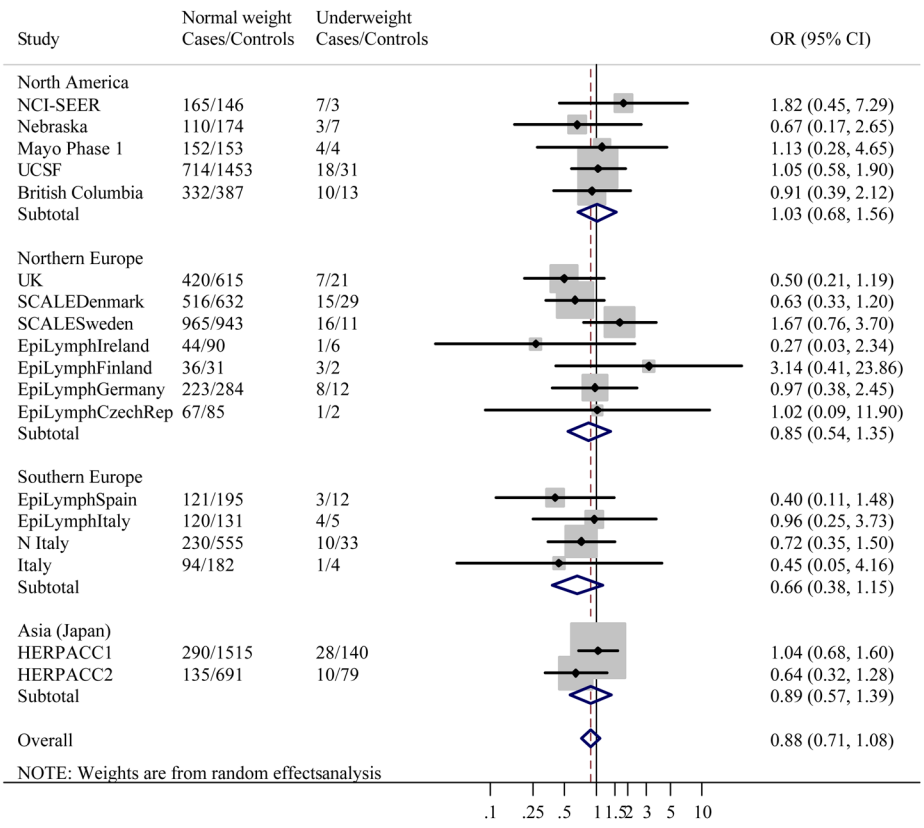
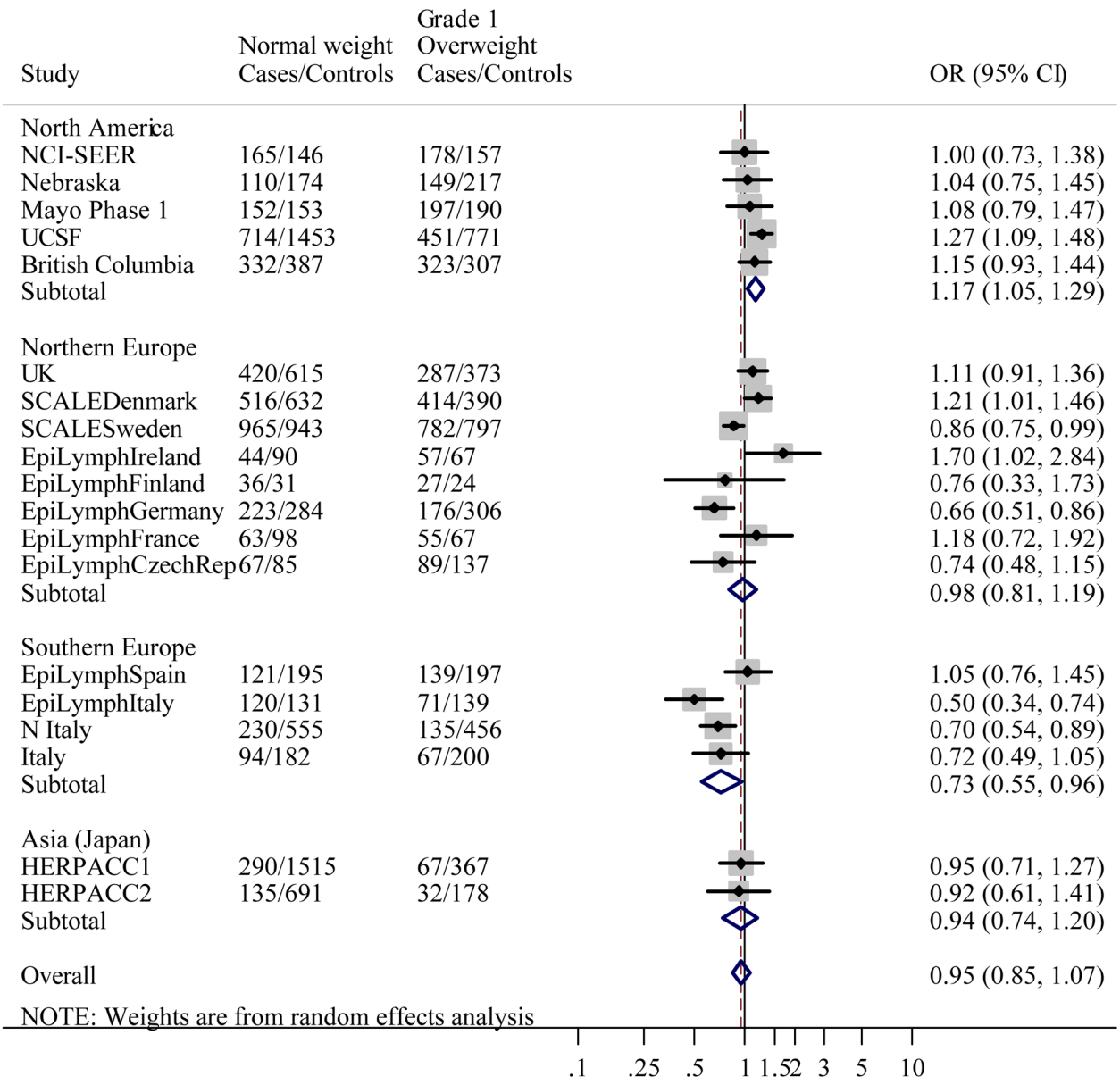


