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Body size and multiple myeloma mortality: a pooled analysis of 20 prospective studies

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Summary

Multiple myeloma (MM) is a rare but highly fatal malignancy. High body weight is associated with this cancer, but several questions remain regarding the aetiological relevance of timing and location of body weight. To address these questions, we conducted a pooled analysis of MM mortality using 1·5 million participants (including 1388 MM deaths) from 20 prospective cohorts in the National Cancer Institute Cohort Consortium. Proportional hazards regression was used to calculate pooled multivariate hazard ratios (HRs) and 95% confidence intervals (CIs). Associations with elevated MM mortality were observed for higher early-adult body mass index (BMI; HR = 1·22, 95% CI: 1·09–1·35 per 5 kg/m^2) and for higher cohort-entry BMI (HR 1·09, 95% CI: 1·03–1·16 per 5 kg/m^2) and waist circumference (HR = 1·06, 95% CI: 1·02–1·10 per 5 cm). In analyses of the joint effect of young adult and baseline BMI, women who were the heaviest, both in early adulthood (BMI 25+) and at cohort entry (BMI 30+) were at greater risk compared to those with BMI 18·5 ≤ 25 at both time points (HR = 1·95, 95% CI: 1·33–2·86) but there was no significant association in men. Waist-to-hip ratio and height were not associated with MM mortality. These observations suggest that overall, and possibly also central, obesity influence myeloma mortality, and women have the highest risk of death from this cancer if they remain heavy throughout adulthood.

Keywords: multiple myeloma, prospective cohort study, pooled analysis, body mass index, and anthropometry.

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Multiple myeloma is a rare but highly fatal malignancy, accounting for approximately 15% of new cases and 20% of deaths among patients diagnosed with haematological malignancies in the US (Siegel *et al*, 2013). Although survival has improved over the past 30 years, the overall 10-year survival is still approximately 20%. Few risk factors have been identified and confirmed for this cancer, and most are not modifiable (e.g., increasing age, male gender, black race, family history of multiple myeloma) (Beason & Colditz, 2012). However, research suggests that excess weight during adulthood may also be associated with risk of developing multiple myeloma (Beason & Colditz, 2012). A recent meta-analysis of 19 prospective studies (Wallin & Larsson, 2011) reported a statistically significant higher risk of multiple myeloma incidence and mortality for overweight or obese individuals relative to those with a lower body mass index (BMI). The meta-analysis was limited in scope, as BMI was the only anthropometric measure studied, and results were not presented stratified by age at BMI report/measurement. Several unresolved questions remain regarding the association between excess weight and multiple myeloma, including the importance of overweight and obesity in early adulthood, of weight gain over several decades of life and of central adiposity independent of BMI. To better understand these relationships, we conducted a pooled analysis of multiple myeloma mortality involving data from 20 prospective cohorts, 14 of which were not included in the previous meta-analysis.

Methods

Study population

Cohorts participating in the National Cancer Institute Cohort Consortium were eligible to join the pooled analysis if they had a baseline year of 1970 or later, more than 5 years of follow-up, more than 1000 deaths among non-Hispanic white participants and baseline height, weight and smoking information (Table S1). For some cohorts, baseline was defined as the date of completion of the first questionnaire in which anthropometric measures and other important covariates (e.g., personal history of chronic diseases)

became available. Height and weight information was self-reported in all but one cohort in which body measurements were taken at study baseline (Giles & English, 2002). Young-adult BMI (recalled BMI at age 18–21 years) was available from 14 cohorts, waist circumference data from 12 cohorts, and waist-to-hip ratio from 10 of the 20 cohorts. All cohorts ascertained information on education, marital status, alcohol consumption and physical activity level. Anthropometric and covariate data from each of the cohorts were harmonized using standard definitions and categories across studies and then combined. Written informed consent was obtained from study participants at entry to the respective cohorts or was implied by participants' return of the corresponding enrollment questionnaire. The present investigation was approved by the Institutional Review Board (IRB) at each participating institution or was considered within the scope of the original IRB protocol.

