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Original Contribution

Body Mass Index and Physical Activity at Different Ages and Risk of Multiple Myeloma in the NIH-AARP Diet and Health Study

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Several studies have reported an increased risk of multiple myeloma associated with excess body weight. We investigated the risk of multiple myeloma in relation to separate measures of adiposity and energy balance at different ages in the National Institutes of Health-AARP Diet and Health Study, a large prospective cohort study in the United States. Participants completed a baseline questionnaire (1995–1996; $n = 485{,}049$), and a subset of participants completed a second questionnaire (1996–1997; $n = 305{,}618$) in which we solicited more detailed exposure information. Hazard ratios and 95% confidence intervals were estimated for the risk of multiple myeloma (overall, $n = 813$; subset, $n = 489$) in relation to several measures of obesity and leisure time physical activity. Multiple myeloma risk was associated with increasing body mass index (BMI) at cohort entry (per 5-kg/m^2 increase, hazard ratio (HR) = 1.10, 95% confidence interval (CI): 1.00, 1.22); similar associations were observed for BMI at age 50 years (HR = 1.14, 95% CI: 1.02, 1.28), age 35 years (HR = 1.20, 95% CI: 1.05, 1.36), and age 18 years (HR = 1.13, 95% CI: 0.98, 1.32) without adjustment for baseline BMI. Risk of multiple myeloma was not associated with physical activity level at any age. These findings support the hypothesis that excess body weight, both in early adulthood and later in life, is a risk factor for multiple myeloma and suggest that maintaining a healthy body weight throughout life may reduce multiple myeloma risk.

body mass index; multiple myeloma; obesity; overweight; physical activity

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; HR_{cont}, hazard ratio corresponding to a 5-kg/m^2 increase in body mass index; MET, metabolic equivalent; WHR, waist-to-hip ratio.

Multiple myeloma is among the most fatal of lymphoid malignancies, with a 5-year survival rate in the United States of less than 40% (1). Established risk factors for multiple myeloma include older age, male sex, African-American race, severe immune dysregulation, family history of lymphohematopoietic cancer, and monoclonal gammopathy of undetermined significance (2). Beyond these factors, the etiology of multiple myeloma remains poorly understood, although the collective evidence from prospective epidemiologic studies suggests that a high body mass index (BMI; weight (kg)/height (m)^2) is associated with an increased risk (3). Most of these studies focused on BMI in midlife (i.e., at cohort entry); only a few studies assessed BMI at different ages throughout adult life (4–7) or evaluated additional measures of adiposity, such as waist circumference or waist-to-hip ratio (WHR) (5, 8–10). Furthermore, to our knowledge, only one study evaluated multiple myeloma incidence in relation to physical activity (11). To address the research gaps regarding the association of the risk of multiple myeloma with measures of adiposity and with physical activity at different ages, we conducted this investigation in the National Institutes of Health-AARP (NIH-AARP) Diet and Health Study, a large prospective cohort study.

MATERIALS AND METHODS

Study population

The design of the National Institutes of Health-AARP Diet and Health Study has been described previously (12). Briefly, a self-administered questionnaire was mailed to 3.5 million AARP members who were between 50 and 71 years of age and lived in California, Florida, Louisiana, New Jersey, North Carolina, or Pennsylvania or the Atlanta, Georgia, or Detroit, Michigan, metropolitan areas. A total of 567,169 questionnaires were completed between October 1995 and February 1997. Records were excluded from our analysis if they met any of the following criteria: the questionnaire was submitted in duplicate ($n = 179$), the participant died or moved out of the study area before returning the questionnaire ($n = 582$), the questionnaire was completed by a proxy respondent ($n = 15{,}760$), the participant had a history of cancer as determined by self-report or registry data ($n = 51{,}234$), or the participant withdrew from the study ($n = 3$). We also excluded participants for whom we were missing information on height or weight ($n = 12{,}153$) and participants with outlying values for BMI (BMI <15, $n = 999$; BMI >50, $n = 1{,}158$). After these exclusions, our final baseline analytical cohort included 485,049 participants (291,471 men and 193,578 women).