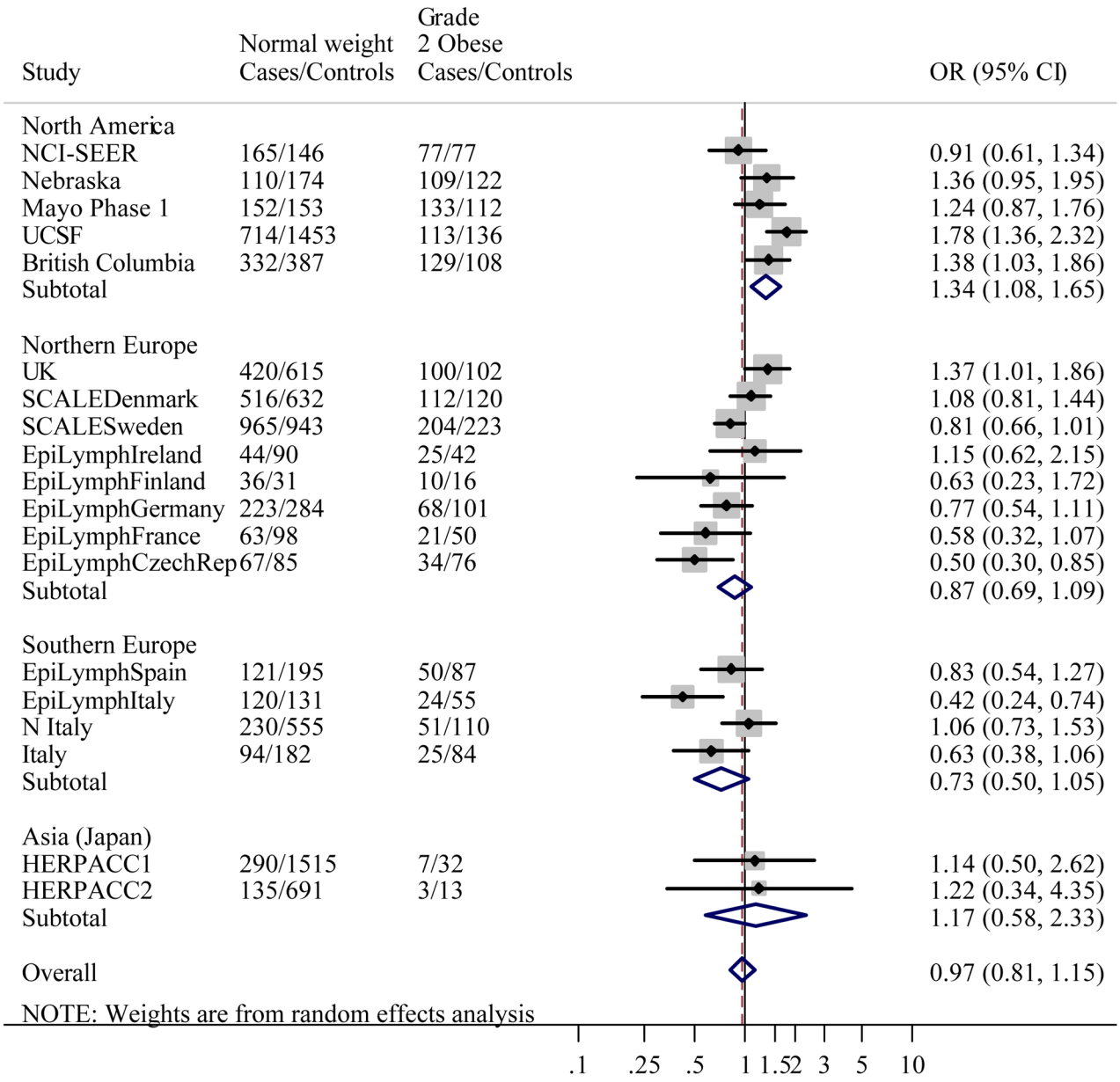
Figure 1.