Participants were excluded from all analyses if they had no baseline questionnaire (n = 4927), had missing or extreme values for baseline BMI (<15·0 or >59·9 kg/m^2) (n = 79 739), were younger than 18 years or older than 85 years at baseline (n = 7317), had missing or extreme values for height (<122 or >244 cm) (n = 26 923), had less than one year of follow-up (n = 19 727) or a personal history of cancer at cohort entry (n = 137 837). In addition, participants from cohorts that did not collect waist and hip circumference (n = 927 186) or those with extreme values of waist circumference (≤51 or ≥190 cm) (n = 111 091) and young-adult BMI (<15·0 or >40 kg/m^2) (n = 549 121) were excluded from analyses in which these characteristics were considered the primary exposure of interest.

Follow-up

Participants were followed-up from the date of completion of the baseline questionnaire to date of death, loss-to-follow-up or administrative end date, whichever occurred first. Causes of death were ascertained from death records or registries and multiple myeloma deaths were coded according to the *International Classification of Diseases, Ninth or Tenth Revision* (ICD-9: 203 and ICD-10: C90).

Statistical methods

Pooled sex-specific and sex-combined hazard ratios (HRs) for multiple myeloma death according to continuous values and predefined categories of height (sex-specific categories), baseline BMI (15·0–18·4, 18·5–20·9, 21·0–22·9 [reference], 23·0–24·9, 25·0–27·4, 27·5–29·9, 30·0–34·9, 35·0–59·9 kg/m^2), waist circumference (10-cm categories), waist-to-hip ratio (sex-specific categories), recalled young adult BMI (15·0–18·4, 18·5–20·9, 21·0–22·9 [reference], 23·0–24·9, 25·0–27·4, 27·5–29·9, 30·0–39·9 kg/m^2) and BMI change between early adulthood and baseline (≤2·5, −2·5 to 0, 0–2·4 (reference), 2·5–4·9, 5·0–7·4, 7·5–9·9, 10+ kg/m^2) were calculated using proportional hazards models stratified by cohort (i.e. in the STRATA statement of the model) to allow for the baseline hazard function to vary between studies. Furthermore, attained age was used as the underlying time metric. The Cox proportional hazards assumption was assessed and no violations were detected. All models were adjusted for race (white, black, Asian, other or unknown), education (less than high school, high school graduate, some college, college, postgraduate or unknown), marital status (married/co-habitating, divorced, widowed, single or unknown), grams of alcohol consumption per day (pooled dataset quartiles or unknown), overall physical activity level (cohort-specific quintiles or unknown) and smoking status (never smoked, former smoker who quit <20 years ago, former smoker who quit 20 or more years ago, former smoker but unknown number of years since quitting, smoker but unknown if current or former smoker, current smoker or smoking status unknown). Additional adjustment for diabetes had no effect on the results so it was not included in the final model. Models of waist circumference were conducted with and without adjustment for baseline BMI and with and without stratification by baseline BMI. Effect modification by baseline age, follow-up time and smoking status was evaluated, as well as restriction of the population to non-Hispanic whites. Differences in results across cohorts were evaluated by comparing the associations of height, BMI, waist circumference, waist-to-hip ratio, early-adulthood BMI and BMI change, all modelled as continuous variables, with multiple myeloma mortality using the I^2 index and Cochran's Q test for heterogeneity. All analyses were conducted using SAS statistical software, version 9.0 (SAS Institute, Cary, NC, USA). P values <0·05 were considered statistically significant.

Results

Details of the participants included in this analysis are shown in Table I. The 1 564 218 participants include 907 447 (58%) women and 656 771 (42%) men and 93% were non-Hispanic white. The median age at entry of these participants was 59 years (range: 19–83 years) and they were followed for an average of 10 years. The median BMI was 25·6 at baseline and 21·1 in early adulthood, and median waist circumference was 88 cm (men: 96·5, women: 80·0) at baseline. During follow-up a total of 1388 multiple myeloma deaths (723 male and 665 female deaths) were identified in this pooled analysis. Tests of heterogeneity for each of the body size measures revealed no strong evidence of study heterogeneity for any of the measures.

