Low levels of circulating adiponectin are associated with multiple myeloma risk in overweight and obese individuals

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Abstract

The association between obesity and multiple myeloma (MM) risk may be partly attributed to reduced circulating levels of adiponectin in obese individuals. To prospectively evaluate MM risk in relation to adiponectin levels overall and stratified by body mass index and other characteristics, we conducted a pooled investigation of pre-diagnosed peripheral blood samples from 624 MM cases and 1,246 individually matched controls from seven cohorts participating in the MM Cohort Consortium. Analysis of circulating analyte levels measured by enzyme-linked immunosorbent assays revealed that higher total adiponectin levels were associated with reduced MM risk overall

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(highest quartile vs. lowest: odds ratio [OR]=0.64, 95% confidence interval [CI]=0.47-0.85; P_{trend} = 0.001). This association was apparent among cases diagnosed six or more years after blood collection (OR=0.60, CI=0.40-0.90; P_{trend} = 0.004) and was similar in magnitude for men and women (OR=0.59 and 0.66, respectively). Interestingly, we observed strong associations among subjects who were overweight (OR=0.41, CI=0.26-0.65) or obese (OR=0.41, CI=0.17-0.98) but not among those with normal weight (OR=1.20, CI=0.73-2.00; overweight/obese vs. normal weight, $P_{interaction}$ = 0.04). Our findings provide the strongest epidemiologic evidence to date that adiponectin protects against MM development, particularly among overweight and obese individuals, and offer a method for risk assessment in this susceptible population of heavier patients.

Introduction

An estimated 26,850 cases of multiple myeloma (MM), a plasma cell malignancy, were diagnosed in the United States in 2015 (1). Currently, there is no established curative treatment for MM, and although clinical outcomes have improved in recent years it remains a highly fatal malignancy, with an estimated 5-year relative survival of 47% in the United States (1). MM is consistently preceded by monoclonal gammopathy of undetermined significance (MGUS), a premalignant plasma cell disorder characterized by the presence of a monoclonal protein in serum and/or urine in the absence of evidence of smoldering or overt MM. The etiology of MM remains poorly understood; established risk factors include older age, male sex, African ancestry, family history of lymphoid malignancies, and severe immune dysregulation (2, 3). Obesity has also been consistently associated with an increased risk of MM (4-6). Decreased circulating levels of adiponectin, a polypeptide hormone with important anti-proliferative, anti-inflammatory and insulin-sensitizing properties (7), have been proposed as a potential mechanism through which obesity contributes to myelomagenesis. Although adiponectin is secreted mainly by visceral adipose tissue, it is well established that, paradoxically, circulating levels are lower among obese individuals compared to those with normal body weight (8). This hormone activates adiponectin receptors, which are expressed by many normal cell types and cancers including myeloma cells (9). Adiponectin receptor activation results in activation of AMP kinase, which in turns regulates cellular energy metabolism in a manner that involves inhibition of mTOR and downregulation of oxidative phosphorylation (9-12).

In a recent prospective investigation of 174 cases and 348 controls in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, we observed a statistically significant reduced risk of MM among participants with higher circulating levels of total adiponectin (13). The study's small sample size limited the interpretation of this finding, and precluded more detailed analyses across population subgroups of body mass index (BMI) categories. However, it is intriguing that the results are consistent with recent experimental evidence from studies conducted *in vitro* and in animal models that adiponectin induces myeloma cell apoptosis (9, 14). Few other obesity- or immune-related biomarkers have been associated with risk of MM in prospective studies, although there is some evidence to suggest that pre-diagnosis levels of IGF binding protein-1 and soluble IL-6 receptor are elevated in the years immediately preceding MM diagnosis (15).

To better understand the relationship between circulating adiponectin and MM risk, both overall and across normal weight, overweight and obese individuals, we conducted a pooled investigation involving 624 cases and 1,246 controls within the MM Cohort Consortium (MMCC).

