EUROPEAN JOURNAL OF CANCER 47 (2011) 2422–2430

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Body mass index and risk of non-Hodgkin's and Hodgkin's lymphoma: A meta-analysis of prospective studies

Susanna C. Larsson *, *Alicja Wolk*

Division of Nutritional Epidemiology, The National Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

ARTICLE INFO

Article history:
Available online 4 July 2011

Keywords:
Body mass index
Prospective studies
Meta-analysis
Lymphoma
Obesity
Review

ABSTRACT

We conducted a meta-analysis of prospective studies to summarise the epidemiologic evidence regarding the association of body mass index (BMI) with non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) incidence and NHL mortality. Pertinent studies were identified by searching PubMed (1966–May 2011) and the reference lists of retrieved articles. For each study, we estimated a relative risk (RR) for a 5 kg/m^2 increase in BMI. A random-effects model was used to combine the RR estimates from individual studies. The summary RRs for a 5 kg/m^2 increase in BMI were 1.07 (95% confidence intervals (CI), 1.04–1.10) for NHL incidence (16 studies, n = 17,291 cases) and 1.14 (95% CI, 1.04–1.26) for NHL mortality (five studies, n = 3407 cases). BMI was significantly positively associated with risk of diffuse large B-cell lymphoma (RR, 1.13; 95% CI, 1.02–1.26), but not other NHL subtypes. The difference in risk estimates for subtypes was not statistically significant (P = 0.10). There was evidence of a nonlinear association between BMI and HL (P for nonlinearity = 0.01) (five studies, n = 1557 cases). The summary RRs of HL were 0.97 (95% CI, 0.85–1.12) for overweight and 1.41 (95% CI, 1.14–1.75) for obesity. These results indicate that BMI is positively associated with risk of NHL and HL as well as with NHL mortality.

1. Introduction

Non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) are malignancies derived from lymphocytes (white blood cells), which are an important part of the immune system. The main difference between NHL and HL is in the specific lymphocyte each involves. In HL, the abnormal lymphocyte is the Reed–Sternberg cell (a B lymphocyte). Other types of lymphomas are called NHL (about 35 recognised subtypes). The causes of malignant lymphomas remain elusive, although various infectious factors as well as autoimmune and chronic inflammatory conditions have been implicated.[1,2]

Obesity is related to altered immune function and a chronic inflammatory response[3] and thus may be a risk factor for malignant lymphomas. Obesity may also cause changes in the metabolism of endogenous hormones, leading to distortion in the normal balance between cell proliferation, differentiation, and apoptosis.[4] The association between body mass index (BMI) and risk of NHL has been summarised in two meta-analysis of studies published to November 2007.[5,6] Since then, several additional prospective studies have published results on BMI in relation to NHL incidence or mortality. Findings on the association between BMI and NHL mortality have not been summarised previously. There is also no meta-analysis of BMI in relation to risk of HL.

The aim of this study was to conduct an updated meta-analysis of prospective studies to summarise the data on BMI in relation to NHL incidence and mortality. We investigated whether the association between BMI and NHL incidence varied by subtypes. Furthermore, we performed a

* *Corresponding author:* Address: Division of Nutritional Epidemiology, The National Institute of Environmental Medicine, Karolinska Institute, P.O. Box 210, SE-17177 Stockholm, Sweden.
E-mail address: susanna.larsson@ki.se (S.C. Larsson).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.06.029

Table 1 – Characteristics of prospective studies of body mass index and non-Hodgkin's lymphoma incidence or mortality and Hodgkin's lymphoma incidence.[a]

Study (Refs. No.)	Country	Sex and age	Cases† (cohort size)	Years of follow-up	Non-Hodgkin's and Hodgkin's lymphoma classification[b]	Adjustments
Incidence						
Zhang et al. (1999)[8]	United States	Women aged 34–60 years	199 (88,410)	14	ICD-8 code 202	Age, smoking, area of residence, height, and energy intake
Cerhan et al. (2002)[11]	United States	Women aged 55–69 years	261 (37,931)	13	Not specified	Age
Oh et al. (2005)[13]	Korea	Men aged ⩾20 years	NHL 190, HL 31 (781,283)	10	Not specified	Age, area of residence, smoking, physical activity, alcohol intake
MacInnis et al. (2005)[15]	Australia	Men and women aged 27–75 years	170 (40,909)	8.4 (mean)	ICD-10 morphology codes 959, 967–971	Age, country of birth, and education
Rapp et al. (2005)[16]	Austria	Men and women aged 19–94 years	84 (67,447) (M) 64 (78,484) (W),	10	ICD-9 codes 200, 202	Age, occupational group, and smoking
Lukanova et al. (2006)[18]	Sweden	Men and women aged 29–61 years	54 (33,424) (M) 35 (35,362) (W),	14	Not specified	Age, calendar year, and smoking
Samanic et al. (2006)[19]	Sweden	Men aged 18–67 years	NHL 1077, HL 211 (362,552)	19	NHL ICD-7 codes 200, 202 HL ICD-7 code 201	Age and smoking
Engeland et al. (2007)[21]	Norway	Men and women aged 20–74 years	NHL 4374, HL 725 (962,901) (M) NHL 4138, HL 499 (1,037,077) (W), 23 years (mean)	40 (mean 23)	Not specified	Age and birth cohort
Lim et al. (2007)[22]	United States	Men and women aged 50–71 years	NHL 1350, HL 57 (465,858)	5.5	NHL ICD-O-2[c] HL ICD-O-2 codes 9650, 9652–9655, 9657–9667	Age, ethnicity, education, smoking, height, physical activity, alcohol and energy intake
Reeves et al. (2007)[23]	United Kingdom	Women aged 50–64 years	1509 (1,222,630)	5.4 (mean)	ICD-10 code C82–C85	Age, geographical region, socioeconomic status, smoking, physical activity, reproductive history, time since menopause, use of hormone replacement therapy, and alcohol intake
Britton et al. (2008)[24]	Europe	Men and women aged 25–70 years	470 (141,425) (M) 481 (230,558) (W)	8.5	ICD-O-2, WHO classification of tumours of haematopoietic and lymphoid tissues	Age, study centre, education, and smoking
Söderberg et al. (2009)[25]	Sweden and Finland	Men and women aged 18–48 (younger cohort) and 43–96 (older cohort)	NHL 291, HL 34 (70,067)	34	NHL ICD-7 codes 200, 202 HL ICD-7 code 201	Age, sex, country, education, smoking, physical activity, diabetes, and alcohol intake
Pylypchuk et al. (2009)[26]	The Netherlands	Men and women aged 55–69 years	537 (120,852)	13.3	ICD-O-3 codes 9675, 9680, 9684, 9690–9698, 9671, 9761, 9699, 9670, 9823	Age and sex