BMI at study entry

BMI at study entry was positively associated with risk of multiple myeloma mortality, with a 9% higher risk of mor-

Table I. Selected characteristics according to prospective cohort study.

				Men				Women			
Cohort	Study entry year	Median entry age, years (range)	Median follow-up, years (max)	Total N (MM deaths)	Mean (SD) baseline BMI in kg/m^2	Mean (SD) young adult BMI in kg/m^2	Mean (SD) WC in cm	Total (MM deaths)	Mean (SD) baseline BMI in kg/m^2	Mean (SD) young adult BMI in kg/m^2	Mean (SD) WC in cm
AARP	1995–97	62 (50–71)	10 (11)	304 632 (275)	27·3 (4·2)	21·7 (3·0)	97·9 (11·0)	195 222 (123)	26·9 (5·6)	20·7 (2·7)	84·6 (13·4)
AHS1	1976–80	53 (25–83)	12 (22)	11 845 (12)	25·1 (3·5)	–	–	16 609 (15)	24·4 (4·7)	–	–
AgHealth	1993–97	46 (19–83)	10 (14)	20 536 (17)	27·5 (4·1)	–	–	21 718 (4)	25·9 (4·9)	–	–
BCDDP	1987–89	61 (40–83)	17 (19)	N/A	N/A	N/A	N/A	36 055 (47)	25·6 (4·9)	–	81·9 (11·7)
CLUEII	1989	52 (19–83)	14 (19)	8678 (14)	26·8 (3·9)	–	–	11 696 (14)	25·9 (5·3)	–	–
COSM	1998	59 (45–79)	10 (10)	43 157 (37)	25·8 (3·4)	21·9 (2·3)	96·0 (10·1)	N/A	N/A	N/A	N/A
CPS-II	1997	68 (45–83)	10 (11)	54 807 (83)	26·6 (3·8)	21·9 (2·9)	98·8 (10·1)	66 113 (74)	25·8 (4·9)	20·7 (2·7)	86·4 (13·1)
CTS	1995–96	52 (22–83)	9 (9)	N/A	N/A	N/A	N/A	111 235 (29)	24·9 (5·1)	21·3 (3·0)	81·8 (13·1)
HPFS	1986–87	54 (39–78)	17 (23)	48 066 (105)	25·5 (3·2)	22·9 (2·7)	95·1 (9·2)	N/A	N/A	N/A	N/A
IWHS	1986	62 (52–71)	19 (19)	N/A	N/A	N/A	N/A	37864 (79)	26·1 (4·9)	21·0 (2·9)	69·4 (10·8)
MCCS	1990–94	56 (28–81)	15 (18)	15 667 (22)	27·2 (3·6)	22·6 (2·8)	93·5 (10·0)	22 348 (6)	26·8 (4·9)	21·5 (2·9)	81·1 (11·8)
NHS-I	1976–78	43 (29–56)	26 (28)	N/A	N/A	N/A	N/A	93 843 (168)	24·4 (4·5)	–	
NYUWHS	1985–91	52 (31–70)	19 (20)	N/A	N/A	N/A	N/A	13 390 (13)	24·9 (4·6)	–	75·1 (11·7)
PHS	1981–00	53 (39–83)	22 (26)	28 272 (59)	25·1 (3·0)	–	–	N/A	N/A	N/A	N/A
PLCO	1993–01	62 (50–78)	9 (13)	70 622 (89)	27·5 (4·2)	–	–	69 819 (49)	27·1 (5·5)	–	–
SMC	1998	60 (48–83)	10 (10)	N/A	N/A	N/A	N/A	33 936 (26)	25·0 (4·0)	20·5 (2·5)	83·6 (10·7)
USRT	1994–98	46 (31–83)	6 (7)	19 105 (1)	27·1 (4·2)	–	–	63 214 (4)	25·3 (5·1)	–	77·0 (9·3)
VITAL	2000–02	61 (50–76)	6 (7)	31 384 (9)	27·6 (4·4)	–	–	31 237 (4)	27·2 (5·8)	–	–
WHS	1993–96	52 (38–83)	13 (15)	N/A	N/A	N/A	N/A	38 927 (0)	26·0 (5·1)	–	–
WLH	1991–92	40 (30–50)	15 (15)	N/A	N/A	N/A	N/A	44 221 (3)	23·5 (3·6)	20·5 (2·5)	77·0 (9·3)
Total	1976–2002	59 (19–83)		656 771 (723)				907 447 (665)			