Materials and Methods

Study population

We selected 627 MM cases and 1,247 individually-matched controls from seven cohorts participating in the MMCC: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC; 59 cases, 118 controls); the Cancer Prevention Study II (CPS-II; 68 cases, 136 controls); the Health Professionals Follow-up Study (HPFS; 28 cases, 55 controls); the Melbourne Collaborative Cohort Study (MCCS; 53 cases, 106 controls); the Nurses' Health Study (NHS; 48 cases, 90 controls); the PLCO Cancer Screening Trial (174 cases, 348 controls); and the Women's Health Initiative (WHI; 197 cases, 394 controls). The majority of subjects (453 cases, 899 controls) were selected from cohorts other than PLCO and are hereafter described as the replication set; the pooled data from all cohorts including PLCO is defined as the combined set. The design and methods of the participating cohorts have been described (16-22). Most (71%) of the selected subjects were included in a previous investigation in the MMCC (15). As in the previous study, we selected cases with archived pre-diagnosis blood samples who had a confirmed incident primary diagnosis of MM (ICDA=203; ICD-O-2-M=9731, 9732, 9830; or ICD-O-3-M=9731-9734). We restricted cases to those diagnosed at least 3 months after the date of phlebotomy, and excluded cases with a history of cancer (other than non-melanoma skin cancer) prior to the MM diagnosis. Controls were also cancer-free as of the corresponding case diagnosis date, and were individually matched to cases with a 2:1 ratio with the exception of a small number of cases (N=7) matched 1:1 to controls. The matching criteria included cohort of origin, birth year (±12 months), sex, race (white, black, Asian, other), type of blood sample (serum, plasma-heparin, plasma-EDTA), date of blood collection (±2 months), and (when available) fasting status at blood draw (<8, ≥8 hours since last meal). Among the selected subjects, one case and one control had insufficient sample volume for analysis, and two additional cases were later adjudicated as not having MM. After excluding these subjects, there remained 450 cases and 898 controls in the replication set and 624 cases and 1,246 controls in the combined set. All of the participating cohorts received Institutional Review Board approval from their respective institutions.

Analyte measurements

Circulating levels of total and high-molecular-weight (HMW) adiponectin were measured among selected subjects from all of the participating cohorts. These analytes were measured in duplicate using standard enzyme-linked immunosorbent assay (ELISA) methods; assays were performed in the laboratory of M.N.P. at McGill University (www.mcgill.ca/assaylab) using reagents purchased from R&D Systems, Inc. (Minneapolis, MN). The lower limits of detection were 3.9 ng/mL for both total and HMW adiponectin. Samples from matched case-control sets were analyzed together in the same batch. Blinded quality control (QC) samples from the participating cohorts were included with the test samples from each cohort, and

pooled QC specimens were added to each of the batches for all of the participating cohorts. Samples from a subset of controls (N=66) from the original study in PLCO were re-tested contemporaneously with those from the other cohorts; these assay results showed excellent agreement with the original measurements (spearman $\rho = 0.96$). For the study-specific QC results, the median (range) overall coefficients of variation (CVs) were 8.3% (4.5%-19.6%) for total adiponectin and 7.0% (2.9%-18.7%) for HMW adiponectin. The CVs for pooled QC specimens were 5.6% and 5.3% for total and HMW adiponectin, respectively; no evidence of laboratory drift across cohorts was observed for either analyte.

Statistical analysis

We evaluated determinants of natural log-transformed analyte concentrations among controls using multivariable linear regression models including cohort, age, sex, race, and BMI as independent variables. Differences in median analyte levels between cases and controls were assessed using the Wilcoxon rank-sum test. For our main analyses, we computed odds ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression models, conditioning on the matched sets, to assess future risk of MM in relation to quartiles of analyte concentrations. Tests for trend were performed by assigning the value of the within-category median to each quartile. As in the previous study (15), we performed a “cohort adjustment” to the original analyte values to reduce the impact of cohort-related variability in analyte levels, and we further adjusted analyte levels for sex to correct for differences between men and women within and across studies; a description of these procedures is available in the Supplemental Methods. We also performed analyses using quartile cut points based on the overall (and sex-specific) distributions among pooled controls. Additional analyses included BMI (modeled categorically as <25, 25-29.9, and ≥30 kg/m^2) as a covariate. To assess whether the relationships between adiponectin and MM risk differed across population subgroups, we stratified analyses by sex, time from blood collection to case diagnosis/control reference date (<6 years, ≥6 years), BMI category (<25, 25-29.9, and ≥30 kg/m^2), and age at blood collection (<65 years, ≥65 years). We used conditional logistic regression models for analyses stratified by matching factors, and unconditional models adjusted for matching factors for analyses stratified by BMI category; tests of multiplicative interaction were based on the same models as those used for the stratified analyses and were performed using likelihood ratio tests comparing models with and without the interaction terms. We also estimated study-specific ORs and 95% CIs, and assessed OR heterogeneity across cohorts using Cochran’s Q test and the I^2 statistic (23).