Lu et al. (2009)[27]	United States	Women aged 22–84 years	574 (121,216)	12	ICD-O-3 codes 9590, 9591, 9670–9675, 9678–9699, 9727, 9823, 9832, 9835, 9836	Age, height, age at menarche, and physical activity
Kanda et al. (2010)[28]	Japan	Men and women aged 40–69 years	188 (94,547)	13 (mean)	ICD-O-3[d]	Age, sex, study area, smoking, and alcohol intake
Troy et al. (2010)[29]	United States	Men and women aged 55–74 years	731 (72,077) (M) 514 (70,905) (W)	8.8 (median)	Not specified	Age, sex, race/ethnicity, and education
Mortality						
Calle et al. (2003)[10]	United States	Men and women aged ⩾30	1355 (404,576)(M) 1029 (495,477) (W)	16	ICD-9 codes 202.0–202.9	Age, sex, education, smoking, physical activity, alcohol, marital status, race, aspirin use, fat consumption, vegetable consumption, and oestrogen replacement therapy (women)
Batty et al. (2005)[14]	United Kingdom	Men middle-aged (age NA)	158 (17,102)	28.1(median)	ICD8/9 codes 200–203, and ICD10 codes C81–C90[e]	Age, employment grade, physical activity, smoking, marital status, disease at entry, weight loss in the last year, blood pressure-lowering medication, height adjusted FEV1, triceps skinfold thickness, systolic blood pressure, plasma cholesterol, glucose intolerance, and diabetes status
Chiu et al. (2006)[17]	United States	Men and women aged 21–58 years (10th and 90th percentiles)	81 (20,314) (M) 48 (15,106) (W)	31 (mean)	ICD-8 codes 200 and 202, ICD-9 codes 200, 202.0–202.2, and 202.8–202.9, and ICD-10 codes C82–85 and C96.3	Age, race, education, smoking, and postload glucose levels
Reeves et al. (2007)[23]	United Kingdom	Women aged 50–64 years	535 (1,222,630)	7	ICD-10 code C82–C85	Age, geographical region, socioeconomic status, smoking, physical activity, reproductive history, time since menopause, use of hormone replacement therapy, and alcohol intake
Parr et al. (2010)[31]	Asia-Pacific region	Men and women aged 20–107 years	201 (401,215)	4 (median)	ICD-9 codes 200–202 and ICD-10 codes C81–C85[f]	Age, sex, study, and smoking

[a] *Abbreviation*: BMI, body mass index (the weight in kilograms divided by the square of height in metres); HL, Hodgkin's lymphoma; ICD, International Classification of Diseases; NHL, non-Hodgkin's lymphoma; WHO, World Health Organization.

[b] When NHL and HL is not specified, the number of cases and lymphoma classification are for NHL.

[c] ICD-O-2 codes 9590–9595, 9670–9675, 9677, 9680–9688, 9690–9698, 9700–9709, 9710–9717, 9761, 9764, 9800–9801, 9820–9828, 9850, 9940–9941, 9970.

[d] ICD-O-3 codes 9675 (B), 9680, 9684, 9690, 9691, 9695, 9698, 9699, 9835, 9670, 9823, 9702, 9673, 9687, 9689, 9700, 9705, 9709, 9714, 9718, 9719, 9832, 9591.

[e] Cases included chronic lymphocytic leukaemia and small lymphocytic lymphoma.

[f] Including Hodgkin lymphoma (ICD-10 code C81).

meta-analysis to summarise the results on BMI in relation to HL incidence.

2. Materials and methods

2.1. Study selection

We searched the PubMed database for prospective studies published from 1966 through May 2011, using the search terms body mass index, BMI, overweight, or obesity combined with lymphoma or Hodgkin's disease. No language restrictions were imposed. We also performed manual searches of references cited by relevant articles.

