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Body Size and Risk of Hodgkin Lymphoma by Age and Gender: A Population-based Case-Control Study in Connecticut and Massachusetts

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Abstract

Purpose—Descriptive studies have indicated a rising trend in Hodgkin lymphoma (HL) incidence in young adults, especially females. Increasing evidence has suggested that some risk factors associated with HL may vary by age or gender. Recent studies have reported an increased risk of HL associated with increasing body mass index (BMI), but the results have been inconsistent. The objectives of this study were to examine whether the associations between measures of body size (height, weight, and BMI) and HL risk vary by age and/or gender.

Methods—A population-based case-control study was conducted in Connecticut and Massachusetts. A total of 567 HL cases and 679 controls were recruited in 1997–2000. Unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CIs).

Results—Among younger women < 35 years old, being overweight (25–29.9 kg/m^2) vs. normal weight (18.5–24.9 kg/m^2) was significantly associated with an increased risk of HL (OR = 2.1, 95% CI = 1.1–4.0). The risk increased with increasing weight and BMI (*P* trends < 0.01). Among women ≥ 35 years old, by contrast, higher weight and BMI were associated with a reduced risk of HL (*P* trends < 0.01). Conversely, there was no significant association between BMI and risk of HL in younger or older males.

Conclusions—These findings show that the associations between body size and risk of HL vary by gender and age, and require confirmation in other populations.

Keywords

Hodgkin lymphoma; body size; body mass index; height; weight

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Introduction

Hodgkin's lymphoma (HL) is a lymphoid malignancy that is one of the most common cancers among young adults [1]. Descriptive studies have indicated a rising trend in HL incidence in young adulthood, particularly among females, through the 1990s in the United States [2–5]. However, factors responsible for the observed increase in young women are currently unknown.

Recently, several studies have suggested that body mass index (BMI) is positively associated with the risk of various malignancies [6–8], including HL, but the overall findings have been inconsistent [8–18]. Moreover, several studies have found that the association between BMI and risk of HL varies specifically by gender [8–13], but these studies did not stratify the data by age. Increasing evidence has suggested that some risk factors associated with HL may vary by age or be more apparent in younger or older individuals, indicating that analyses of risk factors by age group may be informative. Specifically, a previous case-control study by Keegan et al. [17], which was confined to the female population, found a positive association between BMI and HL risk in younger U.S. women, whereas there was a negative association among older women. In addition, a cohort study of Swedish and Finnish twins that included both males and females indicated an increased risk of HL in association with being overweight in the younger cohort, while the association was less apparent in the older cohort [18]. Hence, observations of age variation in associations with HL risk are consistent with the hypothesis that HL in young adults and older adults are separate diseases [19].

Given the increasing concern about the rising prevalence of obesity globally and its potential effects on risk of other chronic diseases; the rising incidence of HL among young adults, particularly among young women; and the inconsistent results for the reported association between BMI and HL in previous studies, we examined associations with anthropometric measures in a population-based case-control study of HL in Connecticut and Massachusetts. Earlier studies have suggested different etiologic profiles for HL diagnosed among younger vs. older patients (< 35 vs. ≥ 35 years), with age groups defined based on the bimodal age distribution of HL incidence [3]. Here, we report the results for the associations with height, weight, and BMI and the risk of HL while considering potential effect modification by gender and/or age. We previously showed that older age, male sex, smoking, and lower education were associated with risk of Epstein-Barr virus (EBV)-positive vs. –negative disease in this population [20]. Therefore, we also examined these associations according to tumor EBV status.

Materials and Methods

Study population

Cases were patients diagnosed with HL from August 1, 1997, to December 31, 2000. Incident HL patients were recruited through a rapid case ascertainment system of hospitals in the study area, with back-up from state cancer registries, for a population-based case-control study in the greater Boston, Massachusetts, metropolitan area and in the state of Connecticut. Eligible patients were 15–79 years of age at diagnosis, living within the described geographic area, and without human immunodeficiency virus infection. Of 677 cases invited to participate, 567 (84%) consented.