A second questionnaire was sent in late 1996 to baseline questionnaire respondents who still lived in the study area and did not have prevalent cancer of the prostate, breast, or colon. This second questionnaire collected more detailed information about anthropometric characteristics and physical activity level during adolescence and at various ages throughout adulthood. After exclusions similar to those for the baseline analytical cohort, a total of 305,618 participants (178,261 men and 127,357 women) were included in the analytical subcohort. The National Institutes of Health-AARP Diet and Health Study was approved by the National Cancer Institute Special Studies Institutional Review Board, and all participants provided written informed consent.

Cohort follow-up and case ascertainment

Incident cases of multiple myeloma were identified through linkage to state cancer registries; ascertainment of cancer cases through these registries is estimated to be 90% complete (13). The vital status of each study participant was determined through linkage with the US Social Security Administration Death Master File. Observation time began on the date that each questionnaire was received and ended when the participant was first diagnosed with cancer (regardless of cancer site or type), moved out of the study area, or died or when the follow-up period ended on December 31, 2006. Multiple myeloma diagnoses preceded by diagnosis of another type of cancer (baseline cohort, $n = 100$; subcohort, $n = 55$) were not considered. We defined multiple myeloma cases as those that were assigned a histology code of 9732 according to the *International Classification of Diseases for Oncology, Third Edition* (14). A total of 813 cases identified during 4,405,154 person-years of follow-up were included in analyses of BMI at baseline in the full cohort, and of the subcohort of participants for whom we had additional information from the second questionnaire, 489 cases were included in the analyses of BMI and physical activity level at different ages and in analyses of other measures of adiposity.

Assessment of anthropometric characteristics and physical activity

Participants were asked to report their current height and weight on the baseline questionnaire; this information was

Table 1. Baseline Characteristics of Study Participants by Body Mass Index Category ($n = 485{,}049$), National Institutes of Health-AARP Diet and Health Study, 1995–2006

Characteristic	Body Mass Index at Study Baseline[a]									
	<18.5 (Underweight)		18.5–24.9 (Normal Weight)		25–29.9 (Overweight)		30–34.9 (Obese)		≥35 (Severely Obese)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Age at baseline, years[b]	62.6 (5.4)		62.2 (5.4)		62.1 (5.3)		61.6 (5.3)		60.9 (5.3)	
Sex										
Male	1,591	38.9	84,053	50.3	143,862	69.4	48,299	62.8	13,666	46.0
Female	2,504	61.1	83,058	49.7	63,352	30.6	28,601	37.2	16,063	54.0
Race										
Non-Hispanic white	3,739	91.3	153,937	92.1	189,604	91.5	64,499	90.4	26,142	87.9
Non-Hispanic black	112	2.7	4,146	2.5	7,819	3.8	4,192	5.5	2,286	7.7
Hispanic	52	1.3	2,825	1.7	4,293	2.1	1,503	2.0	537	1.8
Other[c]	105	2.6	4,200	2.5	2,805	1.4	610	0.8	226	0.8
Missing	87	2.1	2,003	1.2	2,693	1.3	1,096	1.4	538	1.8

[a] Weight (kg)/height (m)^2.
[b] Values expressed as mean (standard deviation).
[c] Asian, Pacific Islander, or American Indian/Alaska Native.

Table 2. Hazard Ratios and 95% Confidence Intervals for the Risk of Multiple Myeloma in Relation to Body Mass Index at Different Ages, National Institutes of Health-AARP Diet and Health Study, 1995–2006[a]