To evaluate a possible non-linear relation between adiponectin and MM risk, we modeled adiponectin levels using restricted cubic splines with 4 automatically placed knots (at the 5^{th}, 32^{nd}, 63^{rd}, and 95^{th} percentiles among controls) in unconditional logistic regression models adjusted for the matching factors (24). Models were fit both overall and within selected strata of BMI (<25, ≥25 kg/m^2). For these analyses, we excluded 19 extreme high values (>3 standard deviations above the mean) and 1 implausibly low value. We repeated the analyses changing the number and placement of the knots to evaluate the robustness of our findings. We assessed non-linearity using likelihood ratio tests comparing the model with only the linear term for adiponectin with the models that included the linear term and the cubic spline terms.

Several sensitivity analyses were performed. We repeated the main analyses after excluding subjects with outlying analyte values (>3 standard deviations above the mean), and performed analyses restricted to non-Hispanic whites. For all analyses, findings were considered to be statistically significant if the two-sided *P*-value was < 0.05.

Results

Consistent with the matched design of this study, the distributions of sex, race, and age at phlebotomy were similar for the cases and controls (Table 1). Levels of total adiponectin among controls increased with age (medians of 9.3 and 12.0 μg/mL for 40-59 years and ≥70 years, respectively) and were lower for obese persons compared to those with normal body weight (medians of 8.8 and 12.7 μg/mL, respectively), for men compared with women (8.0 and 13.7 μg/mL), and for blacks compared with whites (7.2 and 11.0 μg/mL) (all $P < 0.001$; Supplementary Table S1).

As shown in Table 1, cases had significantly lower analyte levels than controls for total adiponectin (medians of 11.5 and 12.8 μg/mL, respectively; $P = 0.001$, Wilcoxon rank-sum test) and HMW adiponectin (medians of 6.6 and 7.4 μg/mL; $P = 0.002$). Total and HMW adiponectin concentrations were almost perfectly correlated (Spearman $\rho = 0.99$ among controls). Thus, we focus on the results for total adiponectin and present the HMW adiponectin results in the online supplement. High total adiponectin levels were associated with a reduced risk of MM in both the independent replication (highest quartile vs. lowest: OR 0.68, 95% CI 0.48-0.96; $P_{trend} = 0.02$) and combined sets (OR 0.64, 95% CI 0.47-0.85; $P_{trend} = 0.001$; Table 2). These findings were unchanged when adjusted for BMI (OR 0.64, 95% CI 0.47-0.87; $P_{trend} = 0.001$). In the restricted cubic spline regression analyses, the relation between total adiponectin and MM was similar to that observed in the categorical analyses (Supplementary Figure 1); an overall test for a linear relation was statistically significant ($P = 0.0007$) and we did not find evidence of a significant departure from linearity in this analysis (P for non-linearity = 0.4) or in the alternative spline models (data not shown).

In logistic regression models stratified by BMI (Table 3), we observed a strong inverse association between adiponectin levels and MM risk among overweight or obese individuals (OR of 0.41 for the highest quartile vs. the lowest in both overweight and obese subjects, $P_{trend} \leq 0.039$), but found no evidence of an association among normal weight persons ($P_{trend} = 0.79$; $P_{interaction} = 0.04$). In the spline models stratified by BMI category (Figure 1), we observed a clear linear relation between adiponectin and MM risk among overweight and obese individuals (P for linearity = 0.0001) but not among normal weight individuals (P for linearity = 0.8). We did not find evidence of a significant departure from linearity in either group (P for non-linearity = 0.4 and 0.8 for overweight/obese and normal weight individuals, respectively).