Box-Whisker Plot of Body Mass Index among Controls by Study.

Body mass index considered to be: Underweight if <18.5 kg m^{-2}; Normal weight-for-height if 18.5–24.99 kg m^{-2}; Grade 1 Overweight if 25–29.99 kg m^{-2}; Grade 2 Obese if 30–39.99 kg m^{-2}; and Grade 3 Obese if ≥40 kg m^{-2} (55).







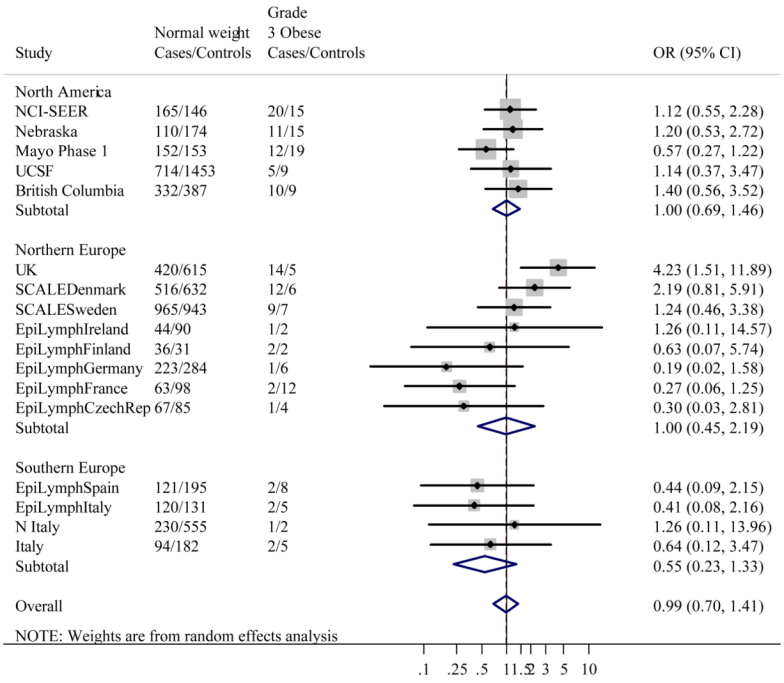


Figure 2.

Figure 2(a). Meta-analysis of the risk of NHL associated with BMI <18.5 kg m^{-2} (Underweight) compared to BMI 18.5–24.99 kg m^{-2} (Normal weight).
Overall test for heterogeneity: Q=13.0, p=0.73; Variation in odds ratios (OR) attributable to heterogeneity: I^2= 0.0%. For continents: North America: Q=1.04, p=0.90, I^2=0.0%; Northern Europe: Q=7.87, p=0.25, I^2=23.7%; Southern Europe: Q=1.03, p=0.80, I^2=0.0%; Asia (Japan): Q=1.38, p= 0.24, I^2=27.5%. Test for heterogeneity between continents: Q=1.82, p=0.61. Pooled odds ratios by study design were: Population-based studies: OR=0.91, 95% CI 0.68–1.21, Q=6.75, p=0.56, I^2=0.0%; Clinic-based studies: OR=0.92, 95% CI 0.65–1.31, Q=1.47, p=0.48, I^2=0.0%; Hospital-based studies: OR=0.67, 95% CI 0.39–1.17, Q=3.79, p=0.58, I^2=0.0%. Test for heterogeneity between study designs: Q=1.04, p=0.59.

Figure 2(b). Meta-analysis of the risk of NHL associated with BMI 25–29.99 kg m^{-2} (Grade 1 overweight) compared to BMI 18.5–24.99 kg m^{-2} (Normal weight).
Overall test for heterogeneity: Q=60.0, p<0.001; Variation in odds ratios (OR) attributable to heterogeneity: I^2=70.0%. For continents: North America: Q=2.76, p=0.60, I^2=0.0%; Northern Europe: Q=25.0, p=0.001, I^2=72.1%; Southern Europe: Q=8.59, p=0.04, I^2=65.1%; Asia (Japan): Q=0.02, p=0.90, I^2=0.0%. Test for heterogeneity between continents: Q=23.4, p<0.001. Pooled odds ratios by study design were: Population-based studies: OR=0.97, 95% CI 0.82–1.14, Q=41.6, p<0.001, I^2=80.8%; Clinic-based studies: OR=0.99, 95% CI 0.82–1.20, Q=0.44, p=0.80, I^2=0.0%; Hospital-based studies: OR=0.91, 95% CI 0.72–1.16, Q=14.0, p=0.03, I^2=57.1%. Test for heterogeneity between study designs: Q=3.93, p=0.14.

Figure 2(c). Meta-analysis of the risk of NHL associated with BMI 30–39.99 kg m^{-2} (Grade 2 obese) compared to BMI 18.5–24.99 kg m^{-2} (Normal weight).
Overall test for heterogeneity: Q=59.7, p<0.001; Variation in odds ratios (OR) attributable to heterogeneity: I^2=69.8%. For continents: North America: Q=8.18, p=0.08, I^2=51.1%; Northern Europe: Q=18.1, p=0.01, I^2=61.2%; Southern Europe: Q=7.88, p=0.05, I^2=62.0%; Asia (Japan): Q=0.01, p=0.93, I^2=0.0%. Test for heterogeneity between continents: Q=25.4, p<0.001. Pooled odds ratios by study design were: Population-based studies: OR=1.06, 95%