BMI[b] Category at Various Ages, Overall and by Sex	No. of Cases	HR	95% CI	P_{trend}[c]	HR[d]	95% CI[d]
Men and women combined						
Baseline[e]						
<18.5	1	0.30	0.04, 2.17	0.008	1.10	1.00, 1.22
18.5–22.49	53	1.0	Referent			
22.5–24.9	99	1.02	0.73, 1.43			
25–29.9	207	1.09	0.80, 1.48			
30–34.9	82	1.26	0.89, 1.78			
≥35	34	1.55	1.01, 2.39			
50 years						
<18.5	3	0.78	0.25, 2.49	0.04	1.14	1.02, 1.28
18.5–22.49	73	1.0	Referent			
22.5–24.9	129	1.14	0.85, 1.52			
25–29.9	193	1.16	0.88, 1.54			
30–34.9	45	1.23	0.84, 1.80			
≥35	18	1.77	1.05, 2.99			
35 years						
<18.5	7	0.77	0.36, 1.66	0.004	1.20	1.05, 1.36
18.5–22.49	136	1.0	Referent			
22.5–24.9	159	1.42	1.12, 1.79			
25–29.9	131	1.27	0.99, 1.63			
30–34.9	22	1.41	0.89, 2.22			
≥35	8	2.53	1.24, 5.18			
18 years						
<18.5	55	0.93	0.69, 1.25	0.015	1.13	0.98, 1.32
18.5–22.49	237	1.0	Referent			
22.5–24.9	86	1.12	0.88, 1.44			
≥25	64	1.38	1.04, 1.82			
Men						
Baseline[e]						
<18.5	1	0.59	0.08, 4.38	0.09	1.08	0.95, 1.24
18.5–22.49	26	1.0	Referent			
22.5–24.9	65	0.94	0.59, 1.47			
25–29.9	159	1.04	0.69, 1.57			
30–34.9	55	1.16	0.73, 1.85			
≥35	17	1.42	0.77, 2.62			
50 years						
<18.5	2	1.15	0.27, 4.80	0.14	1.08	0.95, 1.24
18.5–22.49	30	1.0	Referent			
22.5–24.9	94	1.30	0.86, 1.96			
25–29.9	148	1.19	0.81, 1.77			
30–34.9	31	1.23	0.74, 2.04			
≥35	12	2.29	1.17, 4.48			

Table continues

Table 2. Continued

BMI[b] Category at Various Ages, Overall and by Sex	No. of Cases	HR	95% CI	P_{trend}[c]	HR[d]	95% CI[d]
35 years						
<18.5	3	0.73	0.23, 2.33	0.032	1.19	1.01, 1.40
18.5–22.49	69	1.0	Referent			
22.5–24.9	111	1.34	0.99, 1.81			
25–29.9	113	1.26	0.93, 1.70			
30–34.9	15	1.21	0.69, 2.12			
≥35	6	3.39	1.47, 7.82			
18 years						
<18.5	33	0.83	0.57, 1.21	0.072	1.09	0.91, 1.30
18.5–22.49	165	1.0	Referent			
22.5–24.9	62	0.98	0.73, 1.31			
≥25	51	1.29	0.94, 1.77			
Women						
Baseline[e]						
<18.5[f]	0	N/A	N/A			
18.5–22.49	27	1.0	Referent	0.09	1.12	0.97, 1.29
22.5–24.9	34	1.13	0.68, 1.87			
25–29.9	48	1.08	0.67, 1.73			
30–34.9	27	1.36	0.80, 2.33			
≥35	17	1.62	0.88, 3.00			
50 years						
<18.5	1	0.48	0.07, 3.50	0.18	1.12	0.97, 1.29
18.5–22.49	43	1.0	Referent			
22.5–24.9	35	0.90	0.57, 1.41			
25–29.9	45	1.25	0.82, 1.90			
30–34.9	14	1.34	0.73, 2.46			
≥35	6	1.20	0.51, 2.84			
35 years						
<18.5	4	0. 80	0.29, 2.20	0.058	1.21	0.98, 1.48
18.5–22.49	67	1.0	Referent			
22.5–24.9	48	1.55	1.07, 2.25			
25–29.9	18	1.17	0.69, 1.97			
30–34.9	7	2.02	0.92, 4.40			
≥35	2	1.41	0.34, 5.75			
18 years						
<18.5	22	1.13	0.70, 1.82	0.072	1.25	0.97, 1.62
18.5–22.49	72	1.0	Referent			
22.5–24.9	24	1.63	1.03, 2.59			
≥25	13	1.64	0.90, 2.95			

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; N/A, not applicable.

[a] Adjusted for age at baseline, sex (overall model only), and race. Because of missing data, the reported frequencies may not sum to the full number of cases of multiple myeloma included in this study.

[b] Weight (kg)/height (m)^2.

[c] Values were assigned by BMI category using the within-category median.

[d] Per a 5-kg/m^2 increase in BMI.

[e] Restricted to participants in the subcohort (i.e., those who completed both questionnaires). Results for baseline BMI in the entire cohort are reported in Web Table 3.