Studies were eligible for inclusion in this meta-analysis if the study had a prospective design and reported relative risks (RR) and 95% confidence intervals (CI) (or data to calculate them) for BMI (body weight in kilograms divided by the square of height in meters) in relation to NHL or HL incidence or mortality. Cohorts consisting of patients hospitalised with a diagnosis of diabetes were not included. In the event of multiple publications from the same study population, we included the study with the largest number of cases.

We identified 25 prospective studies[7–31] with data that were potentially eligible for inclusion in the present meta-analysis. Two studies[20,30] were excluded because of overlapping publications from the same study population. We further excluded three studies consisting of patients hospitalised with a diagnosis of obesity.[7,9,12] This left 20 studies for analysis, including 16 studies of NHL incidence,[8,11,13,15,16,18,19,21–29] five studies of NHL mortality,[10,14,17,23,31] and five studies on HL incidence.[13,19,21,22,25]

2.2. Data extraction

For each study, the following data were extracted: first author's last name; publication year; country in which the study was performed; number of cases and sample size; characteristics of participant (sex and age); years of follow-up; method of assessment of body weight and height (self-reported or measured); outcome classification; variables adjusted for in the multivariable analysis; and RRs with corresponding 95% CIs. From each study, we extracted the RRs that were adjusted for the largest number of potential confounders.

2.3. Statistical analysis

For each study, we estimated a RR with corresponding 95% CI for a 5 kg/m^2 increase in BMI. The method proposed by Greenland and Longnecker[32] and Orsini et al.[33] was used to compute the trend from the correlated log RR estimates across BMI categories. We used an increase of 5 kg/m^2 in BMI, which

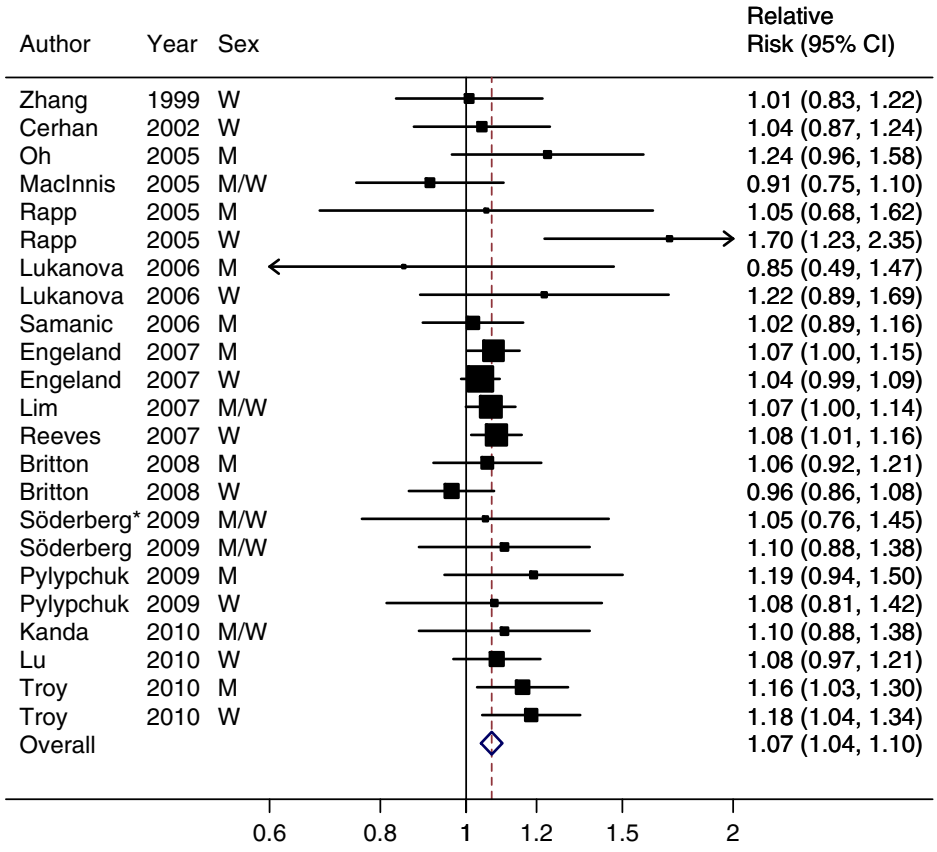

Fig. 1 – Relative risks of non-Hodgkin's lymphoma incidence per 5 kg/m^2 increase in body mass index. *Abbreviations:* M, men; W, women. Relative risks are presented separately for men and women wherever these data were available. Test for heterogeneity: Q = 24.34, p = 0.33, I^2 = 9.6%. *For the study by Söderberg et al. one relative risk is for the younger cohort (18–48 years) and the other for the older cohort (43–96 years).

corresponds to 15.7 kg for a man of an average height (1.77 m) and 13.5 kg for a woman (1.64 m). Study-specific RR estimates were combined using a random-effects model.[34]

Statistical heterogeneity among studies was evaluated using the Q and I^2 statistics.[35] For NHL incidence, we conducted subgroup analyses by sex, geographic region, assessment of body weight and height (self-reported versus measured), adjustment for smoking or physical activity, and NHL subtypes. Publication bias was assessed using the test proposed by Egger et al.[36] All statistical analyses were performed with Stata (version 10.1; StataCorp., College Station, TX). A *P*-value <0.05 was considered statistically significant.

