Body Mass Index, Abnormal Glucose Metabolism, and Mortality from Hematopoietic Cancer

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Abstract

Background: **High body mass index (BMI) and diabetes have been linked to risk of non-Hodgkin's lymphoma (NHL), but results are inconsistent and most studies use self-reported information. No study has evaluated the association of NHL with postload plasma glucose (PLG) levels, which are positively associated with BMI. We analyzed data from a cohort study to investigate associations of interviewer-measured BMI and PLG with risk of NHL mortality and to explore associations with leukemia and multiple myeloma.**
Methods: **Employees of 84 Chicago-area organizations, with an average age of 40 years at baseline, were screened from 1967 to 1973. Height and weight were measured by study nurses. A 50-g oral glucose load was administered to nondiabetic participants. Of the at-risk cohort of 35,420 men and women, 129 died of NHL, 151 died of leukemia, and 66 died of multiple myeloma during an average of 31 years of follow-up. Hazard Ratios (HR) and 95% confidence intervals (95% CI) were derived from Cox proportional hazards regression models.**
Results: **Among men, there were positive dose-response relations of BMI with mortality from NHL (HR, 2.57; 95% CI, 1.24-5.34 for the highest versus lowest quartile; P_{trend} = 0.01) and leukemia (HR, 1.98; 1.07-3.69; P_{trend} = 0.02). PLG also was positively related to NHL mortality (HR, 2.86; 95% CI, 1.35-6.06 for the highest versus lowest category; P_{trend} = 0.004). For women, a higher BMI was positively associated with leukemia mortality (HR, 2.47; 95% CI, 0.96-6.36; P_{trend} = 0.02) and the highest level of PLG was associated with risk of mortality from multiple myeloma (HR, 3.06; 95% CI, 1.05-8.93). The risk estimates for BMI and PLG remained unchanged after adjustment for each factor.**
Conclusions: **High BMI and/or abnormal PLG is associated with higher risk of mortality from NHL and possibly leukemia and from myeloma in women. These findings might have public health significance because BMI and glucose levels are amenable to modification.** (Cancer Epidemiol Biomarkers Prev 2006;15(12):2348–54)

Introduction

The incidence of non-Hodgkin's lymphoma (NHL) in the United States increased by ~80% from 1970 to 1990 (1). Although the steep increase in incidence slowed in the late 1990s, due in part to a decline in acquired immunodeficiency syndrome (AIDS), incidence of NHL types not associated with AIDS (e.g., follicular lymphoma and small lymphocytic lymphoma) and NHL in groups at low risk of AIDS, such as men ages 55 years and older and women of all ages, has continued to increase throughout the 1990s (2, 3). The increasing incidence of NHL is poorly understood (2). The prevalence of obesity increased by 60% between the 1970s and the 1990s (4) and by 74% since 1991 (5). Obesity and weight gain are associated with insulin resistance and hyperinsulinemia, which could lead to the subsequent development of non-insulin-dependent diabetes mellitus, a postulated risk factor for NHL (6, 7). The prevalence of diabetes has increased by 61% since 1991, and 3.4% of U.S. adults are both obese and have diabetes (5). Because the increasing prevalence of obesity and diabetes has paralleled the rapid increase in the incidence of NHL, it is possible that the rising prevalence of obesity and diabetes might explain, at least partly, the upward trend of NHL.

Previous reports on the associations of body weight (8-23) and diabetes (6, 7, 24-27) with risk of NHL have been inconsistent. Four cohort studies (8, 12, 20, 23) reported a positive association between body weight and lymphoma incidence (12, 20, 23) or mortality (8), whereas five cohort studies (9-11, 19, 22) reported no association. Similarly, of the eight cohort studies (6, 7, 22, 24-28) evaluating the association of diabetes and risk of NHL, four found a positive association with NHL incidence (6, 7, 25) or mortality (24), whereas the rest reported no association (22, 27, 28). Major limitations of previous studies include the use of self-reported height, weight, or diabetes, lack of information on type of diabetes, and the use of unrepresentative groups of hospitalized patients with obesity or diabetes.

To address these issues, we investigated the associations of body mass index (BMI) and postload plasma glucose (PLG) levels with NHL mortality in the Chicago Heart Association Detection Project in Industry. We hypothesize that a potential association of BMI with risk of NHL mortality might be mediated through abnormal glucose metabolism. In an early analysis of the Chicago Heart Association cohort based on 12 years of follow-up, individuals who died of hematologic or lymphatic cancer (n = 54) had a higher baseline PLG concentration than the remainder of the cohort (29). We now report data based on 31 years of follow-up with 129 NHL cases. We also explored the associations of BMI and PLG with mortality from leukemia and multiple myeloma because they also are cancers of blood-forming organs (i.e., hematopoietic cancers) and might share common risk factors.

