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Research Article

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Young Adult and Usual Adult Body Mass Index and Multiple Myeloma Risk: A Pooled Analysis in the International Multiple Myeloma Consortium (IMMC)

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Abstract

Background: Multiple myeloma risk increases with higher adult body mass index (BMI). Emerging evidence also supports an association of young adult BMI with multiple myeloma. We undertook a pooled analysis of eight case–control studies to further evaluate anthropometric multiple myeloma risk factors, including young adult BMI.

Methods: We conducted multivariable logistic regression analysis of usual adult anthropometric measures of 2,318 multiple myeloma cases and 9,609 controls, and of young adult BMI (age 25 or 30 years) for 1,164 cases and 3,629 controls.

Results: In the pooled sample, multiple myeloma risk was positively associated with usual adult BMI; risk increased 9% per 5-kg/m^2 increase in BMI [OR, 1.09; 95% confidence interval (CI), 1.04–1.14; $P = 0.007$]. We observed significant heterogeneity by study design ($P = 0.04$), noting the BMI–multiple myeloma association only for population-based studies ($P_{trend} = 0.0003$). Young adult BMI was also positively associated with multiple myeloma (per 5-kg/m^2; OR, 1.2; 95% CI, 1.1–1.3; $P = 0.0002$). Furthermore, we observed strong evidence of interaction between younger and usual adult BMI ($P_{interaction} < 0.0001$); we noted statistically significant associations with multiple myeloma for persons overweight (25–<30 kg/m^2) or obese (30+ kg/m^2) in both younger and usual adulthood (vs. individuals consistently <25 kg/m^2), but not for those overweight or obese at only one time period.

Conclusions: BMI-associated increases in multiple myeloma risk were highest for individuals who were overweight or obese throughout adulthood.

Impact: These findings provide the strongest evidence to date that earlier and later adult BMI may increase multiple myeloma risk and suggest that healthy BMI maintenance throughout life may confer an added benefit of multiple myeloma prevention.
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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Introduction

Multiple myeloma is a malignancy of plasma cells that is expected to account for 30,330 new cancer diagnoses and 12,650 cancer deaths in the United States in 2016 (1). In spite of recent therapeutic breakthroughs (2, 3), the relative 5-year survival of multiple myeloma remains below 50% (4). Prevention strategies informed by knowledge of modifiable risk factors are urgently needed, but the etiology of multiple myeloma is not known. Established risk factors include older age, male gender, African ancestry and a family history of hematologic malignancy (5, 6). The pre-malignant condition, monoclonal gammopathy of undetermined significance (MGUS) precedes essentially all cases of multiple myeloma (7, 8) and appears to share demographic risk factors with multiple myeloma (9), but knowledge of MGUS etiology and risk factors for progression to multiple myeloma is also limited.

Body mass index (BMI) has emerged as the first and only identified modifiable risk factor for multiple myeloma (10–12). Most published studies reported an increased risk of multiple myeloma in relation to adult BMI but lacked sufficient statistical power to examine the association separately by age, sex or race. Comparatively few studies evaluated multiple myeloma risk in relation to earlier life body size, but the available evidence supports a positive association for younger adult BMI with multiple myeloma that may be at least as strong as that for later adult BMI (13, 14).

Obesity is associated with dysregulation of several endogenous hormonal pathways (15, 16) that also contribute to multiple myeloma pathogenesis, including insulin-like growth factor (IGF)-1 (17, 18), insulin (19), interleukin (IL)-6 (20), and adipokines such as adiponectin (21). Furthermore, recent prospective studies have provided evidence for an association of multiple myeloma risk with pre-diagnosis levels of these hormones (22–24), and a recent *in vivo* study demonstrated susceptibility to an multiple myeloma-like condition in mice with diet-induced obesity (25). A clearer understanding of the association of obesity and related anthropometric measures with multiple myeloma would offer valuable insights for the development of urgently needed prevention strategies.

To further elucidate the association of BMI and related anthropometric measures with multiple myeloma, we conducted a pooled analysis of eight case–control studies participating in the International Multiple Myeloma Consortium (IMMC; ref. 26). The pooled total of 2,318 confirmed incident cases of multiple myeloma and 9,609 controls, with young adult BMI data for 1,164 cases and 3,629 controls, makes the present study the largest to date and the best equipped to evaluate the independence of younger and later adult BMI associations with multiple myeloma and the heterogeneity of BMI-multiple myeloma associations across demographically defined multiple myeloma risk strata.

Materials and Methods

Study population

The present study included participants from the eight IMMC case–control studies that collected information on adult height, usual adult weight, and relevant covariables (age, sex, race, education level, tobacco use, alcohol intake). Those included the EpiLymph, Fred Hutchinson Cancer Research Center (FHCRC), National Cancer Institute (NCI) Black-White, NCI-Connecticut, NCI-Surveillance, Epidemiology and End Results (SEER), Nebraska, Roswell Park Cancer Institute (RPCI), and Utah studies (Supplementary Table S1), for which the designs and methods were previously published in detail (27–35). Four of those studies represented multiple study centers, and thus the analysis included a total of 20 study centers. Five study centers used a hospital-based design; the remaining centers used a population-based design, based on the source of controls.