3. Results

3.1. *Non-Hodgkin's lymphoma*

The prospective studies of BMI in relation to NHL incidence ($n = 16$; total 17,291 cases) and/or mortality ($n = 5$; total 3407 cases) were published between 1999 and 2010 (Table 1). Of these, 10 were from Europe, seven from the United States, three from Asia, and one from Australia. Body weight and height were measured by researchers in nine studies[13–19,21,24] and self-reported in 11 studies.[8,10,11,22,23,25–29,31]

When the risk estimates from all studies of BMI and NHL incidence were combined, a 5 kg/m^2 increment in BMI was associated with a 7% increased risk of NHL (RR, 1.07; 95% CI, 1.04–1.10) (Fig. 1). There was no statistically significant heterogeneity among studies ($p = 0.33$, $I^2 = 9.6\%$). Excluding the large study by Engeland et al.[21] did not change the results appreciably (RR, 1.08; 95% CI, 1.04–1.12). We found no evidence of publication bias assessed by Egger's test ($p = 0.27$). There were no statistically significant differences in the association between BMI and NHL incidence across strata of sex, geographic area, years of follow-up, assessment of weight and height, or adjustment for smoking or physical activity (Table 2).

Six studies[11,22,24,26,27,29] reported results for NHL subtypes. Meta-analysis of these studies found that BMI was significantly positively associated with risk of diffuse large B-cell lymphoma but not follicular lymphoma or small lymphocytic lymphoma and B-cell chronic lymphocytic leukaemia (Fig. 2). The difference in risk estimates between subtypes was not statistically significant ($P = 0.10$).

The association between BMI and NHL mortality are presented in Fig. 3. The summary RR of NHL mortality associated with a 5 kg/m^2 increase in BMI was 1.14 (95% CI, 1.04–1.26). However, there was some heterogeneity among studies ($p = 0.04$, $I^2 = 53.6\%$). We found no evidence of publication bias assessed by Egger's test ($p = 0.55$).

3.2. *Hodgkin's lymphoma*

The five studies of BMI and incidence of HL (total of 1557 cases)[13,19,21,22,25] were published between 2005 and 2009

Table 2 – Relative risks of non-Hodgkin's lymphoma for a 5 kg/m^2 increase in body mass index.

	Studies (*n*)	RR (95% CI)	Tests for heterogeneity	
			p-Value	I^{2a} (%)
Sex				
Men	8	1.09 (1.04–1.14)	0.69	0
Women	10	1.07 (1.02–1.13)	0.07	44.1
Men and women	4	1.06 (1.00–1.12)	0.61	0
p-Value difference[b,c]			0.64	
Geographic region				
Europe	8	1.06 (1.02–1.10)	0.31	13.3
United States	5	1.09 (1.04–1.14)	0.55	0
Asia	2	1.16 (0.98–1.37)	0.51	0
p-Value difference[b]			0.15	
Assessment of weight and height				
Measured	7	1.05 (0.99–1.11)	0.08	40.2
Self-reported	9	1.09 (1.05–1.13)	0.95	0
p-Value difference[b]			0.10	
Years of follow-up				
<12 years	6	1.06 (0.99–1.14)	0.03	54.0
⩾12 years	10	1.07 (1.04–1.10)	0.83	0
p-Value difference[b]			0.62	
Adjustment for smoking				
Yes	10	1.07 (1.02–1.11)	0.31	13.6
No	6	1.07 (1.03–1.12)	0.32	13.8
p-Value difference[b]			0.77	
Adjustment for physical activity				
Yes	5	1.08 (1.04–1.12)	0.93	0
No	11	1.07 (1.02–1.11)	0.13	28.7
p-Value difference[b]			0.57	

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

[a] I^2 is interpreted as the proportion of total variation contributed by between-study variation.

[b] *p*-Value for difference in the strength of the association across strata.

[c] *p*-Value for difference between men and women (men and women combined not included).