Materials and Methods

Participants and Baseline Examination. Between November 1967 and January 1973, ~75,000 employees of 84 companies and organizations in the Chicago area were invited to participate in a screening program of cardiovascular disease risk. The number of participants in the screening program was

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39,522 (22,400 men and 17,122 women). Detailed methods for recruitment and data collection have been reported (30). Informed consent was obtained from each study participant. The study has been periodically approved by the Northwestern University Institutional Review Board.

At the screening site, a self-administered questionnaire was used to collect demographic data, smoking history, and information on previous medical diagnoses and treatment. Study nurses or technicians measured height, weight, blood pressure, and electrocardiogram and collected blood for serum total cholesterol. A 50-g oral glucose load was administered to nondiabetic participants without regard to fasting status or time of day. Blood was drawn ~1 h after loading for measurement of plasma glucose. Plasma was separated within 2 h and analysis of glucose concentration was done with an AutoAnalyzer (Technicon Instruments, Tarrytown, NY) using the method described by Hoffman (31).

Mortality Follow-up of the Cohort. Men and women enrolled in the Chicago Heart Association cohort were followed up to determine vital status through December 2002. Before 1979, deaths were ascertained annually through direct mailings to individuals at their last known address, submission of records to the Social Security Administration, mailing to employers, and direct telephone or neighborhood contact. After 1979, cohort records were matched periodically to the National Death Index.

Before 1995, death certificates were obtained from State Departments of Health for all decedents. Physicians coded certificates for underlying and multiple causes of death. Beginning with 1995, National Death Index Plus is being used to identify decedents and to obtain underlying causes of death. Using these serial methods of ascertainment, only 86 individuals (0.22% of the total Chicago Heart Association cohort) have never been traced. The follow-up period covers International Classification of Diseases (ICD) 8 (1968-1978), ICD-9 (1979-1998), and ICD-10 (1999+). Deaths due to NHL were assigned to 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. Deaths due to leukemia were assigned to ICD-8 codes 204-207, ICD-9 codes 202.4, 203.1, and 204-208, and ICD-10 codes C90.1 and C91-C95. Deaths due to myeloma were assigned to ICD-8 code 203, ICD-9 codes 203.0 and 238.6, and ICD-10 codes C90.0 and C90.2.

Data Analysis. Before data analysis, we excluded individuals with missing data for height and weight (n = 13), with self-reported diabetes at baseline (n = 888), as well as subjects who at baseline (a) did not have diabetes and did not receive a 50-g oral glucose load (n = 189), (b) were missing glucose (n = 506), (c) did not answer the question on history of diabetes (n = 125), or (d) had blood drawn <30 min (n = 1) or >65 min (n = 1,728) after the administration of glucose, and (e) whose time of blood drawing was unknown (n = 566). Some individuals were excluded for more than one of the above reasons. After exclusion, the at-risk cohort for this analysis was 35,420 (20,314 men and 15,106 women). In this sample, 129 died of NHL (81 men and 48 women), 151 died of leukemia (101 men and 47 women), and 66 died of multiple myeloma (38 men and 28 women).

BMI, an indirect measure of adiposity, was calculated as weight divided by the square of height (kg/m^2). We calculated quartiles of BMI for men and women separately. We further defined individuals as normal weight (BMI, 18.5-24.9 kg/m^2), overweight (BMI, 25.0-29.9 kg/m^2), and obese (BMI, ≥30.0 kg/m^2) according to categories proposed by the WHO (32). The results were similar using both measurements, and therefore only the quartile analyses are presented.

Participants were grouped into four PLG levels: ≤119, 120 to 159, 160 to 199, and ≥200 mg/dL (≤6.6, 6.7-8.8, 8.9-11.0, and ≥11.1 mmol/L). There are no standard criteria for defining asymptomatic hyperglycemia for a 50-g challenge at 1 h; however, a cut point of 200 mg/dL (11.1 mmol/L) was used in previous publication of this cohort (30). The next two lower categories each represent the range for ~1 SD [40 mg/dL (2.2 mmol/L)] and 2 SD lower PLG levels, respectively.

Person-years of follow-up for each individual were computed as the amount of time from baseline examination date to date of death or until December 31, 2002. Sex-specific, age-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CI) were computed using Cox proportional hazards regression (33). Possible confounding was examined by comparing the prevalence or mean level of covariates across PLG levels or BMI categories.

Independent associations of BMI, PLG levels, and other risk factors with mortality from NHL, leukemia, and myeloma were determined for men, women, and men and women combined. Potential risk factors included in the analysis were age, race, and cigarette smoking status. Trend tests were conducted by assigning to each individual the mean value of a risk factor in its category and modeling this as a continuous variable. Because a potential association of BMI with risk of hematopoietic cancer mortality might be mediated through PLG level, multivariate models for the relations with BMI and with PLG were computed with and without inclusion of the other variable. The possibility that occult or incipient hematopoietic cancer at baseline may be responsible for elevated PLG levels in subjects who subsequently died of hematopoietic cancer was evaluated by testing the proportional hazards assumption using methods described by Cox (33) and Quantin et al. (34). Analyses were conducted using PROC PHREG of the SAS-PC statistical software program (SAS Institute, Inc., Cary, NC).