Multiple myeloma cases were enrolled either through participating hospitals and physicians (4 studies/9 centers) or through population-based cancer registries (4 studies/11 centers). Case participation ranged from 72% to 96% of eligible cases. Hospital-based controls were recruited among patients admitted to the same hospitals as the cases for a variety of non-malignant conditions. Population-based controls were identified through random-digit telephone dialing, random selection from national health insurance registries or the equivalent, and/or through other population-based registries. Controls were individually or frequency-matched to cases on age, sex, and region or center. One study also matched on age, sex, race, and vital status (Nebraska; ref. 34), and another matched on age, sex, region, and race (NCI-SEER; ref. 33). The NCI-Connecticut study was restricted to women and used frequency-matching of controls to cases on age (31, 32). The controls in the NCI-Connecticut and NCI-SEER studies were obtained from related ongoing studies of non-Hodgkin lymphoma (NHL), and were thus frequency-matched to the NHL rather than to the multiple myeloma cases (31, 32); controls for the EpiLymph study were frequency-matched by age and sex to cases enrolled in the broader study of all adult hematologic malignancies. The Utah study enrolled both spouse controls and controls identified through registry of motor vehicle records, with the latter frequency-matched to cases by age and sex; we excluded the spouse controls ($n = 79$) from the present analysis. Control participation ranged from 44% to 96% of eligible controls. The protocols for the participating case–control studies were approved by the institutional review board (IRB) or equivalent at the respective host institutions and at each SEER center, and study participants provided written informed consent. The protocol for the present analysis was approved by the IRB of the NCI and each collaborating institution.

Case definition

Most study centers considered all individuals with histologically confirmed incident primary diagnoses of multiple myeloma that occurred during the respective enrollment periods (ICD-O-3 diagnostic codes of 9731.3, 9732.3, 9734.3, ICD-9 of 203, and the equivalent) as eligible for enrollment. The Utah study included both prevalent and incident cases. Sensitivity analyses conducted without the Utah study sample yielded similar findings to those with all eight studies, and thus we focus on the analyses that include the Utah data in this report.

Data collection

Study data were obtained in person by trained interviewers or by self-administered questionnaire. The vast majority of questionnaires or interviews were completed directly by the enrolled cases or controls; three studies obtained data from a proxy respondent when the enrolled case was too ill or deceased. The interviews/questionnaires included items on the participants' date of birth, sex, education level, race/ethnicity, height, weight during a reference period (typically one year) before interview

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and/or "usual" adult weight, and habits pertaining to use of tobacco or alcohol. Two population-based studies (NCI Black-White, FHCRC) also collected information on weight in younger adulthood, specifically at age 25 or 30, respectively. Participants in the Utah study reported weight at age 40 as a usual adult weight, and therefore cases ($n = 6$) and controls ($n = 1$) from Utah who were younger than 40 years at interview were removed from the analysis.

Classification of anthropometric variables

We determined sex-specific cutoff points for quartiles of height (m), usual adult weight [kg, referring to the year pre-interview or (for Utah) at age 40], and younger adult weight (kg, referring to weight at age 25 or 30) among the pooled control subjects with non-missing data on those variables. We also computed the usual adult and younger adult BMI (kg/m^2) from the height and usual or younger adult weight. We categorized the BMI variables into the World Health Organization (WHO)-defined categories of "underweight" (<18.5 kg/m^2), "normal" (18.5 to <25 kg/m^2), "overweight" (25 to <30 kg/m^2), "obese" (30 to <35 kg/m^2), and "severely obese" ($\geq$ 35 kg/m^2; refs. 36, 37).

Classification of demographic and other potential confounding variables

We categorized age at interview by decade (<50, 50–59, 60–69, 70+ years) and race/ethnicity into three groups (White, Black, Other/unknown). We harmonized education level into five categories (<12 years of study; 12+ years or high school graduate; some attendance at college, technical, or vocational school after high school; graduation from college without further studies; or, other) and defined participants' history of tobacco use (ever, never) and alcohol intake (ever, never; refs. 26, 38).

Statistical analysis

To evaluate the association of usual or younger adult BMI, height and usual or younger adult weight with risk of multiple myeloma, we computed ORs and 95% confidence intervals (CI) using unconditional logistic regression models. We first computed study-specific and study center-specific ORs to evaluate heterogeneity in the associations across the participating studies and study centers. To assess the heterogeneity of the usual adult BMI–multiple myeloma associations across study populations, we performed a meta-analysis of study center-specific ORs and variances from covariable-adjusted models (see below) using both fixed and random effects models.

We also directly pooled the data across all participating study centers and computed ORs and 95% CIs in the combined population using logistic regression. To evaluate possible sources of heterogeneity we conducted additional analyses that included interaction terms for usual or younger adult BMI with potential effect modifiers, including study design (hospital- vs. population-based control ascertainment), study or study center, interview type (participant vs. proxy), age group at interview, sex, and race. We assessed the statistical significance of any apparent interaction with the likelihood ratio test. To control for potential confounding, we included indicator variables for age group at interview, sex, race/ethnicity, study center, height, education level, and history of tobacco use and alcohol intake; we considered a given covariable to be a confounding variable if its inclusion in a model resulted in a 10% or greater change to the corresponding effect estimate. We examined the joint classification of usual (<25, 25 to <30, $\geq$30 kg/m^2) and younger adult BMI (<25, 25 to <30, $\geq$30 kg/m^2) in pooled data from the NCI Black-White and FHRC studies. To evaluate linear trend across the categories of a given anthropometric variable we assigned exposure category medians to ordinal variables that we modeled as continuous variables in additional multivariable logistic regression models. For comparison, we also assessed the increase in multiple myeloma risk per 5-kg/m^2 increase in usual or younger adult BMI.

We used SAS version 9.2 for all statistical analyses except for the meta-analyses, which we performed using the MiMa package (39) in R. All tests of statistical significance assumed a two-tailed alpha error level of 0.05.