Population controls were frequency matched to age (within 5 years), gender, and state of residency of the cases. Eligible controls were living residents of the study area and without prior history of HL. Controls from the Boston metropolitan area (132 cities and towns) were randomly selected from current “Town Books.” The Town Books are annual records that

include the name, gender, street address, and birth year of all residents aged ≥ 17 years and are > 90% complete [21]. If a selected control could not be contacted or refused to participate, the next listed eligible person was selected as a replacement control. Of 720 invited controls, 367 (51%) consented.

Connecticut controls aged 18–65 years were identified by random digit dialing. Approximately 98.9% of Connecticut residents had home telephone service at the time of the study [22]. To avoid overlap of participant responses and clustering by social class, only one participant was recruited per household. To prevent geographic clustering, a maximum of 8 households were screened within a block of 100 telephone numbers. Of the 450 eligible potential controls arising from 5,632 telephone numbers attempted, 276 (61%) consented to participate in the study. Connecticut controls aged 66–79 years were randomly selected from the Health Care Financing Administration (Medicare) files; 36 (52%) of 69 eligible controls consented to participate. In total, 679 controls participated by completing the study interview.

All study participants provided written informed consent (or, if younger than 18 years, assent) at the time of enrollment in the study. This research protocol was approved by the institutional review boards of the Harvard School of Public Health, Yale University School of Medicine, and Johns Hopkins Medical School, as well as 68 participating hospitals, the Massachusetts Cancer Registry, and the Connecticut Tumor Registry in the Connecticut Department of Public Health.

Histopathology

Pathology material was reviewed by study pathologists (M. Borowitz, R. B. Mann, and E. G. Weir at Johns Hopkins University) to confirm the diagnosis of HL [23, 24]. Of the 463 cases with information on pathologic subtype, 447 (97%) were classical HL and 16 were nodular lymphocyte-predominant subtype. The cases without histopathology (n=104) were also included in the analyses. However, we excluded the latter from our analyses, because the nodular lymphocyte-predominant subtype is considered biologically and clinically separate from classical subtypes [25].

Tumor tissue was previously analyzed for the presence of EBV by using in situ hybridization for EBV-encoded RNA transcripts and/or by an immunohistochemical assay for the viral latency membrane protein-1 in the malignant Hodgkin's and Reed-Sternberg cells [20, 26]. A Hodgkin's lymphoma tumor was considered EBV genome positive if results were positive for either of the assays and was considered EBV negative if both assays were negative or if only a single assay was done and its result was negative [27]. Interpretation of EBV assays was done by consensus of all three study pathologists.

Data Collection

Of 551 cases and 679 controls that consented, 97% completed a structured telephone interview, and 3% completed an abbreviated mailed questionnaire assessing known and potential risk factors for HL [23, 24]. The median time between HL diagnosis and case interview was 7.2 months (range: 2.6–44.6 months). Information on the presence of B symptoms (fever, night sweats, and weight loss) and disease stage at diagnosis (150 cases with B symptoms; 52 at stage I, 263 at stage II, 71 at stage III, 51 at stage IV) was abstracted from patients' medical records by study staff and medical personnel. Participants were asked to report their current height (feet and inches) and weight (pounds). BMI, defined as weight in kilograms divided by height in meters squared, was calculated for each subject. Based on World Health Organization standards [28], BMI was categorized as normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥ 30 kg/m^2). Normal weight subjects

were used as a reference group for comparison. Subjects with BMI < 18.5 kg/m^2 (21 cases and 14 controls) were removed in the final analysis because of their small sample size, although including them in the analysis did not affect the results (data not shown). Four indicator variables (1st–4th quartiles) were created separately in men and women for height and weight (converted to meters and kilograms, respectively), using quartiles based on the distribution of controls among gender- and age-specific groups. Because BMI was not evenly distributed in males and females, the World Health Organization categories do not apply to those under 20 years of age (6.4% of the study population), and most young adult subjects had BMIs in the reference range (18.5–24.9 kg/m^2), we also considered quartiles of BMI based on the distribution of controls among gender- and age-specific groups (<35 or ≥ 35 years).