Results

Table 1 shows selected baseline characteristics by sex. Median for age was ~40 years for both men and women. Medians for BMI and PLG level were slightly higher for men than for women. More men than women completed more than a high school education. At baseline, ~44% of men and 39% of women were current smokers. The cohort was predominantly white.

For men and women, medians for age and PLG level were higher with higher levels of BMI (Table 2). Across BMI quartiles, the proportion of participants with less than a high

Table 1. Selected baseline characteristics of men and women in the Chicago Heart Association Detection Project in Industry, 1967-1973

Characteristics	Men	Women
Age (y)*	39.0 (24, 58)	41.0 (21, 58)
BMI*,†	26.3 (22.2, 31.1)	23.2 (19.4, 29.8)
Plasma glucose level (mg/dL)*	125.0 (88.0, 190.0)	120.0 (85.0, 185.0)
Education, n (%)		
<High school	3,976 (19.6)	3,175 (21.0)
High school	6,263 (30.8)	7,527 (49.8)
>High school	10,075 (49.6)	4,404 (29.2)
Cigarette smoking		
Never	5,394 (26.6)	6,761 (44.8)
Former	6,036 (29.7)	2,384 (15.8)
Current		
≤20 cigarettes/d	5,819 (28.7)	4,865 (32.2)
>20 cigarettes/d	3,065 (15.1)	1,096 (7.3)
Race, n (%)		
White	18,333 (90.3)	12,713 (84.2)
African American	1,340 (6.6)	2,005 (13.3)
Other	641 (3.2)	388 (2.6)

*Median value (10th and 90th percentile).
† Weight (kg)/height (m)^2.

Table 2. Selected baseline characteristics by quartiles of BMI in the Chicago Heart Association Detection Project in Industry, 1967-1973

	Men (n = 20,314)				Women (n = 15,106)			
	Q1 (≤24.12)	Q2 (24.13-26.30)	Q3 (26.31-28.61)	Q4 (≥28.62)	Q1 (≤20.98)	Q2 (20.99-23.24)	Q3 (23.25-26.15)	Q4 (≥26.16)
Number	5,085	5,115	5,037	5,077	3,805	3,748	3,780	3,773
Age (y)*	33 (22, 56)	38 (25, 57)	41 (26, 58)	43 (26, 59)	27 (20, 53)	39 (21, 57)	45 (22, 59)	48 (25, 61)
Plasma glucose (mg/dL)*	115 (83, 175)	123 (87, 185)	129 (90, 194)	136 (95, 205)	111 (82, 170)	118 (85, 180)	122 (87, 188)	134 (92, 196)
BMI*,†	22.7 (20.1, 23.9)	25.3 (24.4, 26.1)	27.4 (26.5, 28.4)	30.5 (28.9, 34.7)	19.7 (17.9, 20.8)	22.1 (21.3, 23.0)	24.5 (23.5, 25.8)	28.9 (26.6, 35.0)
Education (%)								
<High school	17.6	16.7	19.8	24.3	10.7	15.7	23.2	34.6
High school	30.6	28.3	31.0	33.4	52.3	52.0	50.5	44.6
>High school	51.8	55.0	49.2	42.3	37.1	32.4	26.4	20.8
Smoking (%)								
Never	24.7	27.3	26.4	27.8	38.8	41.4	46.5	52.3
Former	23.9	30.3	32.8	32.0	15.0	16.1	16.1	16.0
Current								
≤20 cigarettes/d	35.6	27.8	26.5	24.6	37.7	34.0	31.5	25.6
>20 cigarettes/d	15.8	14.6	14.3	15.6	8.5	8.5	6.0	6.1
Race (%)								
White	86.7	91.2	92.0	91.2	82.4	85.3	84.5	84.5
African American	9.1	5.7	5.3	6.3	14.7	12.1	13.1	13.2
Other	4.2	3.1	2.8	2.5	2.9	2.6	2.4	2.3

*Median value (10th and 90th percentile).
† Weight (kg)/height $(m)^2$.

school education increased. The proportion of never smokers increased and the proportion of current smokers decreased as BMI increased. For men, the proportion of African Americans was lower in the higher BMI quartiles, but there was little racial variation across BMI groups for women.