Results

The eight participating case–control studies contributed a total pooled sample of 2,318 cases of incident multiple myeloma and 9,609 controls to the present analysis (Table 1). Differences between cases and controls in the distribution of study design, demographic and lifestyle variables were statistically significant. We did not observe confounding of usual or younger adult BMI associations with multiple myeloma by height, education, tobacco use or alcohol intake, and thus we did not retain those covariables in the final logistic regression models for the BMI variables.

In the meta-analysis of usual adult BMI with multiple myeloma risk, we observed similar findings from the fixed and random effects models, and thus we focus herein on the fixed effects model data. The Forest plots from models comparing overweight (Fig. 1; $P_{\text{heterogeneity}} = 0.06$), obesity (Fig. 2; $P_{\text{heterogeneity}} = 0.23$) and severe obesity (Fig. 3; $P_{\text{heterogeneity}} = 0.80$) with a normal BMI illustrate statistically non-significant variability in the risk estimates across study centers. Across all participating study centers, the summary ORs indicated that multiple myeloma risk increased similarly by 10% for overweight (Fig. 1) and obese (Fig. 2) persons and by 40% for severely obese individuals (Fig. 3) compared with those with a usual adult BMI in the WHO-defined normal range.

We observed a similar positive association of usual adult BMI with multiple myeloma risk in the pooled study sample ($P_{\text{trend}} = 0.008$; Table 2). After controlling for age, sex, race and study center, the ORs for overweight, obesity and severe obesity were virtually identical to those observed in the meta-analysis. When modeled continuously, multiple myeloma risk increased by 9% per 5-kg/m^2 increase in usual adult BMI (OR, 1.09; 95% CI, 1.04–1.14; $P = 0.007$). Likelihood ratio tests indicated significant heterogeneity of the usual adult BMI–multiple myeloma association by study design ($P_{\text{heterogeneity}} = 0.04$) but not by interview type ($P_{\text{heterogeneity}} = 0.98$; Table 2). We therefore performed subsequent analyses within strata defined by study design.

From the population-based studies, we observed a slightly stronger positive association of usual adult BMI with multiple myeloma risk than from the full study sample ($P_{\text{trend}} = 0.0003$); for example, in continuous multivariable models, multiple myeloma risk increased by 11% per 5-kg/m^2 increase in usual adult BMI (OR, 1.11; 95% CI, 1.06–1.17; $P = 0.0001$). When modeled by WHO category, overweight and obese individuals had a 10% (OR, 1.1; 95% CI, 1.0–1.3) and 20% (OR, 1.2; 95% CI, 1.0–1.4) greater risk, respectively, and severely obese participants had a 60% greater risk (OR, 1.6; 95% CI, 1.3–2.1) when compared with those with a normal adult BMI. In contrast, we did not observe an

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Table 1. Selected characteristics of the pooled study population

	Cases *N* (%)	Controls *N* (%)	*P*
Pooled total	2,318	9,609	
Study design[a]			<0.0001
Hospital-based	293 (12.64)	1,817 (18.91)	
Population-based	2,025 (87.36)	7,792 (81.09)	
Interview type			<0.0001
Self	2,074 (89.47)	9,005 (93.71)	
Proxy	244 (10.53)	604 (6.29)	
Sex			0.0001
Men	1,093 (47.15)	4,947 (51.48)	
Women	1,225 (52.85)	4,662 (48.52)	
Age, y			<0.0001
<50	242 (10.44)	1,758 (18.30)	
50–59	515 (22.22)	2,074 (21.58)	
60–69	829 (35.76)	2,880 (29.83)	
70+	730 (31.49)	2,893 (29.97)	
Missing	2 (0.09)	4 (0.04)	
Education level			0.001
<12 years of education	815 (35.16)	3,370 (35.07)	
12+ years or high school graduate	659 (28.48)	2,760 (28.73)	
College, technical or vocational school	425 (18.31)	1,559 (16.22)	
College graduate only	388 (16.72)	1,676 (17.44)	
Other	24 (1.03)	219 (2.28)	
Missing	7 (0.30)	25 (0.26)	
Race/ethnicity			<0.0001
White	1,764 (76.10)	7,940 (82.63)	
Black	478 (20.62)	1,485 (15.45)	
Other/unknown	71 (3.06)	133 (1.38)	
Missing	5 (0.22)	51 (0.53)	
Ever smoke cigarettes			<0.0001
No	1,034 (44.60)	3,972 (41.34)	
Yes	1,104 (47.63)	5,018 (52.22)	
Missing	180 (7.77)	619 (6.44)	
Ever alcohol consumption			<0.0001
No	531 (22.91)	1,983 (20.64)	
Yes	709 (30.59)	3,819 (39.74)	
Missing	1,078 (46.50)	3,807 (39.62)	

[a]As determined by source of control subjects.

association of multiple myeloma risk with usual adult BMI in the hospital-based studies, whether modeled using WHO categories ($P_{trend} = 0.59$; Table 2) or 5-kg/m^2 incremental increases in BMI ($P = 0.48$). Adult BMI had a significant or suggestive positive association with multiple myeloma in each age- and race-related stratum of the population-based study participants (Supplementary Table S2), with no clear evidence of heterogeneity by demographic risk factors (*P* values all ≥0.30). Usual adult BMI was not associated with multiple myeloma for all persons or for any stratum of the hospital-based study participants (P_{trends} all ≥0.26; Supplementary Table S3).