Statistical analysis

Unconditional logistic regression analysis was used to estimate the associations of risk for HL with height, weight, and BMI, which were coded as indicator variables. All multivariable models were adjusted for age (with indicator variables for 5-year intervals), gender (male, female), state of residence (Connecticut, Massachusetts), race (white, nonwhite), education (less than high school, high school, college, advanced degree), and smoking history (ever smokers with more than 10 packs of cigarettes in lifetime, never smokers). Adjustments for the other variables (such as aspirin use, acetaminophen use, total energy intake, and nursery school/daycare attendance) did not result in material changes for the observed associations and thus were not included in final model. Potential confounders were selected based on prior knowledge as well as a 10% change-in-estimate criteria [29] and likelihood ratio tests comparing models with and without the additional variables. We tested for linear trends by modeling the median values of the quartiles as a continuous variable and evaluated statistical significance using the Wald test. Estimates were stratified by age and gender and, among cases, by tumor EBV status, the time between diagnosis and case interview, the presence of B symptoms, or stage at diagnosis. The interactions between each anthropometric measure and gender and age were assessed using a Wald test by including the relevant cross-product terms in the regression models. Analyses were conducted using SAS, version 9.3, software (SAS Institute, Inc., Cary, North Carolina). All statistical tests were 2-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 presents selected characteristics of the cases and controls. There were a slightly higher percentage of smokers in cases compared to controls. Cases and controls were well balanced on age, gender, state of residence, and ethnicity, except that HL cases had less formal education than controls.

There was no significant association between HL risk and any of the anthropometric variables in the overall study population after adjusting for age, race, and other confounding factors (state of residence, education, and smoking history; data not shown). As shown in Table 2, further analyses were stratified by gender and age. The association between BMI and HL risk was found to differ significantly across gender (*P* heterogeneity for gender = 0.01), and across age groups among women (*P* heterogeneity for age = 0.01). However, there were no significant interactions for either height or weight with respect to gender or age, although the *P*-values for heterogeneity for gender and age among women were borderline significant for weight (Table 2). Both increased weight and higher BMI were associated with a significantly increased risk of HL among females < 35-year-old (Table 2). Specifically, compared to the first quartile of weight, an increase in weight was associated with an increased risk of HL for each of the top two weight quartiles (OR for the third quartile = 2.6 (95% CI = 1.1–6.5); OR for the highest quartile = 3.0 (95% CI = 1.2–7.6); *P*

trend < 0.01). Similarly, the higher quartiles of BMI were associated with an increased risk of HL among women < 35-year-old, and a significant trend was observed (*P* trend < 0.01). Compared with the normal BMI reference group, being overweight was significantly associated with risk of HL (OR = 2.1, 95% CI = 1.1–4.0). However, HL risk was not elevated in obese women < 35-year-old, compared with those of normal BMI (OR = 0.9, 95% CI = 0.4–1.9; *P* trend = 0.6). HL risk was also associated with taller height in the women < 35-year-old (OR for subsequent quartiles = 3.3 (95% CI = 1.6–7.1); 2.2 (95% CI = 1.0–4.6); 1.9 (0.9–4.1), compared with the first quartile of height), although the trend was nonsignificant (*P* trend = 0.3).

In contrast, among older women (≥ 35 years), higher weight and BMI quartiles were associated with a reduced risk of HL (Table 2). In particular, the third and fourth weight quartiles showed an inverse association with HL risk compared with the first weight quartile (OR for the third quartile = 0.4 (95% CI = 0.2–0.8); OR for the fourth quartile = 0.3 (95% CI = 0.2–0.7), *P* trend <0.01). Compared with either the normal BMI reference group or the lowest BMI quartile, there was a significant reduced risk of HL for obese women (OR = 0.4, 95% CI = 0.2–0.8, *P* trend <0.01) or those with the highest BMI quartile (OR = 0.4, 95% CI = 0.2–0.8, *P* trend <0.01). Conversely, we did not detect any association between BMI, weight, or height and risk of HL in either younger or older males.