In men (Table 3), BMI was significantly and positively associated with mortality from NHL (P_{trend} = 0.01) and leukemia (P_{trend} = 0.03), but the association with multiple myeloma was weaker and not statistically significant. Similarly, PLG levels also were significantly and positively associated with NHL (P_{trend} = 0.02) and to a lesser extent with leukemia (P_{trend} = 0.11), but not with multiple myeloma. Men who smoked >20 cigarettes a day had a nearly 1.8-fold greater risk of dying of leukemia, although this relationship was only marginally significant (95% CI, 0.99-3.21), and there were no relations of smoking with NHL or multiple myeloma. A higher level of education seemed to be associated with a lower risk of dying of multiple myeloma but there were no associations between education and any of the other cancer types. African American men were at significantly greater risk of dying of multiple myeloma than white/other men, but there were no racial differences in mortality for NHL or leukemia. Self-reported diabetes at baseline was significantly associated with mortality from NHL (HR, 2.31; 95% CI, 1.01-5.32) but not leukemia or multiple myeloma (data not shown).

In women (Table 4), there was a suggestive inverse association between BMI and NHL mortality, although point estimates are only marginally significant and there was no gradient in risk. Conversely, BMI has a positive association with leukemia mortality (P_{trend} = 0.006) but has no association with multiple myeloma. A PLG level ≥200 mg/dL was associated with at least 2- to 3-fold higher risk of mortality due to leukemia or multiple myeloma but was not associated with NHL. There were no significant associations of education, cigarette smoking, or race with risk of mortality due to any malignancy in women. Additionally, there were no associations between self-reported diabetes at baseline and mortality from any types of hematopoietic cancer in women (data not shown).

To understand whether associations of BMI or PLG are related to risk of mortality through a common pathway, multivariable adjusted HRs (95% CI) were computed for each of these risk factors without (model 1) and with (model 2) inclusion of the other risk factor for each tumor type (Table 5). Among both men and women, there were no meaningful differences in the relation of BMI or PLG levels with or without inclusion of the other variable in the model. For men, there were strong, positive dose-response associations of BMI with NHL (HR, 2.57, for the highest versus the lowest quartile of BMI; P_{trend} = 0.01) and leukemia (HR, 1.98; P_{trend} = 0.02). PLG also was positively related to NHL (HR, 2.86, for the highest versus lowest category of PLG; P_{trend} = 0.004). Conversely, for women, the HR of NHL for the highest quartile of BMI was 0.47 (P_{trend} = 0.07). However, a higher BMI was associated with an increasing risk of leukemia mortality. In addition, the highest level of PLG was associated with a significant 3-fold higher risk of mortality from multiple myeloma. The associations with PLG and BMI levels in both men and women were similar after exclusion of deaths in the first 5 years of follow-up (data not shown). Because the associations for BMI with mortality from leukemia or multiple myeloma and PLG with leukemia mortality did not vary by sex, we further combined men and women in the analysis. We found that BMI was significantly associated with mortality from leukemia (HR, 2.11, for the highest versus the lowest quartile of BMI; 95% CI, 1.26-3.54; P_{trend} = 0.003) and PLG levels were also associated with mortality from leukemia (HR, 2.01; 95% CI, 1.20-3.54; P_{trend} = 0.007). Neither BMI nor PLG was associated with mortality from multiple myeloma in analyses combining men and women (data not shown).

Discussion

In this prospective study of U.S. men and women, high BMI was associated with an ~2-fold higher risk of mortality from NHL and leukemia in men and a 2.5-fold higher risk of mortality from leukemia in women. Additionally, high PLG was associated with risk of mortality from NHL in men and multiple myeloma in women. The increased risks for increasing BMI and PLG were independent of each other. The sex differences should be interpreted cautiously, given the small number of women who died of hematopoietic cancers.

Our findings of a positive association between BMI and risk of mortality from NHL and leukemia, but not multiple myeloma, are generally consistent with some studies, although

findings from cohort studies (8-12, 23, 35, 36), case-control studies (13-18), and population-based studies of hospital discharges (19-21) are in general inconclusive. Positive associations of BMI with NHL mortality in men and women were reported in the American Cancer Society Study of more than 900,000 U.S. adults (8), and in women (43 cases) but not in men (9 cases) in a Swedish study of 28,000 obese patients when compared with NHL incidence in the general population (20). A study of 781,283 Korean men (12) showed a positive association between BMI measured at baseline and risk of NHL incidence after 10 years of follow-up. A cohort of 145,000 Austrian adults (23) found that obesity was associated with risk of NHL incidence in women but not in men. In contrast, no association between BMI and NHL incidence was reported in a hospital-based cohort of 4.5 million male U.S. veterans (9), a record linkage study of 44,000 Danish obese individuals (19), and the Nurses' Health Study (11). Case-control studies also present an inconsistent picture of the association, with results ranging from significantly increased risk (13, 14, 17, 18) to no association (16). High BMI was associated with risk of certain subtypes of NHL in some studies (10, 15). In the Iowa Women's Health Study of more than 40,000 older women (10), BMI was not associated with the risk of NHL overall, follicular NHL, or diffuse NHL. However, BMI was positively associated with risk of B-cell chronic lymphocytic leukemia and inversely associated with risk of small lymphocytic lymphoma. In a large population-based case-control study, Chang et al. (15) found that although BMI was not associated with risk of NHL overall or some subtypes of NHL, there was evidence of a positive association with risk of diffuse large B-cell lymphoma. For multiple myeloma, body weight was significantly associated with myeloma incidence (9, 14, 37) and mortality (8), whereas no association with myeloma incidence was reported in two cohorts (20, 21). Few overall multiple myeloma cases may also explain the discrepancy. Positive associations were found in most (8, 9, 14, 19, 35), but not all (20), studies of BMI and risk of leukemia.