MM, multiple myeloma; WC, waist circumference; SD, standard deviation; N/A, not applicable; AARP, National Institutes of Health-American Association of Retired Persons Diet and Health Study; AHS1, Adventist Health Study 1; AgHealth, Agricultural Health Study; BCDDP, Breast Cancer Detection Demonstration Project; CLUEII, Give Us A Clue to Cancer; COSM, Cohort of Swedish Men; CPS-II, Cancer Prevention Study-II; CTS, California Teachers Study; HPFS, Health Professionals Follow-up Study; IWHS, Iowa Womens Health Study; MCCS, Melbourne Collaborative Cohort Study; NHS-I, Nurses' Health Study I; NYUWHS, New York University Women's Health Study; PHS, Physicians Health Study; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SMC, Swedish Mammography Cohort; USRT, U.S. Radiation Technologists Study; VITAL, VITamins And Lifestyle Study; WHS, Womens Health Study; WLH, Women's Lifestyle and Health Study.

tality per 5 kg/m^2 increase in BMI for both men and women (HR 1·09; 95% confidence interval [CI] 1·03–1·16) (Table II). When comparing the heaviest individuals (BMI 35+) to those with a BMI of 21·0–23·0, the HR was 1·52 (95% CI: 1·15–2·02). Individual cohort results for a 5-unit increase in BMI and multiple myeloma mortality are shown in Figures S1A (women) and 1B (men).

Young adult BMI

Information on young adult weight was available for 1 096 492 participants (1024 deaths). Like older-adult BMI, young-adult BMI was positively associated with multiple myeloma mortality (HR = 1·22, 95% CI: 1·09–1·35 per 5 kg/m^2 increase). This association was stronger for women, although a test of interaction with sex was not statistically significant (P = 0·87).

Joint effect of young and older adult BMI

There was a suggestion of a small increased risk of mortality from multiple myeloma with increasing gain of BMI from young adulthood to study entry (HR = 1·06, 95% CI: 0·98–1·14) (Table II). In analyses of the joint effect of young adult and baseline BMI, women in the heaviest BMI categories at both time points had the highest risk of multiple myeloma mortality compared with those with a BMI in the normal range (18·5–25) at both time points (HR = 1·95, 95% CI: 1·33–2·86) but there was no significant association in men (Table III).

Table II. Pooled hazard ratios and 95% confidence intervals for body mass index and risk of multiple myeloma mortality, overall and stratified by sex.