In other stratified analyses (Table 3) the risk estimates were not significantly different for men and women (ORs for highest quartile vs. lowest were 0.59 and 0.66 for men and women, respectively; $P_{interaction} = 0.5$) or for those who were < 65 years or ≥65 years of age at blood collection (OR of 0.61 for both groups; $P_{interaction} = 0.4$). Notably, the association

between adiponectin and MM was present and similarly strong even in cases diagnosed 6 or more years after blood collection (OR 0.62, 95% CI 0.42-0.93; P_{trend} = 0.008; <6 vs. ≥6 years, $P_{interaction}$ = 0.2). We found no evidence of heterogeneity across cohorts (total adiponectin levels above vs. below median: I^2 = 0%, P = 0.8; Figure 2).

Our findings for total adiponectin were unchanged when outliers among analyte values were excluded (highest quartile vs. lowest: OR 0.63, 95% CI 0.47-0.85; P_{trend} = 0.001), when quartile cut points were based on the overall distribution among pooled controls rather than the cohort- and sex-adjusted levels (OR 0.52; 95% CI 0.38-0.73; P_{trend} < 0.001), and after restricting analyses to non-Hispanic white subjects (OR 0.67, 95% CI 0.50-0.92; P_{trend} = 0.003). The results were also essentially the same for total and HMW adiponectin (Supplementary Table S2).

Discussion

This pooled investigation provides the strongest epidemiologic evidence to date that high pre-diagnosis circulating adiponectin levels may help to protect against development of MM, and suggests for the first time that this association may be particularly strong among overweight and obese individuals. We found that high adiponectin levels were associated with a statistically significantly reduced future risk of MM in this study involving MM cases and matched controls from seven cohorts. The consistency in the association between adiponectin and MM across cohorts, with inverse associations observed in all but one study, lends further support to our hypothesis. The association between adiponectin and MM remained when we restricted to cases diagnosed six or more years after blood collection, suggesting that altered adiponectin levels may play a role in the etiology of MM rather than resulting from pre-clinical disease.

Notably, our findings for adiponectin are consistent with recent experimental evidence that this hormone induces myeloma cell apoptosis (9, 14). Several proposed biological mechanisms might explain in part the observed inverse association between adiponectin and risk of MM, such as activation of AMP kinase, and suppression of lipogenesis through protein kinase A activation and downregulated expression of acetyl-CoA-carboxylase (9). Alternately, it is well-established that adipose tissue is metabolically active and that excess adiposity can produce a chronic inflammatory state (25). Adiponectin may in turn prevent MM development by suppressing pro-inflammatory cytokines such as IL-6 and/or inducing anti-inflammatory cytokines such as IL-10 and IL-1RA (26-28). A novel finding from this study is that the inverse association between adiponectin and MM was only apparent among overweight and obese individuals. This pattern suggests that adiponectin may reduce MM risk by suppressing other protumorigenic effects of obesity.

Our findings may be relevant to the prevention and management of MM and its precursor MGUS. Currently, obesity is the only established potentially modifiable risk factor for MM (6); recent findings suggest that central obesity, in addition to excess body weight overall, may be associated with MM risk (5). Efforts to control obesity may reduce the incidence of MM, possibly by modulating circulating adiponectin levels. Given that circulating levels of adiponectin are strongly negatively correlated with the amount of visceral adipose tissue

(25), reducing central obesity may be particularly important. Furthermore, adiponectin receptor agonists are being studied as drug candidates for metabolic diseases (29); our data support the possibility that they may be useful in MM prevention or treatment.

We also note that, in secondary analyses among controls, adiponectin levels were considerably lower among blacks compared with whites even after adjustment for BMI, consistent with previous reports (30, 31). One prior investigation found that among women with comparable levels of visceral adiposity, circulating levels of adiponectin were lower among African Americans compared with whites (32). The well-documented greater than two-fold excess incidence of MM in black men and women persists in the US (33) and remains unexplained. The present findings suggest that differences by race in circulating adiponectin levels may play a role. Studies in more racially diverse populations are warranted to investigate the association between adiponectin and MM among blacks, and whether differences in adiponectin levels contribute to racial disparities in this malignancy.