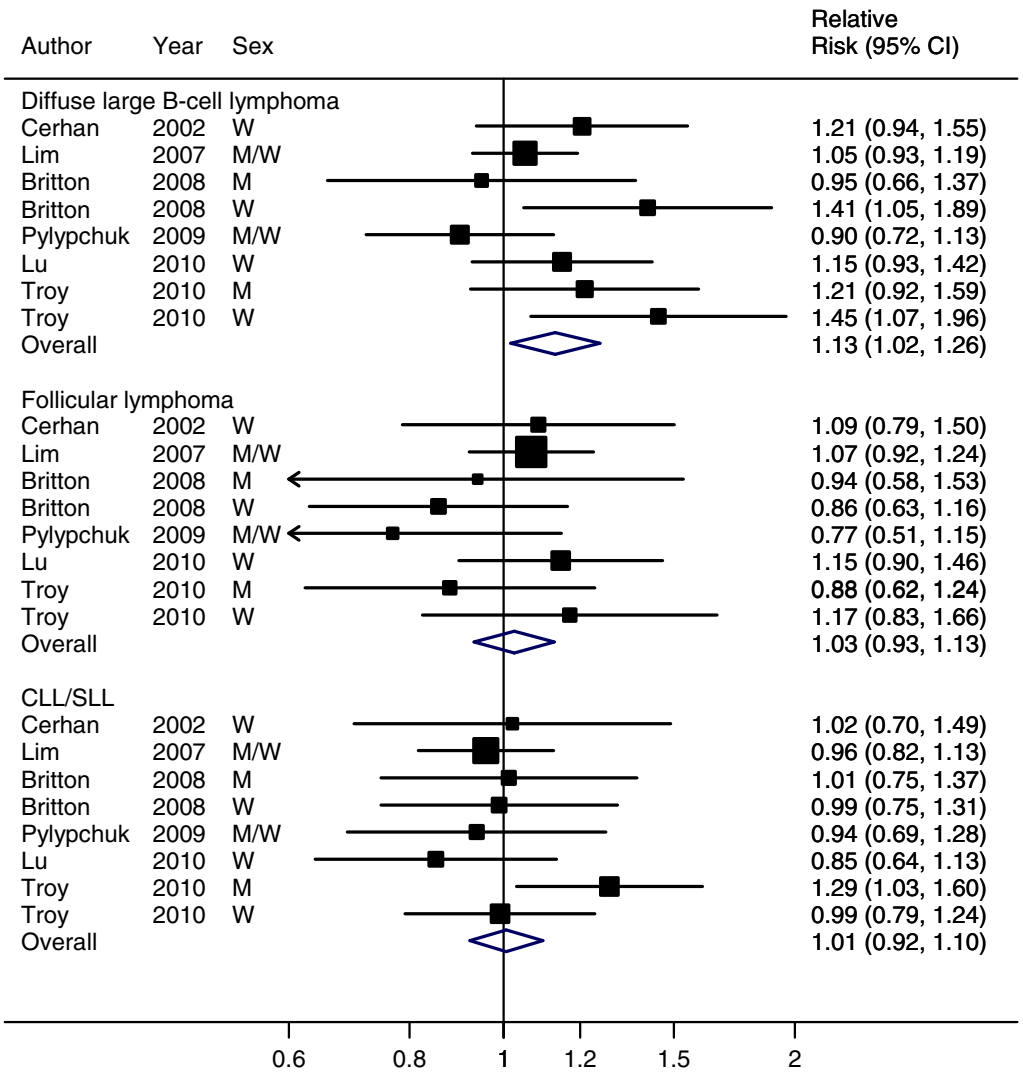

Fig. 2 – Relative risks of non-Hodgkin's lymphoma incidence per 5 kg/m^2 increase in body mass index, stratified by subtype. *Abbreviations:* CLL, B-cell chronic lymphocytic leukaemia; M, men; SLL, small lymphocytic lymphoma; W, women. Tests for heterogeneity: Q = 11.11, p = 0.13, I^2 = 37% for diffuse large B-cell lymphoma; Q = 5.95, p = 0.55, I^2 = 0% for follicular lymphoma; Q = 6.64, p = 0.47, I^2 = 0% for CLL/SLL.

(Table 1). We found evidence of a nonlinear relationship between BMI and HL (P for nonlinearity = 0.01). Therefore, we pooled the RRs for the overweight and obesity categories rather than the RRs per 5 kg/m^2 increase in BMI. Obesity but not overweight was statistically significantly associated with increased risk of HL (Fig. 4). There was no statistically significant heterogeneity among studies. Excluding the large study by Engeland et al.[21] did not change the results appreciably (RR, 1.09; 95% CI, 0.79–1.49 for overweight and RR, 1.44; 95% CI, 0.94–2.19 for obesity). No evidence of substantial publication bias was observed (p = 0.10 for overweight and p = 0.74 for obesity).

4. Discussion

This meta-analysis of prospective studies indicates that BMI is weakly positively associated with risk of NHL, particularly diffuse large B-cell lymphoma. Overall, the risk of total NHL and diffuse large B-cell lymphoma increased by 7% and 13% per 5 kg/m^2 increment in BMI. Moreover, a 5 kg/m^2 increase in BMI was associated with a 14% increase in NHL mortality. Obesity but not overweight was significantly positively associated with risk of HL. Given the high prevalence of overweight and obesity, even small increases in risk of NHL and HL associated with excess body weight have large public health consequences.

In a previous meta-analysis of the association between BMI and risk of NHL, including 10 prospective and six case-control studies published to February 2007, the summary RRs of NHL were 1.07 (95% CI, 1.01–1.14) for overweight and 1.20 (95% CI, 1.07–1.34) for obesity.[5] In another meta-analysis including nine prospective studies of NHL incidence, the summary RRs of NHL for a 5 kg/m^2 increase in BMI were 1.06 (95% CI, 1.03–1.09) in men and 1.07 (95% CI, 1.00–1.14) in women,[6] which are similar to the risk estimates observed in the present meta-analysis.