	Men		Women			All	
	Deaths	HR* (95% CI)	Category	Deaths	HR* (95% CI)	Deaths	HR* (95%CI)
Baseline BMI†							
15·0–18·5	1	–	15·0–18·5	14	1·39 (0·79–2·43)	15	1·21 (0·71–2·06)
18·5 ≤ 21·0	17	0·97 (0·57–1·67)	18·5–21·0	68	1·01 (0·75–1·38)	85	1·02 (0·79–1·32)
21·0 ≤ 23·0	63	1·00 (ref)	21·0 ≤ 23·0	108	1·00 (ref)	171	1·00 (ref)
23·0 ≤ 25·0	176	1·37 (1·03–1·83)	23·0 ≤ 25·0	126	1·08 (0·83–1·39)	302	1·22 (1·01–1·47)
25·0 ≤ 27·5	219	1·20 (0·90–1·59)	25·0 ≤ 27·5	132	1·11 (0·86–1·44)	351	1·15 (0·95–1·38)
27·5 ≤ 30·0	130	1·29 (0·95–1·75)	27·5 ≤ 30·0	85	1·20 (0·90–1·60)	215	1·24 (1·01–1·52)
30·0 ≤ 35·0	93	1·28 (0·93–1·78)	30·0 ≤ 35·0	85	1·18 (0·89–1·58)	178	1·23 (0·99–1·52)
35·0+	24	1·48 (0·91–2·38)	35·0–60·0	47	1·51 (1·06–2·15)	71	1·52 (1·15–2·02)
BMI (per 5 kg/m^2)		1·11 (1·00–1·22)			1·07 (0·99–1·16)		1·09 (1·03–1·16)
Young Adult BMI‡							
15·0–18·5	40	0·85 (0·60–1·21)	15·0–18·5	81	1·11 (0·84–1·47)	121	0·99 (0·80–1·23)
18·5–21·0	136	0·91 (0·73–1·15)	18·5–21·0	183	0·94 (0·75–1·19)	319	0·91 (0·78–1·07)
21·0–23·0	155	1·00 (ref)	21·0–23·0	120	1·00 (ref)	275	1·00 (ref)
23·0–25·0	92	0·88 (0·68–1·14)	23·0–25·0	68	1·31 (0·97–1·76)	160	1·04 (0·85–1·26)
25·0–27·5	62	1·00 (0·74–1·34)	25·0–27·5	30	1·28 (0·86–1·91)	92	1·11 (0·87–1·40)
27·5–30·0	21	1·47 (0·93–2·32)	27·5–30·0	10	1·42 (0·75–2·71)	31	1·49 (1·03–2·16)
30·0+	10	1·36 (0·72–2·59)	30·0+	16	2·32 (1·37–3·92)	26	1·82 (1·22–2·73)
BMI (per 5 kg/m^2)		1·15 (0·98–1·35)			1·27 (1·10–1·47)		1·22 (1·09–1·35)
Change in BMI§							
≤2·5	11	1·04 (0·55–1·97)	≤2·5	23	1·16 (0·72–1·89)	34	1·12 (0·77–1·64)
−2·5 ≤ 0	33	0·96 (0·65–1·42)	−2·5 ≤ 0	34	0·75 (0·51–1·10)	67	0·84 (0·64–1·10)
0–2·5	117	1·00 (ref)	0–2·5	104	1·00 (ref)	221	1·00 (ref)
2·5 ≤ 5·0	147	1·04 (0·81–1·33)	2·5 ≤ 5·0	119	1·02 (0·78–1·33)	266	1·04 (0·87–1·24)
5·0 ≤ 7·5	108	1·05 (0·80–1·38)	5·0 ≤ 7·5	112	1·28 (0·98–1·68)	220	1·17 (0·96–1·41)
7·5 ≤ 10	60	1·18 (0·85–1·64)	7·5 ≤ 10	53	1·00 (0·71–1·40)	113	1·10 (0·87–1·38)
10$^+$	40	1·20 (0·82–1·76)	10$^+$	63	1·12 (0·81–1·56)	103	1·17 (0·92–1·50)
BMI change (per 1 kg/m^2)		1·07 (0·94–1·21)			1·04 (0·95–1·15)		1·06 (0·98–1·14)

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

*HRs computed using Cox regression models adjusted for race, education, sex (overall results only), marital status, grams of alcohol consumption, overall physical activity level and smoking status.

†Tests of heterogeneity BMI at study entry, women: I^2 = 22%, Cochoran Q P = 0·24; men: I^2 = 21%, Cochoran Q P = 0·24.

‡Tests of heterogeneity Young adult BMI, women: I^2 = 32%, Cochoran Q P = 0·13; men: I^2 = 33%, Cochoran Q P = 0·15.