This investigation has several strengths. With 624 MM cases and 1,246 controls, it is the largest study to evaluate the relationship between pre-diagnosis circulating adiponectin and MM, and the first to evaluate this association separately within strata of BMI. Other strengths include the prospective design and the availability of high quality covariate data that were harmonized across cohorts. Limitations of the study include a relatively small number of subjects in some strata (e.g., blacks) and the lack of information on MGUS status at the time of phlebotomy. Priorities for future studies include assessment of whether differences by race and sex in adiponectin levels contribute to disparities in MM incidence, characterization of the role of this metabolic hormone in progression from MGUS to clinically manifest disease, and evaluation of the clinical implications of our findings for risk reduction and therapy among MM patients and overweight/obese patients in particular.

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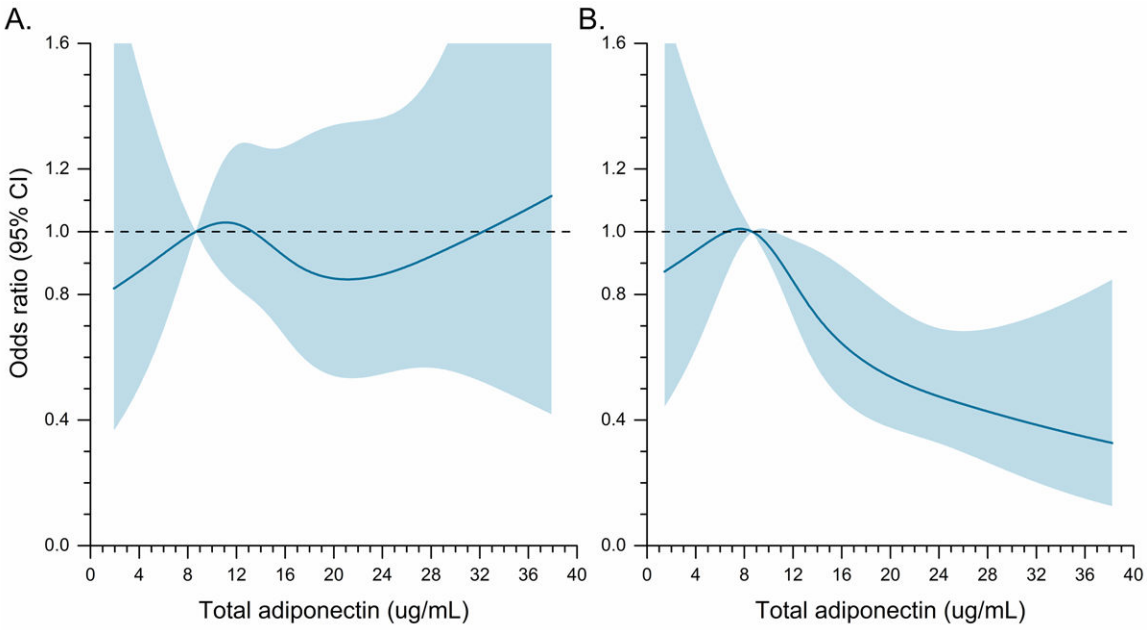

Figure 1.

Risk of MM in relation to circulating total adiponectin levels estimated using restricted cubic spline regression models with 4 knots, among individuals with A) body mass index (BMI) <25 kg/m^2 (P-linear = 0.8, P-nonlinearity = 0.8); and B) BMI ≥25 kg/m^2 (P-linear = 0.0001, P-nonlinearity = 0.4). The odds ratio is represented by the solid line, and the 95% confidence interval (CI) is represented by the shaded area.