In pooled analyses across the two population-based studies (comprising 7 study centers) with data on younger adult weight, we observed a significant positive association of younger adult BMI with risk of multiple myeloma ($P_{trend} = 0.0001$; Table 2). In the continuous models, multiple myeloma risk increased by 20% per 5-kg/m^2 increase in younger adult BMI (OR, 1.2; 95% CI, 1.1–1.3; $P = 0.0002$). Participants who reported severe obesity in younger adulthood had a more than two-fold increase in multiple myeloma risk compared with those with a normal younger adult BMI (multivariable OR, 2.2; 95% CI, 1.1–4.5), and those who were overweight (OR, 1.5; 95% CI, 1.2–1.7) or obese (OR, 1.3; 95% CI, 0.9–1.9) in younger adulthood had suggestive modest increases in risk (Table 2). Younger adult BMI did not demonstrate significant interaction with study center, age, sex or race (all *P*-values for interaction ≥0.46). In this participant subgroup, the association of usual adult BMI with multiple myeloma was similar to that for younger adult BMI (usual adult BMI per 5-kg/m^2; OR, 1.16; 95% CI, 1.07–1.26). Furthermore, usual and young adult weight (Spearman $r = 0.73$, $P = 0.0001$) and BMI (Spearman $r = 0.56$, $P = 0.0001$) were significantly correlated.

We observed a highly significant interaction between younger adult and usual adult BMI ($P_{heterogeneity} < 0.0001$; Table 3). In models that examined a joint classification of younger and usual adult BMI, we observed significantly elevated multiple myeloma risk only for persons classified as overweight or obese at both early and later adulthood compared with individuals with BMI <25 kg/m^2 on both measures. Individuals who were overweight (OR, 1.2; 95% CI, 0.8–1.9) or obese (OR, 1.0; 95% CI, 0.3–3.1) in early adulthood but not in the reference period before diagnosis did not have a clearly increased risk of multiple myeloma, nor did those with both a normal younger adult BMI and a usual adult BMI in the overweight (OR, 1.1; 95% CI, 0.9–1.3) or obese categories (OR, 1.0; 95% CI, 0.7–1.4).

In the analysis of other anthropometric measures (Supplementary Table S4), persons in the highest quartile (Q4) of usual adult weight had a modest increase in multiple myeloma (vs. Q1, multivariable OR, 1.3; 95% CI, 1.1 -1.4; $P_{trend} = 0.15$) that was

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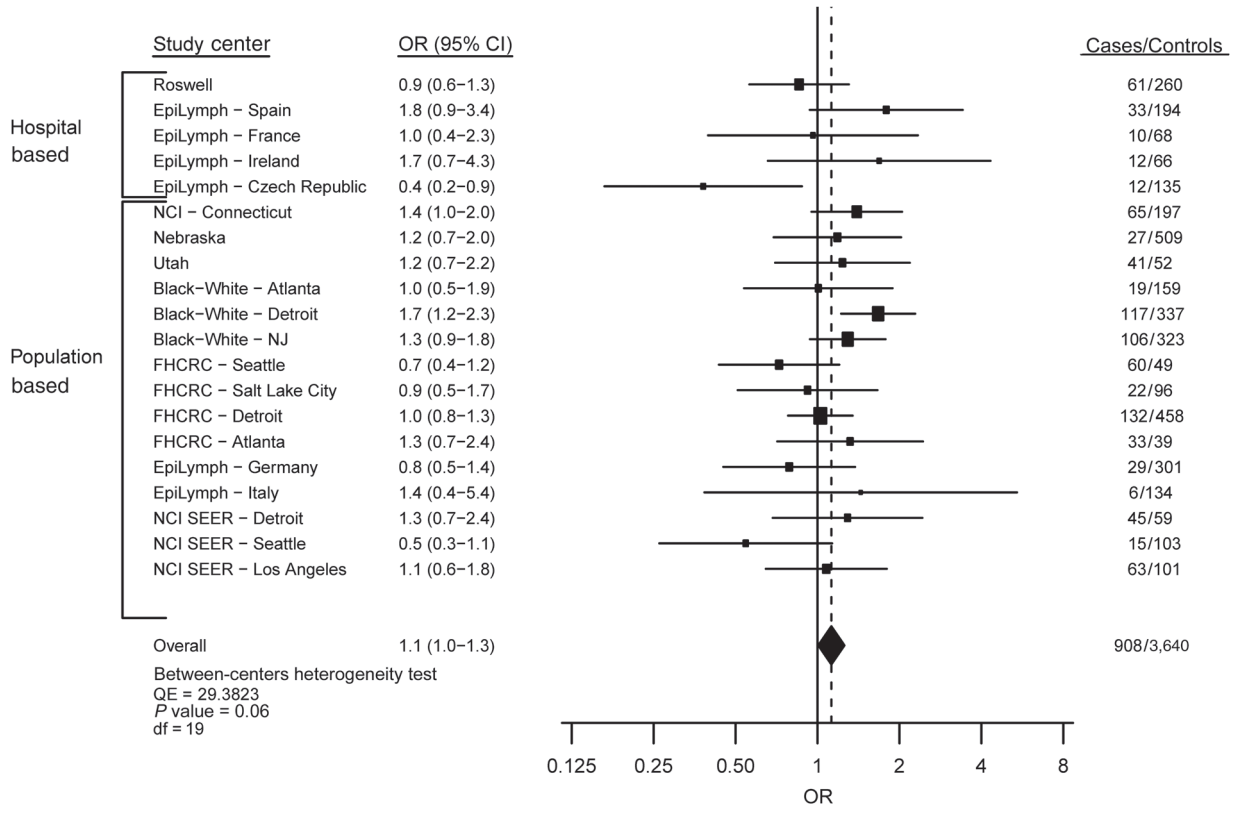

Figure 1.