As a meta-analysis of observational studies, our study has several limitations that are based primarily on the quality and availability of published studies. First, the possibility that the

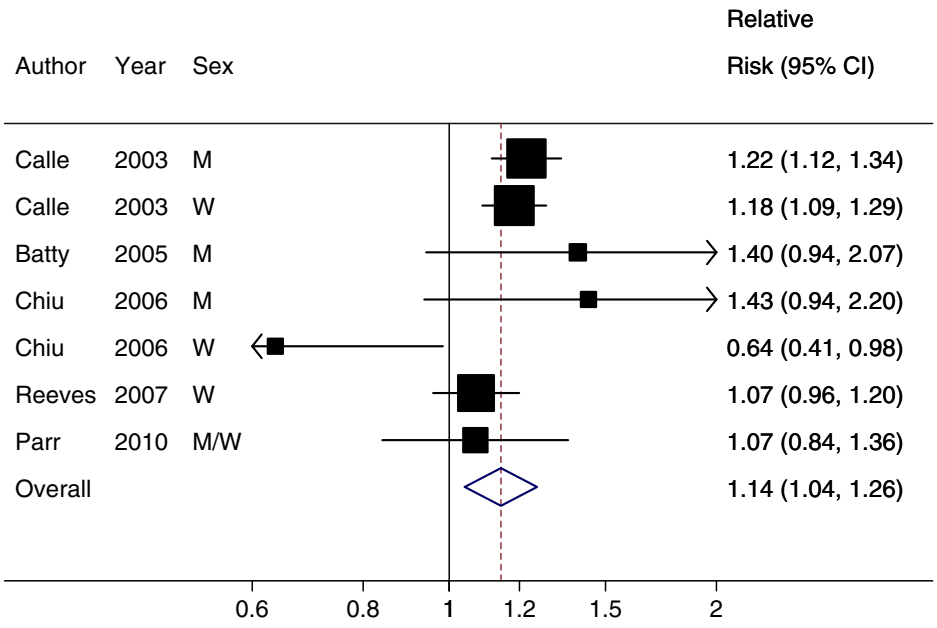

Fig. 3 – Relative risks of non-Hodgkin's lymphoma mortality per 5 kg/m^2 increase in body mass index. *Abbreviations:* M, men; W, women. Test for heterogeneity: Q = 12.94, p = 0.04, I^2 = 53.6%.

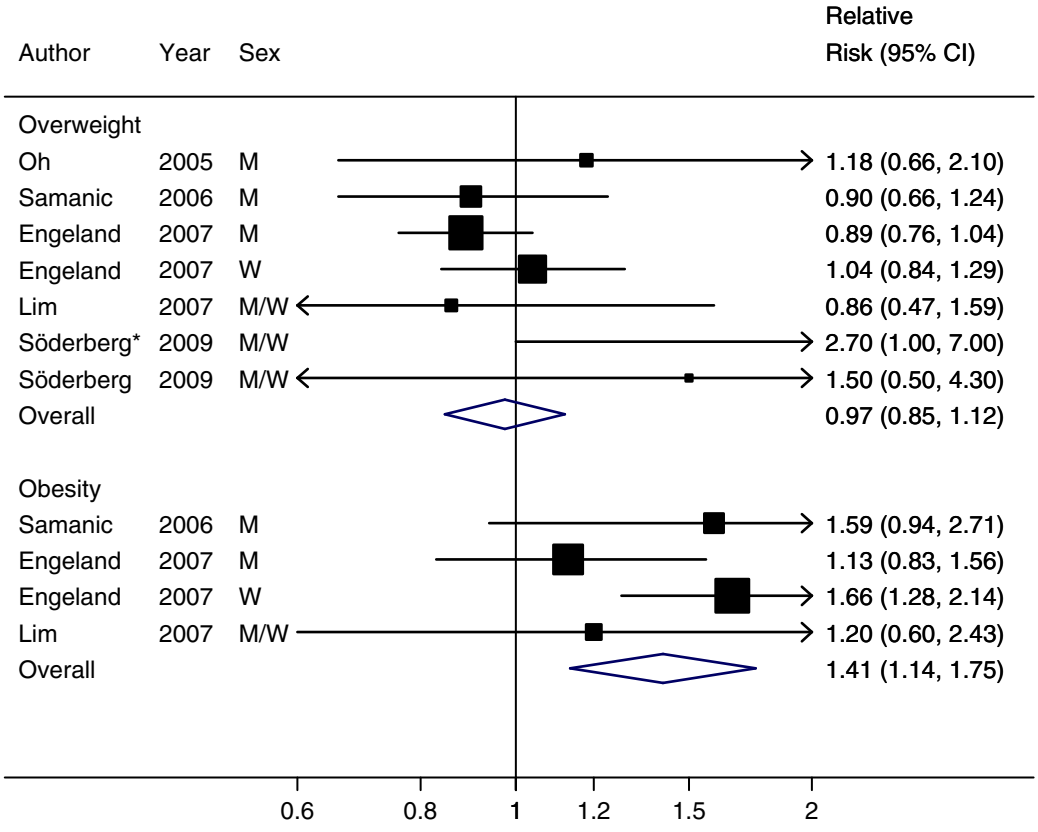

Fig. 4 – Relative risks of Hodgkin's lymphoma incidence associated with overweight (BMI 25.0–29.9 kg/m^2) and obesity (⩾30 kg/m^2). *Abbreviations:* M, men; W, women. Tests for heterogeneity: Q = 7.20, p = 0.30, I^2 = 16.7% for overweight; Q = 3.83, p = 0.28, I^2 = 21.6% for obesity. *For the study by Söderberg et al. one relative risk is for the younger cohort (18–48 years) and the other for the older cohort (43–96 years).