We also explored whether the association between HL risk and body size varied by the presence of EBV in tumor cells. Case-control comparisons were stratified by tumor EBV positivity among cases. Higher weight and BMI, using either the BMI quartiles or WHO category, were inversely associated with the risk of EBV-positive disease (*P* trend <0.01, data not shown), but no associations were observed for the risk of EBV-negative HL. The increased risk of EBV-positive or EBV-negative disease associated with higher BMI was only found among younger women (data not shown). The stratified analyses by the presence of B symptoms at diagnosis, disease stage (I–II vs. III–IV) or the time between diagnosis and interview among cases, indicated the increased risks of HL related to higher weight and BMI were observed among younger women, although results were not statistically significant (data not shown).

DISCUSSION

In this population-based case-control study, we found that associations between various measures of body size and risk of HL varied by gender and age. Higher BMI and weight were associated with an increased risk of HL in younger women, whereas both were associated with a decreased risk in older women. No association was observed between these measures of body size and HL risk among males, either in younger or older groups.

The rising time trend in the incidence rate of HL has been observed to vary by gender and/or age [2–5]. Glaser examined incidence trends of HL by gender and found a rising incidence in young adults, particularly females, based on incidence data from national cancer surveys conducted in 1947, 1969–71, and 1973–80 in parts of the United States [5]. Another descriptive study among young adults from the Connecticut Tumor Registry also found that the incidence rate of HL increased dramatically in females between 1970 and 1992, but seemed to slow in males [2]. Moreover, the current SEER data showed a significant decreasing incidence trend in males and a significant increasing trend in females between 1975–2009 [1]. These observations from descriptive studies suggest possible changes in exposure to risk factors of HL among young-adult females, but not males. Reproductive factors may be partially responsible for the observed diverse patterns of HL incidence between young females and males [30, 31]. However, currently identified major risk factors, such as EBV infection, human immunodeficiency virus infection, and improved standards of

living, cannot adequately explain the observed increase of HL incidence among young females [2].

Anthropometric measures could be related to HL pathogenesis through mechanisms involving the insulin and insulin-like growth factor (IGF) axis and/or sex steroids or adipokines, which can lead to distortion of the normal balance between cell proliferation, differentiation, and apoptosis [32] and which may vary in levels by gender and age [33]. Although the pathways through which these factors may affect lymphoma development remain poorly understood, biologically plausible mechanisms have been identified. For example, the circulating total IGF-I [34] and its main binding protein [35], IGFBP-3, which regulate cell proliferation, differentiation, and apoptosis, are thought to be important in tumor development as both IGF-I and IGFBP-3 are dependent on growth hormone. Their concentrations vary greatly between individuals, which decline with increasing age [33].

The relationship between taller height and elevated risk of HL could involve several mechanisms in women, especially young women. Some studies reported that nascent HL tumors may be promoted by higher circulating levels of IGFs and other growth hormones in taller women [36, 37]. The observed association of height with HL risk could also reflect the effect of other uncontrolled socioeconomic factors, such as nutritional factors. Overnutrition itself may be a risk factor for Hodgkin's disease as it may cause subtle immunodeficiencies that allow lymphoproliferation, including Hodgkin's disease [38]. The positive association of HL risk with taller height in young women reported by Keegan et al. [17] has been observed in previous studies, in which HL has been associated with taller height in childhood, especially at ages 10 and 12 years [39], at age > 13 years [40], and in adulthood [41, 42]. However, two studies did not find an association between height and HL risk [43, 44].

An inverse association between weight and BMI and risk of both EBV-positive and EBV-negative HL was observed in older women in our study. The potential biological mechanism underpinning these findings are unclear, although similar results were reported in two other case-control studies [14, 17]. One potential concern is whether the disease may have caused weight loss and thus the weight measurement in this study may not reflect the pre-disease weight of the subjects, especially for those with B symptoms. However, our stratified analyses by B symptoms and the time between diagnosis and interview showed similar findings among cases both with and without B symptoms. Similarly, further analyses stratified by the stage at diagnosis were consistent with the overall findings. Therefore, it is unlikely that disease-related changes in weight explain the disparate findings in young and old women.