CI 0.83–1.34, Q=41.3, p<0.001, I^2=80.7%; Clinic-based studies: OR=1.22, 95% CI 0.90–1.67, Q=0.03, p=0.99, I^2=0.0%; Hospital-based studies: OR=0.77, 95% CI 0.60–0.98, Q=8.51, p=0.20, I^2=29.5%. Test for heterogeneity between study designs: Q=9.81, p=0.007.
Figure 2(d). Meta-analysis of the risk of NHL associated with BMI ≥40 kg m^{-2} (Grade 3 obese) compared to BMI 18.5–24.99 kg m^{-2} (Normal weight).
Overall test for heterogeneity: Q=21.9, p=0.15; Variation in odds ratios (OR) attributable to heterogeneity: I^2=26.8%. For continents: North America: Q=2.89, p=0.58, I^2=0.0%; Northern Europe: Q=15.3, p=0.03, I^2=54.4%; Southern Europe: Q=0.69, p=0.88, I^2=0.0%. Test for heterogeneity between continents: Q=2.91, p=0.23. Pooled odds ratios by study design were: Population-based studies: OR=1.33, 95% CI 0.88–2.00, Q=11.4, p=0.18, I^2=29.7%; Clinic-based studies: OR=0.57, 95% CI 0.26–1.22, No test for heterogeneity as only 1 study; Hospital-based studies: OR=0.51, 95% CI 0.25–1.05, Q=2.07, p=0.91, I^2=0.0%. Test for heterogeneity between study designs: Q=8.41, p=0.015.