We found positive associations between PLG levels and mortality from NHL in men and multiple myeloma in women. To our knowledge, this is the first study that investigated PLG levels and risk of specific types of hematopoietic cancers. Two previous studies (29, 38) grouped different hematopoietic malignancies together. A positive association was reported in the Chicago Heart Association cohort based on 12 years of follow-up (29), whereas no association was reported in the Whitehall Study of 18,274 men in England over 18 to 20 years of follow-up (38). After 31 years of follow-up of the Chicago Heart Association cohort, a higher PLG level at baseline was a statistically significant predictor of overall hematopoietic cancer mortality in men (HR, 1.88; 95% CI, 1.18-3.00, for the highest versus lowest category; P_{trend} = 0.02) and in women (HR, 2.14; 95% CI, 1.23-3.73; P_{trend} = 0.04). Our data are consistent with findings from the American Cancer Society Study (24), in which a history of diabetes (type unknown) was positively associated with deaths due to NHL (HR, 1.21; 95% CI, 0.99-1.48) and multiple myeloma (HR, 1.27; 95% CI, 0.98-1.66), but not leukemia (HR, 0.88; 95% CI, 0.71-1.10). The Iowa Women's Health Study (6) also found a 2-fold higher risk of NHL among those with adult-onset diabetes (HR, 2.18; 95% CI, 1.22-3.90), and the risk increased with the duration of diabetes. Similarly, in a study of two cohorts of diabetic patients, Hjalgrim et al. (7) found that type II diabetes, but not type I diabetes, was associated with higher risk of NHL incidence. Of the other four studies comparing hematopoietic cancer rates in cohorts of diabetic patients to rates in the general population, two reported elevated risk for NHL incidence (25), one reported an excess risk for multiple myeloma incidence in women but not in men (26), and others found no association for NHL (26, 27) or leukemia incidence (26). In our study, self-reported diabetes at baseline (type unknown) was significantly associated with NHL mortality in men, but not in women, and there were no associations with leukemia and multiple myeloma in either sex.

Table 3. Age-adjusted HR for NHL, leukemia, and multiple myeloma mortality associated with potential risk factors among men in the Chicago Heart Association Detection Project in Industry, 1967-1973

Risk factors	Person-years	NHL		Leukemia		Multiple myeloma	
		No. deaths	HR (95% CI)	No. deaths	HR (95% CI)	No. deaths	HR (95% CI)
BMI*							
Q1 (≤24.12)	142,657	10	1.0	15	1.0	7	1.0
Q2 (24.13-26.30)	142,529	21	1.95 (0.92-4.15)	23	1.41 (0.74-2.71)	7	0.93 (0.33-2.64)
Q3 (26.31-28.61)	136,692	23	2.09 (0.99-4.40)	35	2.07 (1.13-3.80)	12	1.56 (0.61-3.96)
Q4 (≥28.62)	132,152	27	2.56 (1.24-5.30)	31	1.90 (1.02-3.53)	12	1.63 (0.64-4.17)
P_{trend} †			*0.01*		*0.03*		*0.20*
Plasma glucose level (mg/dL)							
≤119	253,926	20	1.0	28	1.0	14	1.0
120-159	183,768	31	1.81 (1.02-3.20)	45	1.74 (1.08-2.82)	19	1.41 (0.70-2.87)
160-199	80,356	18	2.06 (1.07-3.99)	17	1.24 (0.66-2.30)	3	0.41 (0.12-1.47)
≥200	35,981	12	2.82 (1.33-5.99)	14	1.98 (1.01-3.89)	2	0.52 (0.11-2.38)
P_{trend} †			*<0.01*		*0.11*		*0.20*
Cigarette smoking							
Never	153,888	25	1.0	27	1.0	14	1.0
Former	165,503	29	0.98 (0.58-1.68)	37	1.14 (0.70-1.88)	8	0.48 (0.20-1.15)
Current, ≤20 cigarettes/d	156,784	17	0.79 (0.43-1.47)	21	0.92 (0.52-1.62)	11	0.92 (0.41-2.03)
Current, >20 cigarettes/d	77,856	10	1.00 (0.48-2.08)	19	1.78 (0.99-3.21)	5	0.91 (0.33-2.55)
P_{trend} †			*0.69*		*0.21*		*0.97*
Education							
<High school	96,147	15	1.0	17	1.0	14	1.0
High school	169,585	27	1.30 (0.67-2.46)	38	1.74 (0.98-3.11)	14	0.73 (0.34-1.54)
>High school	288,299	39	1.18 (0.64-2.17)	49	1.46 (0.83-2.56)	10	0.33 (0.14-0.75)
P_{trend} †			*0.71*		*0.35*		*<0.01*
Race							
White/Other	518,122	78	1.0	102	1.0	32	1.0
African American	35,908	3	0.67 (0.21-2.12)	2	0.35 (0.09-1.41)	6	3.47 (1.44-8.36)