[f] Women with baseline BMI less than 18.5 were excluded from this analysis (no cases of multiple myeloma were observed among women in this category).

used to calculate BMI. We categorized current BMI at baseline according to the guidelines of the World Health Organization (15), as follows: underweight (<18.5), normal weight (18.5–24.9), overweight (25.0–29.9), obese (30.0–34.9), and severely obese (≥35.0). We also performed analyses with normal-weight individuals subdivided into 2 categories (BMI 18.5–22.49 and 22.5–24.9), with 18.5–22.49 hereafter referred to as the reference category. On the subcohort questionnaire, participants were asked to report their height at age 18 years; weight at ages 18 years, 35 years, and 50 years; and current waist and hip circumferences. We estimated the participants' BMIs when they were 18 years of age using reported height at age 18 years and BMIs at ages 35 years and 50 years using current height reported on the baseline questionnaire. Spearman correlation coefficients for BMI at different ages ranged from 0.34 to 0.82 overall, with slightly lower correlations between BMI at baseline and BMI at younger ages among participants who were 65 years of age or older at baseline (Web Table 1, available at http://aje.oxfordjournals.org/). Categories for BMI at ages 35 years and 50 years were the same as those used in the baseline analyses. The few participants who were obese at age 18 years were included with those in the overweight category (i.e., BMI ≥25.0). On the subcohort questionnaire, participants were asked to record their waist and hip circumferences using a tape measure; if a tape measure was unavailable or measurement was otherwise not possible, participants were asked to leave the answers to these questions blank. Waist circumferences and WHRs were categorized separately for men and women according to quartiles of the sex-specific distributions.

Information about lifetime history of predominantly leisure-time physical activity was collected on the subcohort questionnaire. Participants reported the amount of time (hours per week) spent performing light-intensity activities (e.g., slow walking, light gardening, and fishing) and moderate- or vigorous-intensity activities (e.g., tennis, biking, and running) at ages 15–18 years, 19–29 years, and 35–39 years and during the past 10 years. We estimated participants' levels of physical activity in metabolic equivalent (MET) hours per week using methods described by Moore et al. (16); participants were categorized according to age-specific quartiles of the MET hours/week index.

Statistical analysis

Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards regression models, with person-years as the underlying time metric. All statistical models were adjusted for age at study entry (50–54 years, 55–59 years, 60–64 years, 65–69 years, and ≥70 years), race (non-Hispanic white; non-Hispanic black; Hispanic; Asian, Pacific Islander, or American Indian/Alaskan Native; or missing), and sex (in analyses with men and women combined). Additional adjustments for educational level and smoking status did not materially change our results. We also performed analyses stratified by sex. Analyses of BMI at baseline were performed in both the entire cohort and, using information from the second questionnaire, in the subcohort of participants. Although we have included findings from both analytical cohorts, we focused this report on the baseline BMI results from the subcohort for comparability with results of analyses of BMI at different ages in which we used data available only for the subcohort. Similar models were used to evaluate BMI at different ages. Analyses of BMI at each age were also performed with adjustment for baseline BMI. Risk estimates from these analyses reflect the association between age-specific BMI and multiple myeloma above and beyond the impact of change in BMI through baseline on multiple myeloma risk. We also evaluated the joint associations of BMI at age 18 years and current BMI at baseline and assessed the interaction using a likelihood ratio test. Analyses of physical activity level at different ages were done both with and without adjustment for age-specific BMI. Tests for linear trends across BMI and physical activity categories were conducted using score variables for which the within-category median value for BMI or MET hours/week was assigned to each individual in that category; statistical significance was assessed using the Wald test. Continuous analyses were performed to evaluate the change in risk of multiple myeloma that corresponded to a 5-kg/m^2 increase in BMI. To evaluate the interaction between BMI at study baseline and physical activity level in the past 10 years, we analyzed BMI and physical activity level as continuous variables and included a cross-product term in the statistical model.

Lagged analyses of BMI at study baseline were performed for the full cohort with lag periods of 1 year, 2 years, and 5.9 years (the median follow-up time among cases) to assess whether weight loss related to preclinical disease may have affected risk estimates and to evaluate potential effect modification by time of follow-up. All statistical analyses were performed using Stata, version 10.1 (StataCorp LP, College Station, Texas). Findings were considered statistically significant if 2-sided P values were <0.05.