Study center–specific and summary ORs and 95% CIs for the risk of multiple myeloma with a usual adult BMI of 25 to <30 kg/m^2 compared with the referent category of 18.5 to <25 kg/m^2 in 20 study centers. The study center-specific data are organized by study design (hospital- vs. population-based case–control study). The summary measures were obtained by meta-analysis using fixed effects models.

statistically significant in population-based studies (vs. Q1; OR, 1.3; 95% CI, 1.2–1.6; $P_{trend} = 0.04$) but not evident in hospital-based studies (vs. Q1; OR, 0.8; 95% CI, 0.6–1.2; $P_{trend} = 0.08$; $P_{heterogeneity}$ by study design = 0.01). Quartile of younger adult weight also demonstrated a modest positive association with multiple myeloma risk (in two population-based studies, Q4 vs. Q1, multivariable OR, 1.5; 95% CI, 1.2–1.8; $P_{trend} = 0.001$). We did not observe an association of adult height with multiple myeloma risk for all subjects or for any separately evaluated demographically defined risk stratum (i.e., age, sex, race; P_{trends} all $\geq$0.35).

Discussion

In this large pooled IMMC analysis, we observed a positive association of both usual and younger adult BMI with risk of multiple myeloma, as well as with usual and younger adult weight. Furthermore, we noted that usual and younger adult BMI interact with one another, such that increased multiple myeloma risk was strongest for individuals who were overweight or obese in both time periods, and weaker or absent for those obese or overweight at only one of the time periods.

The positive association that we observed for usual adult BMI and multiple myeloma is consistent with most (but not all) previous studies, as summarized in recent meta-analyses (10–12). Of interest, in our pooled study sample the association of usual adult BMI with multiple myeloma was restricted to the population-based studies, suggesting that one or more attributes of the hospital-based study design, possibly an association of BMI with control diagnoses or factors that influenced participation, may have introduced bias. The increases in multiple myeloma risk that we observed in severely obese, obese, and overweight population-based study participants are roughly consistent in magnitude with the meta-analysis results for obese and overweight persons (10–12); the meta-analyses did not separately report findings for more severe obesity. Our findings are also similar to those from a prospective study of multiple myeloma mortality in the Cancer Prevention Study II population of nearly 1.2 million US residents (36). In that analysis, women and men with a baseline BMI of 35 to 39.9 kg/m^2 (i.e., severely obese) had a 44% and 75% increase in multiple myeloma mortality, respectively, and those with a baseline BMI classified as overweight (25 to 29.9 kg/m^2) or obese (30 to 34.9 kg/m^2) had 12% to 47% higher multiple myeloma mortality, compared with those with a normal baseline BMI (36). The meta-analyses did not separately evaluate the multiple myeloma–BMI association by age, sex, or race, and individual studies had limited statistical power to assess heterogeneity by these multiple myeloma risk factors. Our findings provide strong evidence that the association of usual adult BMI with multiple myeloma is similarly detectable across

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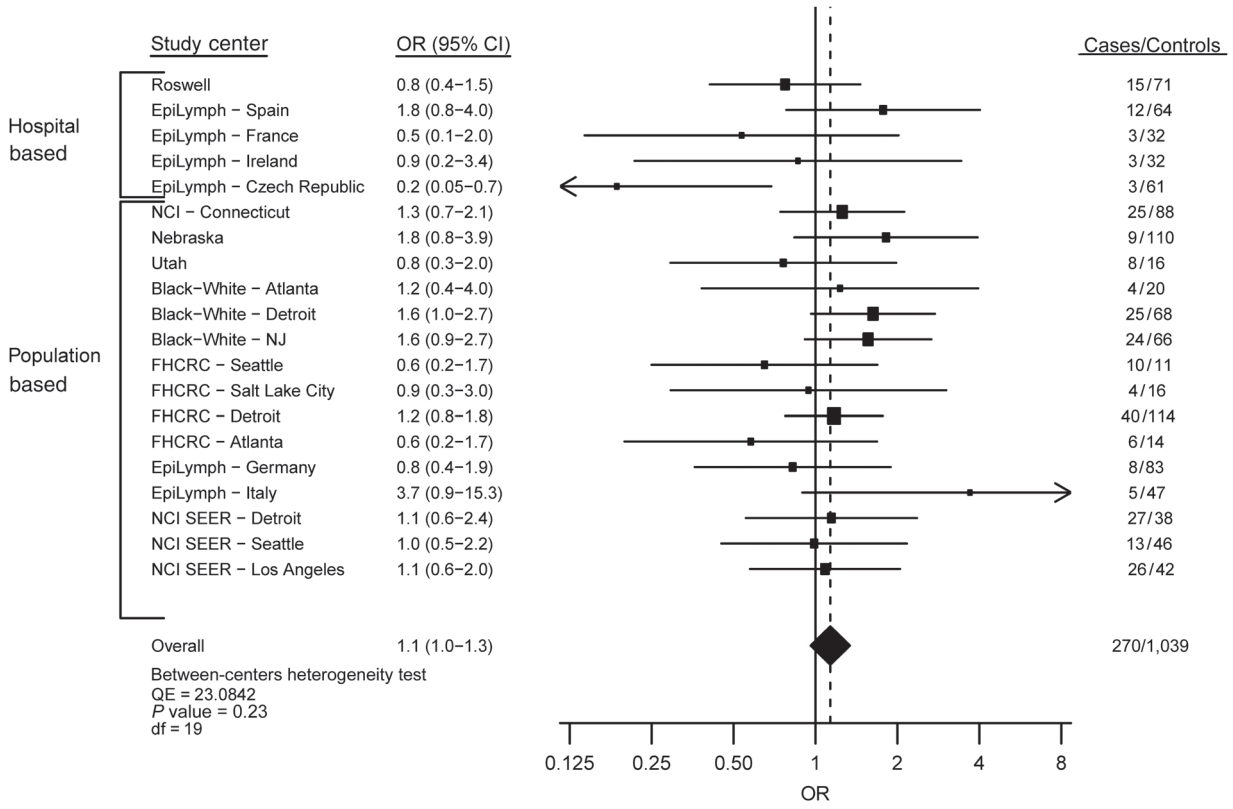

Figure 2.