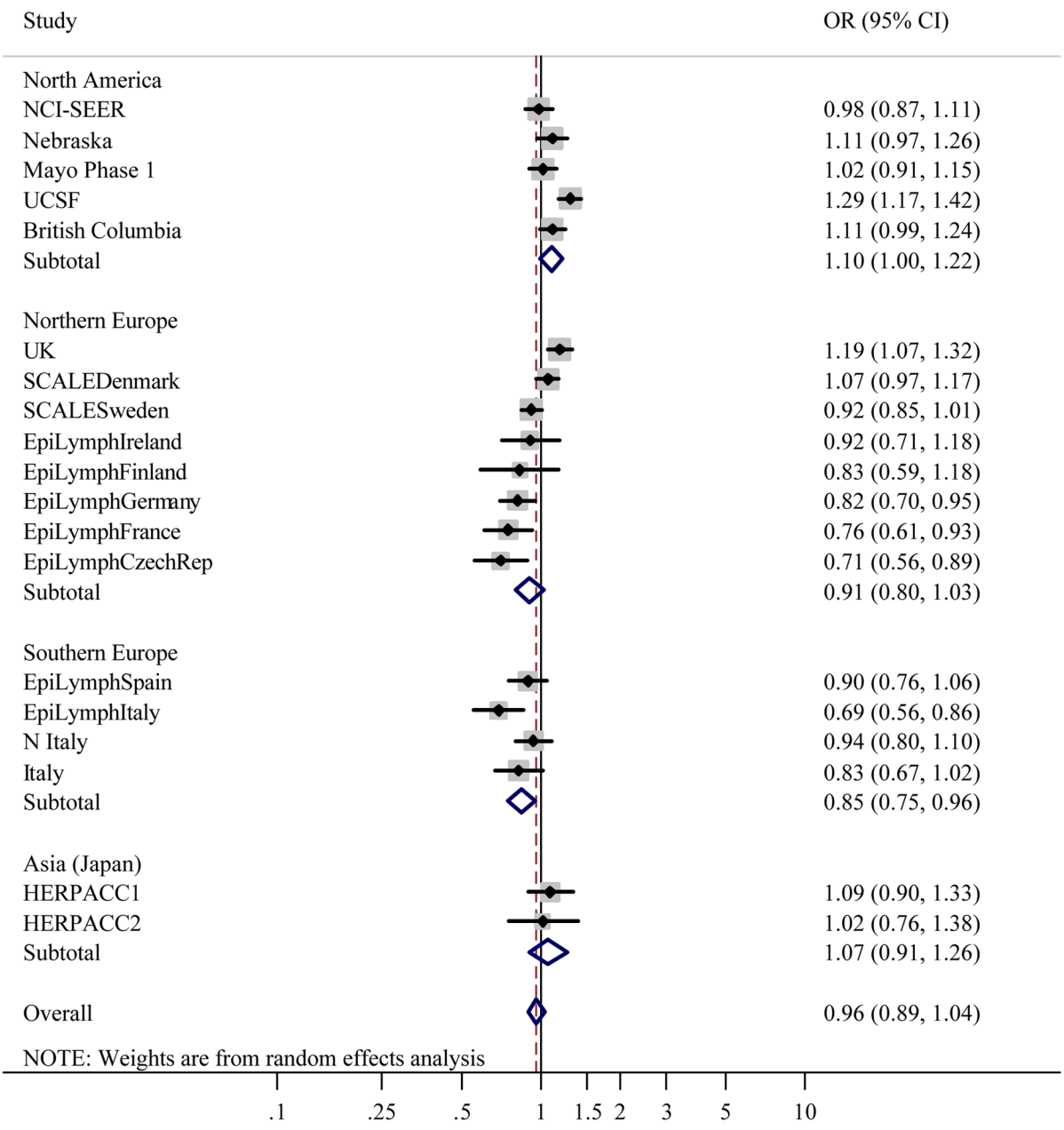


Figure 3.

Meta-analysis of the risk of NHL associated with 5 kg m^{-2} increase in BMI above 18.5 kg m^{-2} (Normal weight and above).

Overall test for heterogeneity: Q=87.5, p<0.001; Variation in odds ratios (OR) attributable to heterogeneity: I^2=79.4%. For continents: North America: Q=15.5, p=0.004, I^2=74.1%; Northern Europe: Q=37.4, p<0.001, I^2=81.3%; Southern Europe: Q=5.32; p=0.15; I^2=43.6%; Asia (Japan): Q=0.12, p=0.73, I^2=0.0%. Test for heterogeneity between continents: Q=29.0, p<0.001. Pooled odds ratios by study design were: Population-based studies: OR=1.02, 95% CI 0.92–1.13, Q=57.7, p<0.001, I^2=86.1%; Clinic-based studies: OR=1.04, 95% CI 0.94–1.14, Q=0.34, p=0.84, I^2=0.0%; Hospital-based studies: OR=0.85, 95% CI 0.79–0.92, Q=6.09, p=0.41, I^2=1.4%. Test for heterogeneity between study designs: Q=23.4, p<0.001.

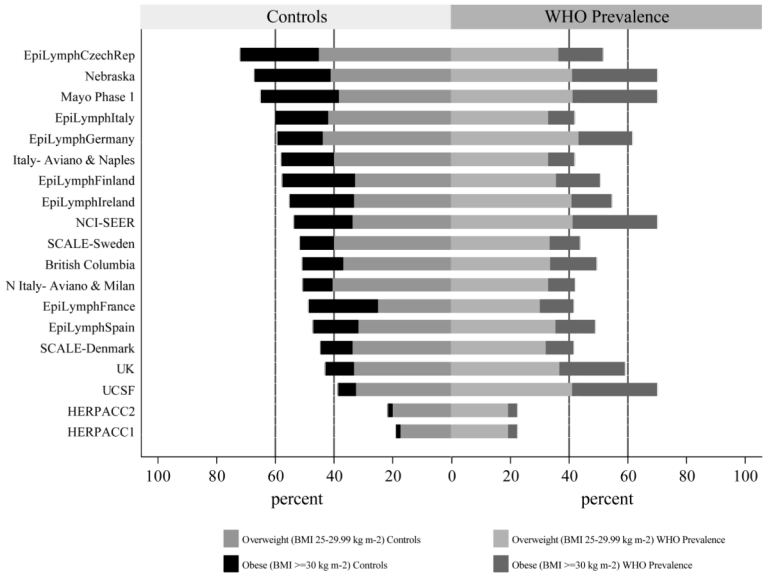


Figure 4.