RESULTS

Participants who had higher BMIs at study baseline tended to be younger and were more likely to be black than were normal weight participants (Table 1). Sex was also related to BMI, with a higher proportion of overweight and obese individuals being male and a higher proportion of severely obese individuals being female.

Among men and women combined, BMI at baseline was positively associated with risk of multiple myeloma (P_{trend} = 0.008; Table 2). When BMI was modeled as a continuous variable, risk of multiple myeloma increased by 10% for each 5-kg/m^2 increase in BMI (hazard ratio for 5-kg/m^2 increase in BMI (HR_{cont}) = 1.10, 95% confidence interval (CI): 1.00, 1.22). Similar associations were observed for BMI at age 50 years (HR_{cont} = 1.14, 95% CI: 1.02, 1.28), age 35 years (HR_{cont} = 1.20, 95% CI: 1.05, 1.36), and age 18 years (HR_{cont} = 1.13, 95% CI: 0.98, 1.32). Risk estimates for BMI at these ages were similar or only slightly attenuated after adjustment for BMI at baseline (age 50 years, HR_{cont} = 1.14, 95% CI: 0.93, 1.38; age 35 years, HR_{cont} = 1.19, 95% CI: 1.02, 1.40; and age 18 years, HR_{cont} = 1.10, 95% CI: 0.93, 1.29). Relative to individuals in the reference category

(BMI 18.5–22.49), those who were severely obese (BMI ≥35) had an increased risk of multiple myeloma when BMI was assessed at baseline (HR = 1.55, 95% CI: 1.01, 2.39), at age 50 years (HR = 1.77, 95% CI: 1.05, 2.99), and at age 35 years (HR = 2.53, 95% CI: 1.24, 5.18). Individuals who were overweight or obese at age 18 years had a higher risk of multiple myeloma (HR = 1.38, 95% CI: 1.04, 1.82) than did individuals in the reference group at that age. Findings for BMI at each age were similar when 18.5–24.9 was used as the reference category (Web Table 2).

In sex-specific analyses of BMI as a continuous variable at different ages, risk estimates were similar or only slightly higher among women than they were among men (Table 2); tests of interaction between BMI and sex were not statistically significant. In analyses stratified by age at baseline (<65 years vs. ≥65 years), risk estimates differed slightly between age strata, but no consistent patterns of association were observed and differences were not statistically significant (data not shown). Results of lagged analyses for baseline BMI were generally consistent with the unlagged results in the baseline cohort, although lagged risk estimates for severe obesity (BMI ≥35) compared with normal weight (BMI 18.5–24.9) were somewhat greater in the overall analysis and among men (e.g., with a 5.9-year lag period, for men and women combined, HR = 1.41, 95% CI: 0.93, 2.15; for men only, HR = 1.27, 95% CI: 0.69, 2.36; and for women only, HR = 1.43, 95% CI: 0.79, 2.57; Web Table 3).

In a joint analysis of BMI at age 18 years and at baseline, we found that participants who were overweight or obese at age 18 years had an estimated 37%–53% nonsignificant elevated relative risk of multiple myeloma compared with individuals who were in the reference category (Table 3). The highest risk estimates were observed for individuals who were consistently overweight throughout adulthood (for BMI ≥25 at age 18 years and BMI 25–29.9 at baseline, HR = 1.53, 95% CI: 1.00, 2.34; for BMI ≥25 at age 18 years and BMI ≥30 at baseline, HR = 1.45, 95% CI: 0.95, 2.20). We did not observe statistically significant associations with multiple myeloma for waist circumference or WHR (Web Table 4). Findings for waist circumference and WHR were unchanged after additional adjustment for BMI (not shown). The mean levels of physical activity MET hours/week were 33.7 (standard deviation, 20.3) MET hours/week in the past 10 years, 35.5 (standard deviation, 20.4) MET hours/week at ages 35–39 years, 37.6 (standard deviation, 20.5) MET hours/week at ages 19–29 years, and 38.4 (standard deviation, 21.1) MET hours/week at ages 15–18 years. No statistically significant associations between level of physical activity at different ages and risk of multiple myeloma were observed (Table 4). There was no evidence of an interaction between BMI at baseline and physical activity level in the past 10 years ($P_{interaction} = 0.9$). Results for physical activity were similar when we did not adjust for age-specific BMI (data not shown). Findings for all measures of adiposity and physical activity level were similar in sensitivity analyses restricted to non-Hispanic whites (data not shown). We repeated the analyses of BMI at different ages after including cases of multiple myeloma that were preceded by another incident cancer diagnosis, and our results were essentially unchanged (per 5-kg/m^2 increase in BMI, at baseline, $HR_{cont} = 1.13$, 95% CI: 1.03, 1.24; at age 50 years, HR = 1.16, 95% CI: 1.05, 1.29; at age 35 years, HR = 1.20, 95% CI: 1.06, 1.35; and at age 18 years, HR = 1.14, 95% CI: 0.99, 1.31).