Study center–specific and summary ORs and 95% CIs for the risk of multiple myeloma with a usual adult BMI of 30 to <35 kg/m^2 compared with the referent category of 18.5 to <25 kg/m^2 in 20 study centers. The study center-specific data are organized by study design (hospital- vs. population-based case–control study). The summary measures were obtained by meta-analysis using fixed effects models.

demographic multiple myeloma risk groups including race. The recent *in vivo* demonstration by Lwin and colleagues (25) of a link between the development of multiple myeloma–like conditions and diet-induced obesity further strengthens the evidence that obesity is causally associated with multiple myeloma.

Our analysis of younger adult BMI and multiple myeloma risk, including 1,164 cases and 3,629 controls, is the largest to date. We observed an association with multiple myeloma for younger adult BMI of comparable size with that for usual adult BMI, and a significant correlation between those two measures. Of the previous studies that have reported on both earlier and later life body size and multiple myeloma risk, three prospective investigations observed significant associations with BMI in early and later adulthood (13, 14, 40, 41). Three other studies, including two prospective analyses restricted to women with 92 and 111 multiple myeloma cases (42, 43) and a pooled case-control analysis (44), did not find an association of multiple myeloma risk with BMI at any age. The latter null studies may reflect limited statistical power from smaller case counts, and in particular from limited numbers of cases included in higher categories of younger adult BMI.

A key finding of our investigation is that a significantly increased multiple myeloma risk was apparent only for participants who were overweight or obese during both early and later adulthood when participants were jointly classified for both time periods. Similar patterns of association with BMI across early and later adulthood were also observed in joint analyses from two cohort investigations of multiple myeloma, although tests of interaction did not reach statistical significance (13, 14). Although it is not possible in our data to conclusively distinguish a long-lasting influence of younger adult BMI from an influence of persistent obesity throughout adulthood, our findings are consistent with a conceptual model in which pathogenic effects of BMI influence myelomagenesis both at earlier and later stages, a model also supported by recent evidence relating BMI to MGUS prevalence (45) and to progression from MGUS to multiple myeloma (46). These findings also have important public health implications; they suggest that maintaining a healthy body size throughout adulthood is optimal for reducing multiple myeloma risk and further, that adults with a history of carrying excess weight may reduce their multiple myeloma risk by achieving a normal BMI later in life.

The present findings for usual and younger adult weight and multiple myeloma risk were weaker than our observations for usual and younger adult BMI but were generally consistent with a positive association of weight with multiple myeloma risk at both time periods. Likewise, in other studies that reported findings for both weight and BMI at a given age, the results for weight tended to be similar to or weaker than those for BMI (41, 43, 44, 47, 48). Some studies (43, 44, 47, 49) also reported a suggestive, usually

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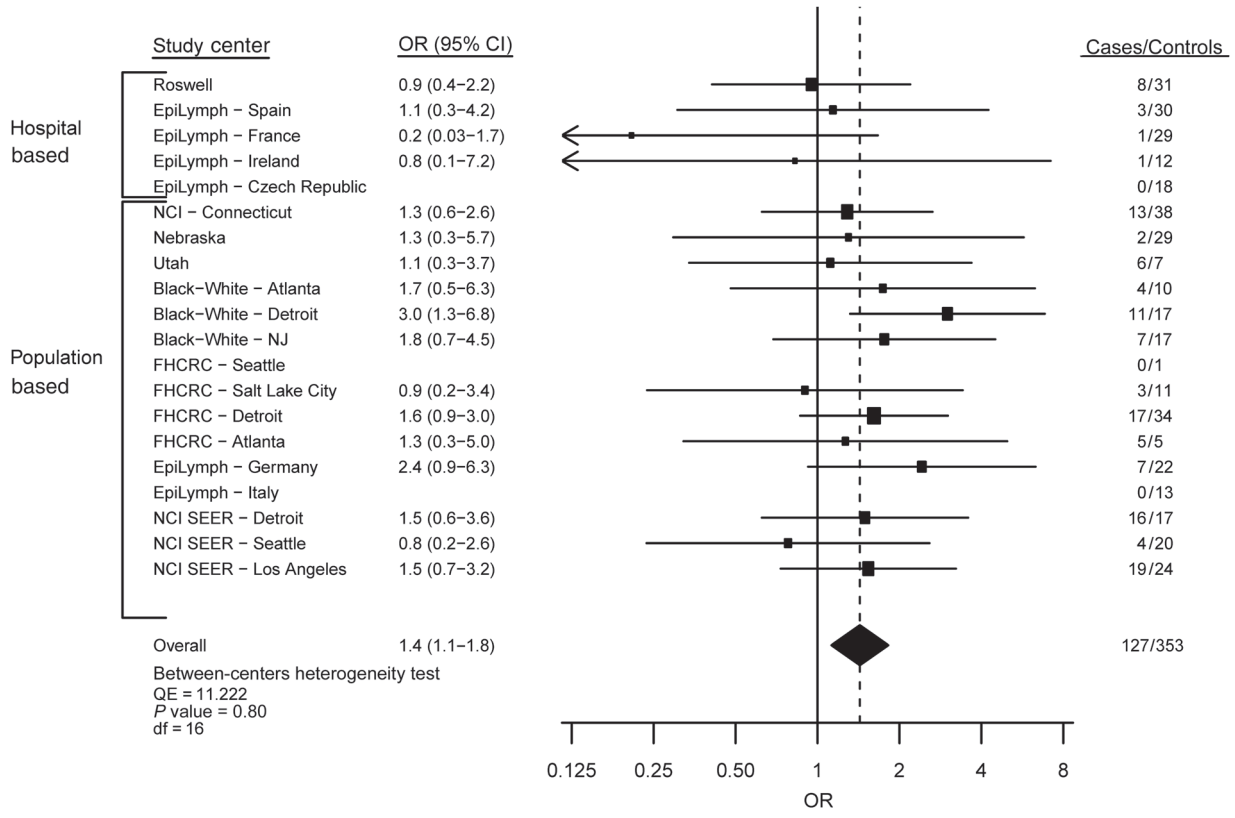