Comparison of Control and WHO Overweight/Obesity Prevalences by Study. Overweight (BMI 25–29.99 kg m^{-2}) and Obesity (BMI ≥ 30 kg m^{-2}) prevalence from the World Health Organisation (WHO) Global Database on Body Mass Index (http://www.who.int/bmi/). WHO prevalence was derived from the most recent published age- and sex- standardised BMI data calculated from height and weight measured in clearly defined population samples; these data were largely from around the year 2000. The relative order of control overweight/obesity prevalences across studies was not similar to that from data reported on the WHO Global database for BMI (Spearman's ρ=0.41, p=0.08).

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Table 1

Characteristics of case-control studies included in the pooled analysis.

Study	Location	Year of Diagnosis	Age Range	Cases (N=10453)	Controls (N=16507)				Reference
				N	Participation (%)	Source	N	Participation (%)	
NCI-SEER	Detroit, Michigan; Iowa; Los Angeles, California; Seattle, Washington, USA	1998–2001	20–70	527	76	<65 years RDD; 65+ years random selection from Centers for Medicare and Medicaid Services, stratified by study area, age, sex and race	468	52	(8)
Nebraska NHL Study	Nebraska, USA	1999–2002	20–75	387	74	RDD, frequency matched by age and sex	535	78	(14)
Mayo Clinic Phase 1	Iowa, Wisconsin, Minnesota, USA	2002–2005	18+	499	66	Frequency matched by age, sex and county of residence	499	70	n/a
UCSF	San Francisco, USA	1988–1995	21–74	1304	72	RDD, frequency matched by age, sex, and county of residence	2402	78	(3)
British Columbia Study	Vancouver and Victoria, British Columbia, Canada	2000–2004	20–82	828	78	Random selection from Client Registry of the Ministry of Health, frequency matched by age, sex and region	848	46	(36)
UK	Yorkshire, Lancashire, South Lakeland and parts of Southwest England	1998–2003	16–69	833	70	Random selection from general practice lists, individually matched by age, sex and region of residence	1141	69	(29)
SCALE	Denmark and Sweden	2000–2002	18–74	3055	81	Random selection from population register, frequency matched by sex and age	3187	71	(24)
EpiLymph Ireland	Six hospitals on the East Coast of the Republic of Ireland	2001–2003	18–80	135	90	Hospital controls matched by age (±5 years), sex and study region	208	75	(30)
EpiLymph Finland	Finland	2001–2003	18–80	87		Hospital controls matched by age (±5	75		n/a

Study	Location	Year of Diagnosis	Age Range	Cases (N=10453)	Controls (N=16507)				Reference
				N	Participation (%)	Source	N	Participation (%)	
						years), sex and study region			
EpiLymph Germany	Ludwigshafen/Upper Palatinate, Heidelberg/Rhine-Neckar County, Würzburg/Lower Frankonia, Hamburg, Bielefeld and Munich	1999–2002	18–80	496	88	Random selection from population register, individually matched by sex, age and study region	710	44	(31)
EpiLymph France	Amiens, Dijon and Montpellier	2000–2003	18–80	206	91	Hospital controls matched by age (±5 years), sex and study region	276	74	(30)
EpiLymph Czech Republic	1 centre in Czech Republic	2001–2003	18–80	195	90	Hospital controls individually matched by age (±5 years), sex and study region	304	60	(30)
EpiLymph Spain	Barcelona, Tortosa, Reus and Madrid	1998–2002	18–80	428	82	Hospital controls matched by age (±5 years), sex and study region	631	96	(32)
EpiLymph Italy	2 centres in Italy	1998–2004	18–80	222	93	Random selection from population census list, matched by age (±5 years), sex and study region	336	66	(30)
Northern Italy	Aviano & Milan	1983–1992	17–79	429	>97	Patients admitted for acute, nonneoplastic, nonimmunologic conditions in the hospitals where cases diagnosed	1157	>97	(18)
Italy	Aviano & Naples	1999–2002	18–84	225	97	Hospital controls, frequency matched by age (in 5-year bands), sex and study centre to cases of lymphohematopoietic neoplasms including NHL and hepatocellular carcinoma	504	91	(33)
HERPACC1	Aichi Cancer Centre, Nagoya, Japan	1988–2000	18–79	416	≈99	Random sample of patients not diagnosed with cancer, individually	2260	≈99	(34;35)