DISCUSSION

In this large prospective cohort of US adults, we observed a modest positive association between baseline BMI and the risk of multiple myeloma. These findings are consistent with prior evidence showing that excess body weight confers an increased risk of multiple myeloma; our observed risk estimates for overweight and obese persons were similar in magnitude to those reported in a recent meta-analysis of 15 prospective studies in which investigators evaluated multiple myeloma incidence (3).

We also observed associations between multiple myeloma risk and high BMI earlier in adult life. This study is, to our knowledge, the largest prospective investigation of potential associations between BMI at different ages throughout adulthood and the risk of multiple myeloma. Of the other studies that assessed both BMI in midlife (cohort baseline) and in early adulthood (age 18–20 years), 1 (involving 243 multiple myeloma cases) observed a stronger association with obesity at age 20 years (7), another (with 291 cases) did not observe notable differences in risk estimates by age (6), and 2 others (with 92 and 111 cases, respectively) found no association between multiple myeloma risk and BMI at

Table 3. Risk of Multiple Myeloma in Relation to Body Mass Index at 18 Years of Age and Body Mass Index at Baseline, National Institutes of Health-AARP Diet and Health Study, 1995–2006[a]

BMI[b] at Age 18 Years	BMI at Baseline									$P_{interaction}$
	<25			25–29.9			≥30			
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	
<22.5	113	1.0	Referent	124	1.06	0.82, 1.37	48	1.24	0.88, 1.74	
22.5–24.9	22	1.41	0.90, 2.24	36	1.03	0.70, 1.50	26	1.38	0.90, 2.11	
≥25	7	1.37	0.64, 2.94	27	1.53	1.00, 2.34	28	1.45	0.95, 2.20	0.70

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age at study entry, sex, and race.
[b] Weight (kg)/height (m)^2.

Table 4. Hazard Ratios and 95% Confidence Intervals for the Risk of Multiple Myeloma in Relation to Level of Physical Activity at Different Ages, National Institutes of Health-AARP Diet and Health Study, 1995–2006[a]

Quartile of Physical Activity Level at Various Time Periods, Overall and by Sex	No. of Cases	HR	95% CI	P_{trend}[c]
Men and women combined				
Past 10 years				0.19
1	125	1.0	Referent	
2	85	1.10	0.83, 1.45	
3	113	1.10	0.85, 1.43	
4	148	1.19	0.93, 1.52	
Ages 35–39 years				0.064
1	125	1.0	Referent	
2	105	1.02	0.78, 1.33	
3	119	1.10	0.85, 1.43	
4	120	1.27	0.97, 1.64	
Ages 19–29 years				0.94
1	119	1.0	Referent	
2	113	1.07	0.82, 1.39	
3	100	1.01	0.77, 1.33	
4	139	1.03	0.79, 1.33	
Ages 15–18 years				0.30
1	126	1.0	Referent	
2	102	0.80	0.61, 1.05	
3	123	0.99	0.76, 1.28	
4	119	0.83	0.63, 1.08	
Men				
Past 10 years				0.42
1	94	1.0	Referent	
2	50	0.93	0.66, 1.32	
3	83	1.07	0.79, 1.45	
4	92	1.10	0.82, 1.48	
Ages 35–39 years				0.25
1	97	1.0	Referent	
2	78	1.12	0.83, 1.52	
3	76	1.07	0.79, 1.46	
4	68	1.23	0.90, 1.69	
Ages 19–29 years				0.52
1	81	1.0	Referent	
2	85	1.27	0.93, 1.74	
3	71	1.14	0.82, 1.59	
4	84	1.15	0.84, 1.58	
Ages 15–18 years				0.86
1	79	1.0	Referent	
2	73	0.81	0.58, 1.13	
3	85	1.04	0.76, 1.42	
4	84	0.92	0.67, 1.27	