Figure 3.

Study center–specific and summary ORs and 95% CIs for the risk of multiple myeloma with a BMI of 35+ kg/m^2 compared with the referent category of 18.5 to <25 kg/m^2 in 20 study centers. The study center–specific data are organized by study design (hospital- vs. population-based case–control study). The summary measures were obtained by meta-analysis using fixed effects models.

modest positive association of multiple myeloma risk with height, primarily for women (43, 44, 47), whereas other large prospective studies did not note any associations for height (13, 40, 41, 48). Our observation of no clear association for height with multiple myeloma risk supports the collective evidence that adiposity is the more important component of body size underlying the association of BMI with multiple myeloma. We could not assess measures of central adiposity in the present study to further clarify whether specific types of adiposity have a stronger association with multiple myeloma (13, 47, 48).

A rapidly expanding body of literature addresses biologic processes that are active or dysregulated in both obesity and oncogenesis and may underlie observed associations of obesity with cancer (recently reviewed by De Pergola and Silvestris; ref. 16). Several of the implicated pathways are known contributors to multiple myeloma pathogenesis (15). For example, IGF-1 (17, 18), insulin (19), and IL-6 (20) are growth factors for multiple myeloma. Furthermore, some byproducts of lipid metabolism can activate nuclear factor (NF)-κB, a transcription factor that mediates aspects of normal B-cell hematopoiesis but is upregulated in multiple myeloma and cooperates with other pathways to promote cell proliferation and survival (50). More recently, it has also been recognized that adiponectin, an anti-inflammatory adipocyte-derived cytokine that is inversely correlated with BMI, has anti-proliferative effects on multiple myeloma *in vivo* (21). In support of a role for these pathways in multiple myeloma etiology, prediagnosis peripheral blood concentrations of IGF-1–binding protein (IGFBP)-1, the soluble IL6 receptor (sIL6R), and adiponectin demonstrated significant associations with the development of multiple myeloma in recent prospective studies (22–24).

The major strength of the current study is its large sample size, which enabled the separate examination of severe obesity and the joint analysis of BMI in early and later adulthood. However, we recognize that small numbers in some of the joint analysis categories of BMI in early and later adulthood, in particular, the small number of participants who were heavy in younger but not later adulthood, limit our ability to assess the relative importance of excess weight in one age period versus the other in affecting multiple myeloma risk. Another limitation is the lack of information on other potentially relevant anthropometric measures such as waist and hip circumference, other measures of adiposity and on MGUS status as a second outcome. The IMMC member studies reported varying levels of participation among eligible cases and controls, and we cannot rule out an influence of selection or other biases on our results. However, the overall consistency of our findings with those from prospective studies is reassuring, as is the noted biologic plausibility of our observations. Finally, notwithstanding our large pooled sample size, we had limited statistical power for analyses of non-White strata and

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Table 2. Pooled relative risk of multiple myeloma by category of usual and younger adult BMI, study design, and interview type

		Usual BMI (kg/m^2)[b]					
Stratification	***N*[a]**	**<18.5**	**18.5–<25**	**25–<30**	**30–<35**	**35+**	**$P_{heterogeneity}$[c]**
Usual adult BMI							
All subjects							N/A
Case *N* (%)	2,318	36 (1.5)	977 (42.1)	908 (39.2)	270 (11.7)	127 (5.5)	
Control *N* (%)	9,609	191 (2.0)	4,354 (45.3)	3,640 (37.9)	1,039 (10.8)	385 (4.0)	
OR (CI)[d]		0.8 (0.5–1.1)	1.0 (ref)	1.1 (1.0–1.3)	1.1 (1.0–1.3)	1.4 (1.1–1.7)	
						P_{trend} = 0.008[e]	
Study design							0.042
Hospital based							
Case *N* (%)	293	4 (1.4)	112 (38.2)	128 (43.7)	36 (12.3)	13 (4.4)	
Control *N* (%)	1,817	36 (2.0)	678 (37.3)	723 (37.8)	260 (14.3)	120 (6.6)	
OR (CI)[d]		0.8 (0.3–2.2)	1.0 (ref)	1.0 (0.7–1.3)	0.8 (0.6–1.3)	0.6 (0.3–1.2)	
						P_{trend} = 0.59[e]	
Population based							
Case *N* (%)	2,025	32 (1.6)	865 (42.7)	780 (38.5)	234 (11.6)	114 (5.6)	
Control *N* (%)	7,792	155 (2.0)	3,676 (47.2)	2,917 (37.4)	779 (10.0)	266 (3.4)	
OR (CI)[d]		0.8 (0.5–1.2)	1.0 (ref)	1.1 (1.0–1.3)	1.2 (1.0–1.4)	1.6 (1.3–2.1)	
						P_{trend} = 0.0003[e]	
Interview type							0.98
Self							
Case *N* (%)	2,074	33 (1.6)	862 (41.2)	813 (39.2)	249 (12.0)	117 (5.6)	
Control *N* (%)	9,005	177 (2.0)	4,054 (45.0)	3,417 (38.0)	990 (11.0)	367 (4.0)	
OR (CI)[d]		0.8 (0.6–1.2)	1.0 (ref)	1.1 (1.0–1.3)	1.2 (1.0–1.4)	1.4 (1.1–1.8)	
						P_{trend} = 0.01[e]	
Proxy							
Case *N* (%)	244	3 (1.2)	115 (45.3)	95 (37.4)	21 (8.3)	10 (3.9)	
Control *N* (%)	604	14 (2.2)	300 (46.7)	223 (34.7)	49 (12.3)	18 (2.8)	
OR (CI)[d]		0.4 (0.04–4.2)	1.0 (ref)	0.9 (0.4–1.7)	1.1 (0.4–3.3)	1.2 (0.3–5.9)	
						P_{trend} = 0.91[e]	
Younger adult BMI (kg/m^2)[b]							
Case *N* (%)	1,164	70 (5.6)	791 (62.9)	253 (20.1)	37 (2.1)	13 (1.0)	N/A
Control *N* (%)	3,629	220 (5.8)	2,655 (67.8)	632 (16.6)	101 (2.7)	21 (0.6)	
OR (CI)[d]		0.9 (0.7–1.3)	1.0 (ref)	1.5 (1.2–1.7)	1.3 (0.9–1.9)	2.2 (1.1–4.5)	
						P_{trend} = 0.0001[e]	