NOTE: HRs adjusted for six categories of age (≤49, 50-54, 55-59, 60-64, 65-69, and ≥70 y) using Cox proportional hazards regression.
*Weight (kg)/height $(m)^2$.
† *P* for trend was computed by modeling the within-category mean level of each risk factor as a continuous variable.

Our findings that BMI and PLG are both significantly associated with NHL mortality suggest that high BMI and diabetes might be related to risk of NHL through multiple pathways. First, high BMI, insulin resistance, and adult-onset diabetes may be associated with a proinflammatory state (39). The adipocyte secretes several inflammatory mediators, including tumor necrosis factor-α, a proinflammatory cytokine, and adiponectin, a protein with anti-inflammatory activities (39, 40). Obese individuals have higher plasma concentrations of tumor necrosis factor-α and interleukin-6 (39) and a lower level of adiponectin (40). Increased release of tumor necrosis factor-α and interleukin-6 gives rise to insulin resistance by suppressing insulin signal transduction (39). Consequently, this might interfere with the anti-inflammatory effect of insulin, which in turn promotes inflammation. Chronic inflammation may stimulate B-cell proliferation and predispose to B-cell malignancy, which accounts for 90% of NHL in the United States.

In addition, our findings that high BMI remains significantly associated with mortality for NHL and leukemia after adjustment for PLG suggest that the immunomodulatory effects of high BMI may act through mechanisms other than insulin resistance. Tumor necrosis factor is also involved in T-cell–dependent B-cell responses, T-cell proliferation, and receptor expression (41). A recent study found that a *G-308A* mutation of the tumor necrosis factor-α promoter was associated with risk of NHL (42). Leptin, another adipocyte-specific protein, is also elevated in obese individuals (39). Leptin, alone and in combination with other cytokines, stimulates proliferation of hematopoietic and leukemia cells (43). Increased level of leptin in obese individuals may shift the immune system toward a proinflammatory T helper-1 cell population while reducing the regulatory T helper-2 phenotype (44). Chronically, this proinflammatory shift may predispose to B-cell malignancy. A recent study found that genetic polymorphisms in the leptin and leptin receptor genes are associated with risk of NHL (13). Nevertheless, the specific role of leptin in the development of NHL has yet to be confirmed. Women generally have higher leptin levels than men (45) and have lower NHL risk (1).

High BMI is associated with several behaviors and lifestyles that might predispose to NHL or leukemia. For example, in obese individuals, total energy and fat intakes are higher and fruit and vegetable intakes are lower (46), a dietary pattern that has been associated with risk of NHL (2, 47, 48) and leukemia (49). In addition, obese individuals have increased storage and subsequent mobilization of fat-soluble pesticides and pesticide metabolites (50), risk factors associated with NHL (2, 51) and leukemia (52) and, possibly, multiple myeloma (53).

We found that higher levels of BMI and PLG are associated with NHL in men but not in women, and, indeed, there is a suggestive inverse association between BMI and NHL mortality in women. This inconsistency suggests that our findings may be due to chance. However, our data on BMI and mortality from leukemia and myeloma are consistent between men and women, arguing against this possibility. High BMI might be associated with only certain subsets of NHL (15-17), and there is evidence that some subtypes are distributed differently between men and women (54). Unfortunately, we do not have data on subtypes of NHL and leukemia to assess this possibility. In the Iowa Women's Health Study (10), there was an inverse association between baseline BMI and risk of small lymphocytic lymphoma. It is also possible that central adiposity, which occurs more frequently in men, may be a stronger risk factor than peripheral adiposity or general overweight. Finally, the discrepancy between men and women may be due to different effects of sex hormones on the immune response, with female hormones (e.g., estrogens) stimulating immune response and male hormones (e.g., androgens and testosterone) being immunosuppressive (55). This hypothesis is speculative, although exogenous estrogens in the form of hormone replacement therapy have been linked to lower risk of NHL in women (56).