§Tests of heterogeneity BMI change, women: I^2 = 0%, Cochoran Q P = 0·50; men: I^2 = 0%, Cochoran Q P = 0·78.

Table III. Pooled hazard ratios and 95% confidence intervals for the joint effect of young adult body mass index and body mass index at study entry on risk of multiple myeloma mortality, overall and stratified by sex.

			BMI at study entry*									
			BMI 18·5–25·0	BMI25 ≤ 30	BMI 30+	BMI 18·5–25·0	BMI 25 ≤ 30	BMI 30+	BMI 18·5–25·0	BMI 25 ≤ 30	BMI 30+
			Men			Women			All		
Young	BMI	Deaths	156	181	46	171	132	64	327	313	110
Adult BMI*	18·5–25·0	HR†	1·00	0·88	0·94	1·00	1·17	1·21	1·00 (ref)	1·02	1·09
		(95% CI)	(ref)	(0·71–1·09)	(0·67–1·32)	(ref)	(0·93–1·48)	(0·90–1·62)		(0·87–1·20)	(0·87–1·36)
	BMI	Deaths	6	51	36	10	14	32	16	65	68
	25·0+	HR†	0·65	1·19	1·12	1·31	1·31	1·95	0·96	1·32	1·47
		(95% CI)	(0·29–1·46)	(0·87–1·64)	(0·77–1·61)	(0·69–2·47)	(0·76–2·27)	(1·33–2·86)	(0·58–1·59)	(1·01–1·73)	(1·13–1·92)

HR, hazard ratio; CI, confidence interval; BMI, body mass index.
*BMI < 18·5 not shown due to sparse data.
†HRs computed using Cox regression models adjusted for race, education, marital status, grams of alcohol consumption, overall physical activity level and smoking status.

Other anthropometric measures

Waist circumference data were available for 647 478 participants (589 deaths) and waist-to-hip ratio was available for 528 928 participants (445 deaths). Like overall obesity, waist circumference was positively associated with multiple myeloma mortality (HR = 1·06, 95% CI: 1·01–1·12 per 5 cm) (Table IV). The association was virtually unchanged when the estimate was adjusted for baseline BMI (HR = 1·07, 95% CI: 1·01–1·13 per 5 cm). Waist-to-hip ratio was not associated with multiple myeloma mortality in any analysis. Height was weakly associated with multiple myeloma mortality for the tallest compared with the shortest women, but not men (Table IV). Sensitivity analyses restricting the study population to non-Hispanic whites and stratifying on follow-up time or smoking minimally changed the results (data not shown).

Discussion

Our results from this large, pooled analysis of prospective data suggest that excess weight in early adulthood and at cohort entry is associated with increased multiple myeloma mortality, with the highest relative risk observed for individuals in the highest BMI categories at both time points. These results were stronger and only statistically significant in women. We are unsure if the sex differences we observed in this study were due to chance or reflect real differences. Central adiposity, as measured by waist circumference, was also positively associated with multiple myeloma mortality but waist-to-hip ratio was not. Results for height were less clear but a weak association with multiple myeloma mortality was suggested among women.

A modest association between adult BMI and multiple myeloma incidence and mortality is well-documented (Hofmann *et al*, 2013; Lichtman, 2010; Murphy *et al*, 2013; Renehan *et al*, 2008; Wallin & Larsson, 2011). The magnitude of association we observed in this pooled analysis was almost identical to that of a recent meta-analysis (Wallin & Larsson, 2011) of five studies, which reported a 15% and 54% higher risk of multiple myeloma mortality for overweight and obese individuals, respectively. Less is known, however, about the association between early-adult BMI and multiple myeloma. No associations with multiple myeloma incidence were observed between BMI at age 18 or 20 years, respectively, in the Women's Health Initiative Observational Study (WHI OS; $n = 91$ cases) (De Roos *et al*, 2010) or a subcohort of the Netherlands Cohort Study on Diet and Cancer (NCSDC; $n = 279$ cases) (Pylypchuk *et al*, 2009). The discrepancy between these results and ours may be explained by the small sample sizes in both studies, particularly for cases with BMI > 25 (WHI OS, $n = 8$; NCSDC, $n = 144$). In women in particular, the highest risk of multiple myeloma mortality was among those who were heavier both in young adulthood and later in adulthood. Those who developed excess weight

Table IV. Pooled hazard ratios and 95% confidence intervals for other anthropometric measures and risk of multiple myeloma mortality, overall and stratified by sex.