[a]Counts across recent BMI categories may not add up to N total because of missing data.
[b]Usual adult BMI was calculated from height at study enrollment and weight as of the study-specific reference period before interview. In the two population-based study populations with data on younger adult weight, younger adult BMI was calculated from height at study enrollment and weight reported for younger adulthood.
[c]*P* values for heterogeneity were obtained from likelihood ratio tests that compared logistic regression models with only main effects variables to models that also included a term for the interaction of BMI with the specified stratifying variable.
[d]From logistic regression models controlling for age (<50, 50–59, 60–69, >70), sex, race (White, Black, Other/unknown), and study center.
[e]*P* values for trend were obtained by modeling category of BMI as an ordinal variable in logistic regression models with the same covariables as in the models that generated the corresponding ORs.

Table 3. Joint classification of younger adult BMI and usual adult BMI and pooled relative risk of multiple myeloma in two population-based case–control studies

		Younger adult BMI (kg/m^2)[b]			
Stratification	***N*[a]**	**<25**	**25–<30**	**30+**	
Usual adult BMI (kg/m^2)[c]					P^d= <0.0001
<25					
Case *N* (%)	560	523 (93.4)	33 (5.9)	4 (0.7)	
Control *N* (%)	1,861	1,772 (95.2)	77 (4.1)	12 (0.6)	
OR (CI)[e]		1.0 (ref)	1.2 (0.8–1.9)	1.0 (0.3–3.1)	
25–<30					
Case *N* (%)	454	283 (19.5)	156 (79.5)	15 (1.0)	
Control *N* (%)	1,384	936 (67.6)	412 (29.8)	36 (2.6)	
OR (CI)[e]		1.1 (0.9–1.3)	1.4 (1.1–1.8)	1.3 (0.7–2.5)	
30+					
Case *N* (%)	150	55 (36.4)	64 (43.0)	31 (20.5)	
Control *N* (%)	384	167 (43.4)	143 (37.2)	74 (19.3)	
OR (CI)[e]		1.0 (0.7–1.4)	1.7 (1.2–2.3)	1.7 (1.1–2.6)	

[a]Percentages across rows may not add up to 100% due to rounding. 389 subjects were excluded from analysis due to missing data.
[b]Calculated from height at study enrollment and weight reported for young adulthood.
[c]Calculated from height at study enrollment and weight as of the study-specific reference period before interview.
[d]A *P* value for heterogeneity from a likelihood ratio test that compared logistic regression models with only main effects variables to a model that also included a term for the interaction of younger adult BMI with usual BMI.
[e]From logistic regression models controlling for age (<50, 50–59, 60–69, >70), sex, race (White, Black, Other/unknown), and study center.

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could not evaluate anthropometric measure associations with multiple myeloma separately for Asian and Hispanic participants for whom multiple myeloma risk factor data are generally more limited. Further evaluation of these associations using larger and more diverse study samples would provide important insights to clarify whether individuals from those understudied racial/ethnic groups could also expect an multiple myeloma risk reduction from maintaining a healthy BMI throughout adulthood.

In conclusion, we have reported some of the strongest evidence to date in support of a positive association of BMI with multiple myeloma. In particular, our study demonstrates that these effects begin in young adulthood, and are most apparent for individuals who carry excess weight throughout adulthood. Whether those findings reflect a persistent influence of younger adult obesity or a cumulative influence of lifelong BMI on myelomagenesis warrants further investigation. Given that obesity remains the only known modifiable risk factor for this as yet incurable malignancy, public health efforts to reduce the prevalence of obesity among both younger and older adults currently represents the best available strategy for reducing even a modest proportion of the incidence and burden of multiple myeloma.

Disclosure of Potential Conflicts of Interest

M. Maynadié is a consultant/advisory board member for Roche and Janssen. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute, the NIH, the American Cancer Society or other funding agencies noted above.

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Young Adult and Usual Adult Body Mass Index and Multiple Myeloma Risk: A Pooled Analysis in the International Multiple Myeloma Consortium (IMMC)

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