Table continues

Table 4. Continued

Quartile of Physical Activity Level at Various Time Periods, Overall and by Sex	No. of Cases	HR	95% CI	P_{trend}[c]
Women				
Past 10 years				0.27
1	31	1.0	Referent	
2	35	1.53	0.94, 2.50	
3	30	1.16	0.69, 1.94	
4	56	1.43	0.90, 2.26	
Ages 35–39 years				0.092
1	28	1.0	Referent	
2	27	0.79	0.46, 1.35	
3	43	1.15	0.70, 1.90	
4	52	1.30	0.80, 2.09	
Ages 19–29 years				0.42
1	38	1.0	Referent	
2	28	0.68	0.41, 1.13	
3	29	0.76	0.46, 1.25	
4	55	0.78	0.49, 1.24	
Ages 15–18 years				0.12
1	47	1.0	Referent	
2	29	0.80	0.50, 1.29	
3	38	0.91	0.58, 1.43	
4	35	0.64	0.39, 1.06	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

[a] Adjusted for age at baseline, sex (overall model only), race, and age-specific BMI. Results were similar without BMI adjustment. Because of missing data, the reported frequencies may not sum to the full number of cases of multiple myeloma included in this study.

[b] Age-specific quartiles of the metabolic equivalent hours/week were assigned as follows: In the past 10 years: <16.25, 16.25–29.9, 30–49.9, and ≥50; ages 35–39 years: <16.25, 16.25–34.9, 35–51.9, and ≥52; ages 19–29 years: <18, 18–40.9, 41–51.9, and ≥52; and ages 15–18 years: <18, 18–41.9, 42–63.9, and ≥64.

[c] Values were assigned by physical activity category using the within-category median.

either age (4, 5). We note that in our study, the associations were slightly stronger for high BMI in early adulthood than for high BMI at baseline, although the confidence intervals for these risk estimates overlap. It has been suggested that BMI in early adulthood may be more representative of lifetime body size than BMI at study baseline (3). If so, the observed associations for BMI at ages 18 years and 35 years may reflect a more accurate estimation of the true relative risk for obesity throughout adult life. It is also possible that excess body weight during early adulthood may be more etiologically relevant to multiple myeloma development than excess body weight later in life, as is the case for other chronic diseases (discussed by Perry et al. (17)). Our findings for the joint impact of BMI at age 18 years and at baseline, as well as those for age-specific BMI analyses adjusted for baseline BMI, are consistent with this hypothesis. However, these findings need to be replicated in other large studies or in pooled analyses before meaningful inferences regarding obesity at different ages can be drawn.

There was no evidence of an association between waist circumference or WHR and multiple myeloma risk in this study. Findings from previous studies of multiple myeloma risk in relation to waist circumference have been inconsistent. Waist circumference was positively associated with multiple myeloma risk in the Iowa Women's Health Study (8), but other studies found no association among women (5) or in sex-specific (9) or sex-combined (10) analyses. Findings from prior studies of multiple myeloma risk in relation to WHR have been null (5, 8–10), similar to what we found. Collectively, results from the present study and other studies suggest that overall adiposity, rather than abdominal adiposity, may be a risk factor for multiple myeloma.

We did not observe any association between leisure-time physical activity and the risk of multiple myeloma in this study, and we found no evidence of an interaction with BMI. To our knowledge, only one other study has evaluated the risk of incident multiple myeloma in relation to physical activity (11); findings from that study regarding physical

activity were similarly null. In another study, Khan et al. (18) found a 2-fold increased risk of death from multiple myeloma among individuals who walked for 30 minutes per day or less compared with those who walked 1 hour or more per day. To follow up on this finding, we performed analyses of light leisure-time physical activity (which includes slow walking), but we did not find evidence of an association. However, our findings may not be comparable because Khan et al. did not report associations for other types of physical activity and analyzed mortality rather than incidence. Overall, there is little evidence to suggest that physical activity level plays an important role in the etiology of multiple myeloma, but the possibility of a modest association cannot be excluded.