Although our study population of HL cases was one of the largest to date, statistical power was limited, especially for analyses within age and gender subgroups. With respect to potential biases, participation rates were rather low in controls, and a particular concern is whether controls are representative of the populations from which cases were drawn. We attempted to limit this potential selection bias by replacing nonparticipating Massachusetts controls with individuals drawn from the same residential area, and Chang et al. [24] further showed that the income distribution across census tracts of our consented Massachusetts controls was representative of the source population. However, data to evaluate this potential source of bias were not available among Connecticut controls. Recall bias is another potential limitation, since risk factor data were self-reported and relied on the participant's ability to recall exposures in the previous year. Participants were asked to report their current height and weight which were assessed after diagnosis of HL, since we did not have pre-diagnosis height and weight. It is possible that weight loss may have influenced the recall of cases differently from that of controls. The possibility of uncontrolled or residual confounding also need to be considered when interpreting the results of our study. For

example, diet and physical activity are strongly related to weight/BMI, although we note that adjustment for total energy intake in our analyses did not meaningfully impact our results. It may be that early life body size is most important in terms of risk. Future studies with information on childhood or young adult body size could help to clarify the possible role of body size in the etiology of HL. Lastly, analyses of risk of EBV-related HL, involving the 72% of cases for whom specimens could be obtained, were affected by limited statistical power due to the low prevalence of EBV-positive HL in our study population [20].

In summary, the associations between body size and risk of HL varied by gender and age, for EBV-positive HL in particular. Our findings warrant future investigations of addressing HL risk associated with nutrition related to weight or BMI.

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In Massachusetts, participating case patients were identified from the following sources with institutional review board approval: AtlantiCare Medical Center, Beth Israel Deaconess Medical Center, Beverly Hospital, Boston Medical Center, Brigham and Women's Hospital, Brockton Hospital, Brockton VA/West Roxbury Hospital, Cambridge Hospital, Caritas Southwood Hospital, Carney Hospital, Children's Hospital Boston, Dana-Farber Cancer Institute, Deaconess Glover Memorial Hospital, Deaconess Waltham Hospital, Emerson Hospital, Faulkner Hospital, Good Samaritan Medical Center, Harvard Vanguard, Holy Family Hospital and Medical Center, Jordan Hospital, Lahey Hitchcock Medical Center, Lawrence General Hospital, Lawrence Memorial Hospital of Medford, Lowell General Hospital, Massachusetts Cancer Registry, Massachusetts Eye and Ear Infirmary, Massachusetts General Hospital, Melrose-Wakefield Hospital, MetroWest Medical Center, Morton Hospital, Mount Auburn Hospital, New England Baptist Hospital, New England Medical Center, Newton-Wellesley Hospital, North Shore Medical Center, Norwood Hospital, Quincy Hospital, Saint's Memorial Hospital, South Shore Hospital, St. Elizabeth's Hospital, Sturdy Memorial Hospital, University of Massachusetts Medical Center, and Winchester Hospital.

In Connecticut, participating case patients were identified from the following sources with institutional review board approval: Bridgeport Hospital, Bristol Hospital, Charlotte Hungerford Hospital, Connecticut Department of Public Health Human Investigation Committee, Danbury Hospital, Day-Kimball Hospital, Greenwich Hospital, Griffin Hospital, Hartford Hospital, Johnson Memorial Hospital, Lawrence and Memorial Hospital, Manchester Memorial Hospital, MidState Medical Center, Middlesex Memorial Hospital, Milford Hospital, New Britain General Hospital, New Milford Hospital, Norwalk Hospital, Rockville General Hospital, Sharon Hospital, St. Francis Hospital and Medical Center, St. Mary's Hospital, St. Raphael's Hospital, St. Vincent's Hospital, Stamford Hospital, WW Backus Hospital, Waterbury Hospital, Windham Hospital, and Yale-New Haven Hospital.