Study	Location	Year of Diagnosis	Age Range	Cases (N=10453)	Controls (N=16507)				Reference
				N	Participation (%)	Source	N	Participation (%)	
						matched by age and sex			
HERPACC2	Aichi Cancer Centre, Nagoya, Japan	2001–2004	18–79	181	≈99	Random sample of patients not diagnosed with cancer, individually matched by age and sex	966	≈99	(35)

Table 2

Number of cases and controls, pooled odds ratios and 95% confidence intervals for body mass index by all NHL subtypes and the three most common NHL subtypes in studies with the highest prevalence of overweight/obese controls[a].

BMI[b]	Controls (N=2963)	NHL[c] (N=2108)	OR[d]	95% CI	DLBCL[c] (N=659)	OR[d]	95% CI	FL[c] (N=457)	OR[d]	95% CI	CLL/SLL[d] (N=381)	OR[c]	95% CI
WHO category (kg m^{-2}):													
<18.5	36	24	0.85	0.50–1.44	8	1.09	0.48–2.49	5	0.96	0.36–2.59	3	1.47	0.40–5.42
18.5–24.99	**1040**	**802**	**1**	**-**	**273**	**1**	**-**	**182**	**1**	**-**	**121**	**1**	**-**
25–29.99	1213	776	0.79	0.69–0.90	222	0.68	0.56–0.84	149	0.71	0.56–0.91	163	0.96	0.74–1.25
30–39.99	566	403	0.84	0.72–0.99	111	0.72	0.56–0.93	100	0.96	0.73–1.26	85	1.09	0.80–1.49
≥40	56	31	0.63	0.40–0.99	14	0.94	0.51–1.72	5	0.54	0.21–1.40	2	0.37	0.09–1.61
Missing	52	72			31			16			7		
Test for heterogeneity[e]			*χ^2=32.2*	*p=0.12*		*χ^2=25.6*	*p=0.27*		*χ^2=24.7*	*p=0.05*		*χ^2=17.8*	*p=0.16*

[a] Studies with highest prevalence of overweight/obese controls were EpiLymph Czech Republic, Nebraska, Mayo Phase 1, EpiLymph Italy, EpiLymph Germany, Italy-Aviano & Naples, and EpiLymph Finland.

[b] Body mass index grouped: using WHO categories where <18.5 kg m^{-2} is considered Underweight; 18.5–24.99 kg m^{-2} Normal weight; 25–29.99 kg m^{-2} Grade 1 Overweight; 30–39.99 kg m^{-2} Grade 2 Obese; and ≥40 kg m^{-2} Grade 3 Obese.

[c] NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; CLL/SLL: chronic lymphocytic leukaemia/ small lymphocytic lymphoma.

[d] Odds ratios and 95% confidence intervals adjusted for study, sex, age, and race were estimated using unconditional logistic regression.

[e] Test for heterogeneity was conducted by testing for evidence of interaction between BMI and studies using the likelihood ratio test.

[f] Confidence interval estimated using exact methods.