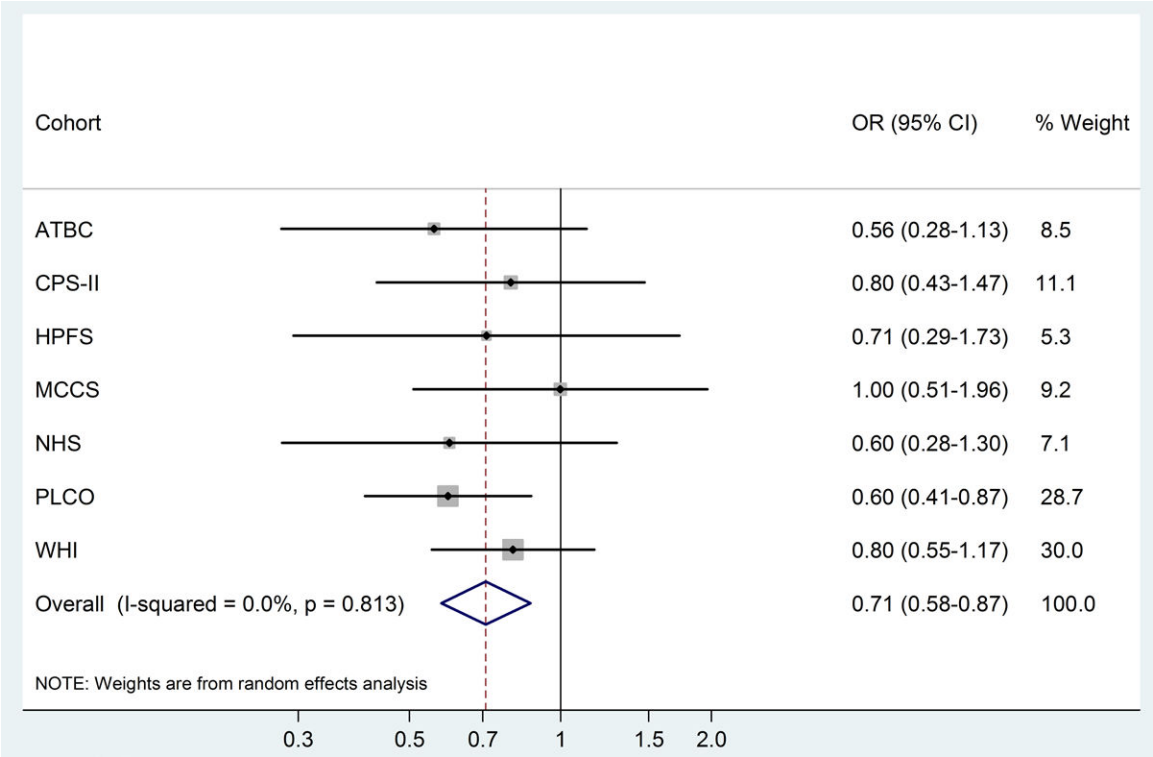

Figure 2.

Cohort-specific and meta-analysis summary odds ratios (OR) and 95% confidence intervals (CI) for the relationship between circulating total adiponectin levels (above vs. below median) and risk of MM.

Table 1

Selected characteristics of cases and controls in the Multiple Myeloma Cohort Consortium*

Characteristic	Cases	Controls
No. of persons	624 (100)	1,246 (100)
Cohort		
Alpha-Tocopherol, Beta-Carotene Study (ATBC)	59 (9.5)	117 (9.4)
Cancer Prevention Study II (CPS-II)	67 (10.7)	136 (10.9)
Health Professionals Follow-up Study (HPFS)	28 (4.5)	55 (4.4)
Melbourne Collaborative Cohort Study (MCCS)	52 (8.3)	106 (8.5)
Nurses' Health Study (NHS)	48 (7.7)	90 (7.2)
PLCO Cancer Screening Trial[a]	174 (27.9)	348 (27.9)
Women's Health Initiative (WHI)	196 (31.4)	394 (31.6)
Mean age at blood draw, years (SD)	63.9 (7.0)	63.9 (7.0)
Sex		
Female	355 (56.9)	708 (56.8)
Male	269 (43.1)	538 (43.2)
Race		
White	568 (91.2)	1,138 (91.4)
Black	35 (5.6)	68 (5.5)
Other	20 (3.2)	39 (3.1)
Mean BMI at blood draw, kg/m^2 (SD)	27.4 (5.0)	27.2 (4.9)
Type of blood sample		
EDTA plasma	288 (46.2)	579 (46.5)
Heparin plasma	274 (43.9)	544 (43.7)
Serum	62 (9.9)	123 (9.9)
Time from blood draw to diagnosis		
< 6 years	282 (45.2)	
≥ 6 years	342 (54.8)	
Median biomarker concentration (IQR)[b]		
Total adiponectin, μg/mL	11.5 (8.0-16.5)[c]	12.8 (8.6-17.8)
High-molecular-weight (HMW) adiponectin, μg/mL	6.6 (4.3-10.1)[c]	7.4 (4.7-10.8)

*Reported as frequency (%) unless otherwise noted

[a]Analyzed separately in a previous investigation (13)

[b]Reported as cohort- and sex-corrected analyte levels. Differences between cases and controls were also observed for uncorrected total and HMW adiponectin levels ($P \leq 0.005$).