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Table 1

Distribution of Select Characteristics Among Hodgkin Lymphoma Cases and Controls, in Massachusetts and State of Connecticut, 1997–2000

Characteristic	Cases (n=530)		Controls (n=665)	
	No.	%	No.	%
Age, years				
<20	40	7.5	36	5.4
20–29	136	25.7	172	25.9
30–39	157	29.6	185	27.8
40–49	89	16.8	119	17.9
50–59	47	8.9	55	8.3
60–69	37	7.0	52	7.8
>=70	24	4.5	46	6.9
Gender				
Male	281	53.0	360	54.1
Female	249	47.0	305	45.9
State of residence				
Massachusetts	306	57.7	356	53.5
Connecticut	224	42.3	309	46.5
Race/ethnicity				
White	471	88.9	574	86.3
Black	19	3.6	33	5.0
Hispanic	23	4.3	31	4.7
Other	17	3.2	27	4.1
Participant's education				
Less than high school	56	10.6	47	7.1
High school	141	26.6	162	24.4
College	263	49.6	340	51.1
Advanced degree	70	13.2	116	17.4
Smoke				
Smoker[a]	278	52.5	311	46.8
Nonsmoker	252	47.5	354	53.2

[a] More than 10 packs of cigarettes in lifetime.

Table 2

Risk of Hodgkin Lymphoma Associated with Body Size, Stratified by Gender and Age, in Massachusetts and State of Connecticut, 1997–2000[a]

Variables	Men						Women						*P*-value for heterogeneity by gender
	< 35 years (147/163)[b]			≥ 35 years (134/197)[b]			< 35 years (119/145)[b]			≥ 35 years (130/160)[b]			
	Ca/Co	OR	95%CI	Ca/Co	OR	95%CI	Ca/Co	OR	95%CI	Ca/Co	OR	95%CI	
Weight[c], kg													
Q1	32/37	1.0		31/44	1.0		10/25	1.0		50/40	1.0		0.05
Q2	40/44	1.1	0.5,2.1	40/59	1.0	0.5,1.9	39/48	2.1	0.9,5.1	42/38	0.9	0.5,1.7	
Q3	26/41	0.7	0.4,1.5	25/43	0.8	0.4,1.7	34/36	2.6	1.1,6.5	22/42	0.4	0.2,0.8	
Q4	49/41	1.3	0.7,2.5	38/51	1.1	0.6,2.1	36/36	3.0	1.2,7.6	16/40	0.3	0.2,0.7	
P for trend			0.6			0.9			<0.01			<0.01	
P for heterogeneity by age						0.08						0.06	
Height[d], cm													
Q1	35/42	1.0		26/39	1.0		17/41	1.0		33/36	1.0		0.45
Q2	41/47	1.0	0.6,2.0	34/50	1.1	0.6,2.2	41/30	3.3	1.6,7.1	37/40	0.9	0.4,1.7	
Q3	37/36	1.1	0.6,2.2	33/52	1.1	0.5,2.1	35/40	2.2	1.0,4.6	29/42	0.7	0.3,1.4	
Q4	34/38	1.0	0.5,2.0	41/56	1.2	0.6,2.3	26/34	1.9	0.9,4.1	31/42	0.7	0.3,1.4	
P for trend			0.9			0.7			0.3			0.2	
P for heterogeneity by age						0.20						0.68	
BMI[e], kg/m^2													
Q1	43/40	1.0		35/49	1.0		24/36	1.0		45/40	1.0		<.0001
Q2	29/42	0.7	0.4,1.3	33/49	1.0	0.5,1.9	21/37	0.8	0.4,1.8	42/40	0.9	0.5,1.7	
Q3	24/40	0.5	0.3,1.0	30/49	0.8	0.4,1.6	37/36	1.6	0.8,3.2	27/40	0.6	0.3,1.2	
Q4	51/41	1.1	0.6,2.0	36/50	1.0	0.6,2.0	37/36	1.8	0.9,3.8	16/40	0.4	0.2,0.8	
P for trend			0.9			1.0			<0.01			<0.01	
P for heterogeneity by age						0.25						0.01	
BMI, kg/m^2													
Normal, 18.5 to <25	70/77	1.0		42/52	1.0		74/99	1.0		77/69	1.0		0.01
Overweight, 25 to <30	52/68	0.8	0.5,1.3	62/104	0.7	0.4,1.3	31/22	2.1	1.1,4.0	32/44	0.6	0.4,1.2	
Obese, >=30	25/18	1.4	0.7,3.0	30/41	0.9	0.5,1.8	14/24	0.9	0.4,1.9	21/47	0.4	0.2,0.8	