Table 4. Age-adjusted HRs for NHL, leukemia, and multiple myeloma mortality associated with potential risk factors among women in the Chicago Heart Association Detection Project in Industry, 1967-1973

Risk factors	Person-years	NHL		Leukemia		Multiple myeloma	
		No. deaths	HR (95% CI)	No. deaths	HR (95% CI)	No. deaths	HR (95% CI)
BMI*							
Q1 (≤20.98)	111,580	15	1.0	6	1.0	3	1.0
Q2 (20.99-23.24)	108,559	13	0.73 (0.34-1.54)	7	1.07 (0.36-3.18)	6	1.73 (0.43-6.94)
Q3 (23.25-26.15)	106,251	9	0.43 (0.18-1.00)	13	1.81 (0.68-4.82)	9	2.24 (0.59-8.46)
Q4 (≥26.16)	102,561	11	0.48 (0.22-1.09)	21	2.83 (1.11-7.02)	10	2.33 (0.62-8.77)
P_{trend} †			0.08		<0.01		0.25
Plasma glucose level (mg/dL)							
≤119	214,146	21	1.0	18	1.0	10	1.0
120-159	134,418	14	0.82 (0.41-1.64)	15	1.07 (0.53-2.15)	8	0.96 (0.37-2.48)
160-199	56,232	7	0.83 (0.34-2.02)	7	1.04 (0.42-2.56)	4	0.96 (0.29-3.20)
≥200	24,154	6	1.59 (0.62-4.09)	7	2.32 (0.93-5.79)	6	3.13 (1.07-9.14)
P_{trend} †			0.57		0.14		0.08
Cigarette smoking							
Never	193,517	20	1.0	28	1.0	15	1.0
Former	69,000	8	1.28 (0.56-2.90)	9	0.99 (0.47-2.11)	8	1.70 (0.72-4.03)
Current	166,433	20	1.58 (0.84-2.98)	10	0.53 (0.25-1.09)	5	0.52 (0.19-1.45)
P_{trend} †			0.16		0.10		0.32
Education							
<High school	84,934	18	1.0	16	1.0	11	1.0
High school	216,354	17	0.51 (0.26-1.02)	23	0.76 (0.39-1.48)	12	0.63 (0.27-1.47)
>High school	127,663	13	0.70 (0.33-1.47)	8	0.48 (0.20-1.14)	5	0.48 (0.16-1.44)
P_{trend} †			0.33		0.10		0.17
Race							
White/other	368,882	46	1.0	43	1.0	26	1.0
African American	60,068	2	0.39 (0.09-1.62)	4	0.85 (0.30-2.44)	2	0.81 (0.19-3.57)

NOTE: HRs adjusted for six categories of age (≤49, 50-54, 55-59, 60-64, 65-69, and ≥70 y) using Cox proportional hazards regression.
*Weight (kg)/height $(m)^2$.
† *P* for trend was computed by modeling the within-category mean level of each risk factor as a continuous variable.

Table 5. Multivariable-adjusted HRs for NHL, leukemia, and multiple myeloma mortality associated with BMI and plasma glucose level in the Chicago Heart Association Detection Project in Industry, 1967-1973

Risk factors	NHL		Leukemia		Multiple myeloma	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Men						
BMI*,†						
Q1 (≤24.12)	1.0	1.0	1.0	1.0	1.0	1.0
Q2 (24.13-26.30)	1.94 (0.91-4.12)	1.84 (0.86-3.92)	1.43 (0.75-2.74)	1.40 (0.73-2.68)	0.97 (0.34-2.77)	0.99 (0.35-2.83)
Q3 (26.31-28.61)	2.08 (0.99-4.39)	1.93 (0.91-4.08)	2.13 (1.16-3.90)	2.06 (1.12-3.79)	1.55 (0.61-3.98)	1.61 (0.63-4.13)
Q4 (≥28.62)	2.57 (1.24-5.34)	2.31 (1.10-4.81)	1.98 (1.07-3.69)	1.89 (1.01-3.53)	1.52 (0.59-3.92)	1.62 (0.63-4.19)
P_{trend}‡	0.01	0.03	0.02	0.03	0.29	0.22
Plasma glucose level (mg/dL)§						
≤119	1.0	1.0	1.0	1.0	1.0	1.0
120-159	1.81 (1.02-3.21)	1.72 (0.97-3.04)	1.75 (1.08-2.83)	1.67 (1.03-2.71)	1.42 (0.70-2.88)	1.36 (0.67-2.77)
160-199	2.07 (1.07-4.00)	1.89 (0.98-3.67)	1.23 (0.66-2.30)	1.14 (0.61-2.13)	0.42 (0.12-1.51)	0.39 (0.11-1.42)
≥200	2.86 (1.35-6.06)	2.60 (1.22-5.52)	1.97 (1.00-3.87)	1.82 (0.93-3.58)	0.54 (0.12-2.46)	0.50 (0.11-2.29)
P_{trend}‡	<0.01	0.01	0.11	0.18	0.22	0.18
Women						
BMI*,†						
Q1 (≤20.98)	1.0	1.0	1.0	1.0	1.0	1.0
Q2 (20.99-23.24)	0.73 (0.34-1.54)	0.73 (0.35-1.55)	1.03 (0.35-3.09)	1.04 (0.35-3.10)	1.67 (0.42-6.73)	1.69 (0.42-6.80)
Q3 (23.25-26.15)	0.42 (0.18-0.99)	0.42 (0.18-0.99)	1.68 (0.63-4.50)	1.68 (0.63-4.50)	2.07 (0.55-7.85)	2.06 (0.54-7.83)
Q4 (≥26.16)	0.47 (0.21-1.08)	0.48 (0.21-1.09)	2.47 (0.96-6.36)	2.43 (0.94-6.30)	2.00 (0.52-7.65)	1.97 (0.51-7.53)
P_{trend}‡	0.07	0.07	0.02	0.02	0.40	0.47
Plasma glucose level (mg/dL)§						
≤119	1.0	1.0	1.0	1.0	1.0	1.0
120-159	0.82 (0.41-1.64)	0.85 (0.42-1.69)	1.04 (0.51-2.09)	0.98 (0.49-1.98)	0.94 (0.36-2.42)	0.91 (0.35-2.36)
160-199	0.83 (0.34-2.01)	0.89 (0.36-2.15)	1.01 (0.41-2.48)	0.93 (0.38-2.28)	0.94 (0.28-3.12)	0.91 (0.27-3.00)
≥200	1.57 (0.61-4.02)	1.65 (0.64-4.25)	2.26 (0.91-5.64)	2.10 (0.84-5.22)	3.06 (1.05-8.93)	2.98 (1.02-8.68)
P_{trend}‡	0.59	0.49	0.16	0.23	0.08	0.09