observed associations of obesity with NHL and HL were due to bias should be considered. Because this meta-analysis was based on data from prospective studies, selection and non-differential recall bias was minimised. Second, individual studies may have failed to control for potential confounders. All studies were adjusted for age and sex (where

applicable). Several studies also adjusted for smoking and/or physical activity, although these factors have only been weakly or not associated with risk of NHL[22,29,37–39] and HL[22,38,40,41] in epidemiologic studies. The observed positive association between obesity and risk of NHL persisted in analyses restricted to studies adjusting for smoking or physical activity. Among the five studies of HL, four adjusted for smoking[13,19,22,25] and three for physical activity.[13,22,25] However, because of the observational design of the included studies we cannot exclude the possibility that the observed association between excess body weight and NHL and HL may be due to residual or unmeasured confounding. A third limitation is that all cohort studies assessed body weight only once (at baseline), and changes in weight during follow-up may have attenuated the association between BMI and lymphoma risk. Fourth, the nomenclature and classification of NHL has changed over the past 2 decades and this could introduce heterogeneity among studies. Evidence of significant heterogeneity was only observed for NHL mortality. The study by Chiu et al.[17] which had a small number of cases, appeared to be the source of heterogeneity in the analysis of BMI and NHL mortality. Finally, as a meta-analysis of published studies, the possibility of publication bias should be considered because small studies with null results tend not to be published. In this meta-analysis, we found no evidence for such bias.

There are several potential mechanisms whereby excess body weight may increase the risk of NHL and HL. First, obesity leads to changes in circulating levels of adipocytokines, including adiponectin, resistin, and leptin. These adipocyte-derived hormones affect insulin resistance, immunity, and inflammation.[3] Several autoimmune and chronic inflammatory conditions are associated with increased risk of NHL.[2] Studies *in vitro* and in animal models have shown that adiponectin have anti-inflammatory properties and reduces cell proliferation, whereas leptin have pro-inflammatory properties and promotes the growth of some cancer cells.[3] Moreover, *in vitro* studies have shown that leptin stimulates the proliferation of normal haematopoietic cells[42] and circulating monocytes producing pro-inflammatory cytokines.[43]

Obesity may also increase the risk of malignant lymphoma through insulin resistance and compensatory hyperinsulinemia. Elevated insulin levels lead to increased bioavailable insulin-like growth factor-I (IGF-I). IGF-I act as growth factor that promote cell proliferation and inhibit apoptosis through IGF-I receptor-mediated signalling mechanisms in various tissues, including haematopoietic cells.[44,45] It has been found that IGF-I affects in a dose-dependent manner the proliferation of lymphoma cell lines.[45]

In summary, this meta-analysis of prospective studies indicates that BMI is positively associated with risk of NHL, especially diffuse large B-cell lymphoma. Results also showed a significant positive association between obesity and risk of HL. Additional studies are needed to assess whether the association between excess body weight and NHL is limited to diffuse large B-cell lymphoma. In addition, more studies are warranted to establish a potential causal relationship between BMI and risk of HL.

Conflict of interest statement

None declared.

Acknowledgements

This work was supported by research Grants from the Swedish Cancer Foundation. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

REFERENCES

1. Smedby KE, Askling J, Mariette X, Baecklund E. Autoimmune and inflammatory disorders and risk of malignant lymphomas – an update. *J Intern Med* 2008;**264**:514–27.
2. Smedby KE, Baecklund E, Askling J. Malignant lymphomas in autoimmunity and inflammation: a review of risks, risk factors, and lymphoma characteristics. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:2069–77.
3. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006;**6**:772–83.
4. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004;**4**:579–91.
5. Larsson SC, Wolk A. Obesity and risk of non-Hodgkin's lymphoma: a meta-analysis. *Int J Cancer* 2007;**121**:1564–70.
6. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;**371**:569–78.
7. Møller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. *Eur J Cancer* 1994;**30A**:344–50.
8. Zhang S, Hunter DJ, Rosner BA, et al. Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. *J Natl Cancer Inst* 1999;**91**:1751–8.
9. Wolk A, Gridley G, Svensson M, et al. A prospective study of obesity and cancer risk (Sweden). *Cancer Causes Control* 2001;**12**:13–21.
10. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med* 2003;**348**:1625–38.
11. Cerhan JR, Janney CA, Vachon CM, et al. Anthropometric characteristics, physical activity, and risk of non-Hodgkin's lymphoma subtypes and B-cell chronic lymphocytic leukemia: a prospective study. *Am J Epidemiol* 2002;**156**:527–35.
12. Samanic C, Gridley G, Chow WH, et al. Obesity and cancer risk among white and black United States veterans. *Cancer Causes Control* 2004;**15**:35–43.
13. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. *J Clin Oncol* 2005;**23**:4742–54.
14. Batty GD, Shipley MJ, Jarrett RJ, et al. Obesity and overweight in relation to organ-specific cancer mortality in London (UK): findings from the original Whitehall study. *Int J Obes (Lond)* 2005;**29**:1267–74.