Variables	Men						Women						*P*-value for heterogeneity by gender
	< 35 years (147/163)[b]			≥ 35 years (134/197)[b]			< 35 years (119/145)[b]			≥ 35 years (130/160)[b]			
	Ca/Co	OR	95%CI	Ca/Co	OR	95%CI	Ca/Co	OR	95%CI	Ca/Co	OR	95%CI	
P for trend			0.7			0.9			0.6			<0.01	
P for heterogeneity by age						0.51						0.01	

Abbreviations: BMI, body mass index; ca/co; numbers of cases and controls; CI, confidence interval; OR, odds ratio; Q, quartile.

[a] Adjusted for age (with indicator variables for 5-year intervals), gender (male, female), state of residence (Connecticut, Massachusetts), race (white, nonwhite), education (less than high school, high school, college, advanced degree), and smoking history (ever, never).

[b] The number of cases/the number of controls.

[c] Weight quartiles based on distributions of the control group in total subjects: Q1 (< 65.9), Q2 (65.9 to < 77.3), Q3 (77.3 to < 88.6), Q4 (≥ 88.6); in male and young adults: Q1 (< 72.7), Q2 (72.7 to < 80.9), Q3 (80.9 to < 90.9), Q4 (≥ 90.9); in male and older adults: Q1 (< 75.0), Q2 (75.0 to < 84.1), Q3 (84.1 to < 94.5), Q4 (≥ 94.5); in female and young adults: Q1 (< 54.5), Q2 (54.5 to < 61.4), Q3 (61.4 to < 71.4), Q4 (≥ 71.4); in female and older adults: Q1 (< 59.5), Q2 (59.5 to < 72.7), Q3 (72.7 to < 85.2), Q4 (≥ 85.2).

[d] Height quartiles based on distributions of the control group in total subjects: Q1 (< 165.1), Q2 (165.1 to < 172.7), Q3 (172.7 to < 177.8), Q4 (≥ 177.8); in male and young adults: Q1 (< 172.7), Q2 (172.7 to < 177.8), Q3 (177.8 to < 182.9), Q4 (≥ 182.9); in male and older adults: Q1 (< 172.7), Q2 (172.7 to < 177.8), Q3 (177.8 to < 182.9), Q4 (≥ 182.9); in female and young adults: Q1 (< 157.5), Q2 (157.5 to < 165.1), Q3 (165.1 to < 167.6), Q4 (≥ 167.6); in female and older adults: Q1 (< 160.0), Q2 (160.0 to < 165.1), Q3 (165.1 to < 170.2), Q4 (≥ 170.2).

[e] BMI quartiles based on distributions of the control group in total subjects: Q1 (< 22.8), Q2 (22.8 to < 25.5), Q3 (25.5 to < 28.9), Q4 (≥ 28.9); in male and young adults: Q1 (< 23.6), Q2 (23.6 to < 25.1), Q3 (25.1 to < 27.4), Q4 (≥ 27.4); in male and older adults: Q1 (< 24.5), Q2 (24.5 to < 26.7), Q3 (26.7 to < 30.0), Q4 (≥ 30.0); in female and young adults: Q1 (< 21.2), Q2 (21.2 to < 22.7), Q3 (22.7 to < 26.6), Q4 (≥ 71.4); in female and older adults: Q1 (< 22.5), Q2 (22.5 to < 26.1), Q3 (26.1 to < 30.7), Q4 (≥ 30.7).