NOTE: HRs from Cox proportional hazards regression.

*Weight (kg)/height $(m)^2$.

† model 1 adjusted for six categories of age (≤49, 50-54, 55-59, 60-64, 65-69, and ≥70 y), education (<high school, high school, and >high school), smoking (never, former, and current), and race (African American versus white/other, multiple myeloma males only). model 2 adjusted for all variables in model 1 and postload glucose level (4 levels).

‡ *P* for trend was computed by modeling the within-category mean level of each risk factor as a continuous variable.

§model 1 adjusted for six categories of age (≤49, 50-54, 55-59, 60-64, 65-69, and ≥70 y), education (<high school, high school, and >high school), and smoking (never, former, and current). model 2 adjusted for all variables in model 1 and body mass index (quartiles).

A major strength of the present study is the use of interviewer-measured height and weight to calculate BMI. Although self-reported height and weight correlate well with measured height and weight (57), obese individuals tend to underreport their weight, whereas underweight subjects, in general, overestimate their body size and short individuals overreport their height (58). Consequently, using self-reported height and weight may attenuate BMI and hematopoietic cancer associations. Another main strength is the use of PLG levels measured at baseline, which avoided bias due to self-reported history of diabetes and patients hospitalized for diabetes. The continuous nature of PLG further allows us to evaluate dose response. Other strengths included the prospective study design and virtually complete mortality follow-up.

Our findings should be interpreted cautiously because the numbers of deaths in our cohort are small and, consequently, risk estimates may be imprecise. Another limitation is that we were not able to evaluate the effect of weight change or weight cycling throughout the follow-up period. We had no direct measure of central or total adiposity or of lean body mass. Third, we do not have information on prevalence of hematopoietic cancer at baseline. However, the number of prevalent cases might be small because all cohort members were in the labor force at the time of screening. In addition, the associations with BMI and PLG levels in both men and women were similar after exclusion of deaths in the first 5 years of follow-up. Fourth, measurement error remains possible for PLG levels because intraindividual variation in one plasma glucose measurement is large in comparison with interindividual variation (59). Another limitation is the lack of information on HIV and AIDS because both are risk factors for some types of NHL, and this may confound other etiologic exposure information if the viral status is unknown. Survival with AIDS-related NHL may not be the same as that of non-AIDS NHL. Moreover, in Chicago Heart Association cohort, mortality was the end point and information on subtypes of NHL and leukemia from the death certificates, if available, might not be accurate, particularly during the early follow-up period. Therefore, certain subtypes of NHL and leukemia with poor prognosis may be overrepresented in the current study. Finally, we do not have information on stage and treatment. However, there is no convincing evidence linking body weight to stage or the clinical outcome of hematopoietic cancer patients.

In conclusion, we found a positive association between BMI and mortality from NHL and leukemia, but not myeloma, in men. PLG level was also positively associated with NHL in men. For women, a higher BMI was associated with leukemia mortality. In addition, the highest level of PLG was associated with a significant 3-fold higher risk of mortality from multiple myeloma in women. The increased risks associated with BMI and PLG were independent of each other. With the increasing prevalence of obesity and diabetes in the United States, our findings, if confirmed, suggest that decreasing or preventing high BMI and diabetes could play a significant role in the long-term reduction of NHL and hematopoietic cancer deaths.

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