15. MacInnis RJ, English DR, Hopper JL, Giles GG. Body size and composition and the risk of lymphohematopoietic malignancies. *J Natl Cancer Inst* 2005;**97**:1154–7.
16. Rapp K, Schroeder J, Klenk J, et al. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. *Br J Cancer* 2005;**93**:1062–7.
17. Chiu BC, Gapstur SM, Greenland P, Wang R, Dyer A. Body mass index, abnormal glucose metabolism, and mortality from hematopoietic cancer. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:2348–54.
18. Lukanova A, Bjor O, Kaaks R, et al. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. *Int J Cancer* 2006;**118**:458–66.
19. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF. Relation of body mass index to cancer risk in 362, 552 Swedish men. *Cancer Causes Control* 2006;**17**:901–9.
20. Fernberg P, Odenbro A, Bellocco R, et al. Tobacco use, body mass index and the risk of malignant lymphomas – a nationwide cohort study in Sweden. *Int J Cancer* 2006;**118**:2298–302.
21. Engeland A, Tretli S, Hansen S, Bjorge T. Height and body mass index and risk of lymphohematopoietic malignancies in two million Norwegian men and women. *Am J Epidemiol* 2007;**165**:44–52.
22. Lim U, Morton LM, Subar AF, et al. Alcohol, smoking, and body size in relation to incident Hodgkin's and non-Hodgkin's lymphoma risk. *Am J Epidemiol* 2007;**166**:697–708.
23. Reeves GK, Pirie K, Beral V, et al. Cancer incidence, mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 2007;**335**:1134.
24. Britton JA, Khan AE, Rohrmann S, et al. Anthropometric characteristics and non-Hodgkin's lymphoma and multiple myeloma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Haematologica* 2008;**93**:1666–77.
25. Söderberg KC, Kaprio J, Verkasalo PK, et al. Overweight, obesity and risk of haematological malignancies: a cohort study of Swedish and Finnish twins. *Eur J Cancer* 2009;**45**:1232–8.
26. Pylypchuk RD, Schouten LJ, Goldbohm RA, Schouten HC, van den Brandt PA. Body mass index, height, and risk of lymphatic malignancies: a prospective cohort study. *Am J Epidemiol* 2009;**170**:297–307.
27. Lu Y, Prescott J, Sullivan-Halley J, et al. Body size, recreational physical activity, and B-cell non-Hodgkin lymphoma risk among women in the California teachers study. *Am J Epidemiol* 2009;**170**:1231–40.
28. Kanda J, Matsuo K, Inoue M, et al. Association of anthropometric characteristics with the risk of malignant lymphoma and plasma cell myeloma in a Japanese population: a population-based cohort study. *Cancer Epidemiol Biomarkers Prev* 2010;**19**:1623–31.
29. Troy JD, Hartge P, Weissfeld JL, et al. Associations between anthropometry, cigarette smoking, alcohol consumption, and non-Hodgkin lymphoma in the prostate, lung, Colorectal, and ovarian cancer screening trial. *Am J Epidemiol* 2010;**171**:1270–81.
30. Tsai HT, Cross AJ, Graubard BI, et al. Dietary factors and risk of chronic lymphocytic leukemia and small lymphocytic lymphoma: a pooled analysis of two prospective studies. *Cancer Epidemiol Biomarkers Prev* 2010;**19**:2680–4.
31. Parr CL, Batty GD, Lam TH, et al. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424, 519 participants. *Lancet Oncol* 2010;**11**:741–52.
32. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose–response data, with applications to meta-analysis. *Am J Epidemiol* 1992;**135**:1301–9.
33. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose–response data. *Stata Journal* 2006;**6**:40–57.
34. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88.
35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–58.
36. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.
37. van Veldhoven CM, Khan AE, Teucher B, et al. Physical activity and lymphoid neoplasms in the European Prospective Investigation into Cancer and nutrition (EPIC). *Eur J Cancer*; 2010.
38. Cerhan JR, Bernstein L, Severson RK, et al. Anthropometrics, physical activity, related medical conditions, and the risk of non-hodgkin lymphoma. *Cancer Causes Control* 2005;**16**:1203–14.
39. Morton LM, Hartge P, Holford TR, et al. Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (interlymph). *Cancer Epidemiol Biomarkers Prev* 2005;**14**:925–33.
40. Besson H, Brennan P, Becker N, et al. Tobacco smoking, alcohol drinking and Hodgkin's lymphoma: a European multicentre case-control study (EPILYMPH). *Br J Cancer* 2006;**95**:378–84.
41. Nieters A, Deeg E, Becker N. Tobacco and alcohol consumption and risk of lymphoma: results of a population-based case-control study in Germany. *Int J Cancer* 2006;**118**:422–30.
42. Gainsford T, Willson TA, Metcalf D, et al. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. *Proc Natl Acad Sci U S A* 1996;**93**:14564–8.
43. Santos-Alvarez J, Goberna R, Sanchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. *Cell Immunol* 1999;**194**:6–11.
44. Le Roith D. Regulation of proliferation and apoptosis by the insulin-like growth factor I receptor. *Growth Horm IGF Res* 2000;**10**(Suppl. A):S12–3.
45. Mitsiades CS, Mitsiades NS, McMullan CJ, et al. Inhibition of the insulin-like growth factor receptor-1 tyrosine kinase activity as a therapeutic strategy for multiple myeloma, other hematologic malignancies, and solid tumors. *Cancer Cell* 2004;**5**:221–30.