[c]$P \leq 0.002$ for cases vs. controls, Wilcoxon rank-sum test

Table 2

Circulating levels of total adiponectin and risk of multiple myeloma[a]

	Quartile[b]				
	Q1	**Q2**	**Q3**	**Q4**	P_{trend}
Total adiponectin					
No. of cases	183	178	139	124	
No. of controls	311	311	311	313	
Base model					
Replication set[c]	1.0 (ref)	0.88 (0.64-1.21)	0.74 (0.53-1.02)	0.68 (0.48-0.96)	0.020
Combined set[d]	1.0 (ref)	0.95 (0.73-1.24)	0.74 (0.56-0.97)	0.64 (0.47-0.85)	0.001
Multivariate model including body mass index	1.0 (ref)	0.95 (0.72-1.24)	0.73 (0.55-0.97)	0.64 (0.47-0.87)	0.001

[a] Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression models.

[b] Quartile cut points were defined based on the distribution of cohort- and sex-adjusted analyte levels among controls, as follows: Q1, ≤8.64 μg/mL; Q2, 8.65-12.79 μg/mL; Q3, 12.80-17.79 μg/mL; Q4, ≥17.80 μg/mL.

[c] Excluding PLCO

[d] Including PLCO

Table 3

Circulating levels of total adiponectin and risk of multiple myeloma (MM) in stratified analyses[a]

	Cases	Controls	Quartile[b]				P_{trend}	P_{int}[c]
			Q1	Q2	Q3	Q4		
By sex								
Female	355	708	1.0 (ref)	0.85 (0.59-1.23)	0.66 (0.45-0.96)	0.66 (0.44-0.98)	0.029	
Male	269	538	1.0 (ref)	1.08 (0.73-1.61)	0.85 (0.57-1.28)	0.59 (0.38-0.93)	0.011	0.526
By time to MM diagnosis								
<6 years	282	562	1.0 (ref)	0.76 (0.51-1.14)	0.58 (0.38-0.89)	0.64 (0.42-0.99)	0.039	
≥6 years	342	678	1.0 (ref)	1.13 (0.79-1.62)	0.88 (0.61-1.27)	0.62 (0.42-0.93)	0.008	0.215
By body mass index (BMI) at blood draw[d]								
<25 kg/m^2	212	463	1.0 (ref)	1.40 (0.82-2.38)	0.85 (0.50-1.43)	1.20 (0.73-2.00)	0.785	
25-29.9 kg/m^2	270	492	1.0 (ref)	0.76 (0.51-1.13)	0.70 (0.46-1.07)	0.41 (0.26-0.65)	<0.001	
≥30 kg/m^2	136	277	1.0 (ref)	0.93 (0.56-1.55)	0.73 (0.40-1.35)	0.41 (0.17-0.98)	0.039	0.041
By age at blood draw[e]								
<65 years	314	623	1.0 (ref)	1.10 (0.77-1.58)	0.88 (0.60-1.29)	0.61 (0.39-0.95)	0.020	
≥65 years	310	617	1.0 (ref)	0.80 (0.54-1.19)	0.61 (0.41-0.91)	0.61 (0.41-0.92)	0.017	0.400

[a] Based on conditional logistic regression models unless otherwise noted.

[b] Quartile cut points were defined based on the distribution of cohort- and sex-adjusted total adiponectin levels among controls, as follows: Q1, ≤8.64 μg/mL; Q2, 8.65-12.79 μg/mL; Q3, 12.80-17.79 μg/mL; Q4, ≥17.80 μg/mL.

[c] Tests of multiplicative interaction were based on the same models as those used for the stratified analyses and were performed using likelihood ratio tests comparing models with and without the interaction terms.

[d] Based on unconditional logistic regression models adjusted for cohort, sex, age, race, and fasting status.

[e] Strata were defined based on the age at blood draw for cases; matched sets were preserved.