Although the specific biologic mechanisms underlying the association between excess body weight and multiple myeloma have not yet been elucidated, inflammatory, hormonal, and insulin-related pathways are suspected to play a role (19). Severe immune dysregulation is associated with an increased risk of multiple myeloma (20–22), and it is possible that subclinical immunologic effects of excess adiposity may lead to myelomagenesis. The proinflammatory cytokine interleukin-6 plays an important role in the survival and proliferation of myeloma cells (23), and elevated levels of interleukin-6 are positively associated with obesity (24). Alterations in circulating levels of adipokines (e.g., adiponectin, leptin), which are secreted by adipose tissue and associated with obesity, influence expression of pro- and anti-inflammatory cytokines (25) and have been linked to myelomagenesis (26). Increased insulin resistance and chronic hyperinsulinemia can lead to elevated concentrations of bioavailable insulin-like growth factor-1 (19), which is associated with the survival and proliferation of myeloma cells (27, 28).

Strengths of this study include its large sample size and prospective design. With 813 incident cases of multiple myeloma in the baseline cohort and 489 cases in the subcohort, we had sufficient statistical power to detect modest associations with BMI both overall and stratified by sex. To our knowledge, only one other prospective study that evaluated risk of plasma cell neoplasms in relation to BMI included a larger number of cases (29); findings for BMI assessed at the start of follow-up (at ages 20–74 years) were similar to our results for baseline BMI. However, Engeland et al. (29) did not report results for BMI assessed at different ages. The availability of detailed information on BMI and physical activity at various ages during adolescence and adulthood, as well as data on waist circumference and WHR, are also important strengths of this analysis.

This study also has limitations. Data on BMI, body size, and physical activity level were based on self-report and may be subject to measurement error. In particular, we would expect some error in measures of height and body weight from adolescence and early adulthood because participants were required to recall this information from a period several decades prior to the administration of the questionnaire. Assuming that such measurement error is independent of a future diagnosis of multiple myeloma, the resulting bias of the analyses of BMI as a continuous variable would be expected to attenuate the observed associations toward the null; thus, actual associations between BMI modeled continuously and the risk of multiple myeloma might be stronger than what we observed. Assessment of physical activity level may also be subject to measurement error and attenuation in the magnitude of the associations observed (30, 31). Because of this, our null findings for physical activity should be interpreted with caution; we cannot rule out a modest association with multiple myeloma.

Because questions about height and weight at different ages were not asked on the baseline questionnaire, we could only evaluate BMI earlier in adult life in the subcohort. Most participants (63%) completed both the baseline questionnaire and the second questionnaire. Relative to participants who completed both questionnaires, those who only completed the baseline questionnaire were slightly younger (mean age of 61.6 years vs. 62.3 years), were more likely to be male (62.3% vs. 58.7%), were more likely to be non-white (10.8% vs. 7.4%), and had slightly higher BMI (mean of 27.3 vs. 26.9). Despite these differences, the risk estimates for baseline BMI modeled continuously were similar for the overall cohort and the subcohort (per 5-kg/m^2 increase in BMI, HR = 1.08 and 1.10, respectively). Although the hazard ratio for severe obesity (BMI ≥35) at baseline was higher for the subcohort than the overall cohort, in this category, there were relatively few cases who completed the baseline questionnaire only ($n = 15$); consequently, the observed differences may be due to chance. The hazard ratios for other categories were similar in the subcohort and overall analyses.

Because the vast majority of study participants were non-Hispanic whites (91%), we could not perform analyses stratified by race. However, our findings were essentially unchanged in sensitivity analyses restricted to non-Hispanic whites.

In conclusion, the findings from this large prospective study are consistent with previous reports of an increased risk of multiple myeloma among overweight and obese individuals and suggest that excess body weight in both early adulthood and later in life is a risk factor for multiple myeloma. Maintaining a healthy body weight throughout adult life may reduce the risk of multiple myeloma. Additional studies are needed to replicate our age-specific findings for BMI and to evaluate the biologic mechanisms through which adiposity influences myelomagenesis. Our null findings for physical activity also need to be confirmed in other studies.

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