	Men		Women			All	
	Deaths	HR* (95% CI)	Category	Deaths	HR* (95% CI)	Deaths	HR* (95%CI)
Waist Circumference (WC)† (cm)							
<90	62	1·00 (ref)	<70	50	1·00 (ref)	112	1·00 (ref)
90 ≤ 100	144	1·25 (0·93–1·69)	70 ≤ 80	72	1·32 (0·90–1·94)	216	1·28 (1·01–1·62)
100 ≤ 110	83	1·26 (0·90–1·77)	80 ≤ 90	70	1·42 (0·94–2·13)	153	1·32 (1·02–1·71)
110+	38	1·38 (0·91–2·08)	90+	70	1·54 (1·00–2·36)	108	1·47 (1·10–1·96)
WC (per 5 cm)		1·06 (1·01–1·12)			1·05 (1·00–1·11)		1·06 (1·02–1·10)
Waist:Hip (W:H) Ratio‡							
<0·90	46	1·00 (ref)	<0·75	36	1·00 (ref)	82	1·00 (ref)
0·90 ≤ 0·95	83	1·08 (0·75–1·55)	0·75 ≤ 0·80	44	0·85 (0·55–1·33)	127	0·98 (0·74–1·30)
0·95–1·0	66	1·19 (0·81–1·74)	0·80–0·85	52	1·00 (0·65–1·54)	118	1·11 (0·83–1·48)
1·0+	51	1·22 (0·81–1·83)	0·85+	67	0·92 (0·61–1·40)	118	1·08 (0·81–1·44)
W:H ratio (per 0·1)		1·07 (0·90–1·29)			1·02 (0·85–1·22)		1·05 (0·92–1·19)
Height (cm)§							
<170	82	1·00 (ref)	<160	167	1·00 (ref)	249	1·00 (ref)
170 ≤ 175	145	0·95 (0·72–1·25)	160 ≤ 165	188	0·97 (0·79–1·20)	333	0·98 (0·83–1·16)
175 ≤ 180	199	0·90 (0·69–1·18)	165 ≤ 170	174	1·01 (0·82–1·25)	373	0·98 (0·83–1·16)
180+	297	0·95 (0·73–1·22)	170+	136	1·21 (0·96–1·53)	433	1·07 (0·90–1·26)
Height (per 5 cm)		1·00 (0·95–1·05)			1·06 (1·00–1·13)		1·03 (0·99–1·07)

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

*HRs computed using Cox regression models adjusted for race, education, marital status, grams of alcohol consumption, overall physical activity level, and smoking status.

†Tests of heterogeneity Waist circumference, women: I^2 = 0%, Cochoran Q P = 0·86; men: I^2 = 0%, Cochoran Q P = 0·62.

‡Tests of heterogeneity W:H ratio, women: I^2 = 43%, Cochoran Q P = 0·09; men: I^2 = 0%, Cochoran Q P = 0·80.

§Tests of heterogeneity Height, women: I^2 = 10%, Cochoran Q P = 0·34; men: I^2 = 15%, Cochoran Q P = 0·29.

later in adulthood were not at increased risk of multiple myeloma mortality. This finding suggests that, particularly for women, long-term high body weight is important to multiple myeloma mortality and that the effects of obesity may play a role in both early and late stages of myeloma pathogenesis. In support of this hypothesis, previous studies report that obese individuals have a higher prevalence of monoclonal gammopathy of undetermined significance (MGUS), a precursor condition necessary for myeloma development (Landgren *et al*, 2010), and that elevated expression of adiponectin (an adipokine inversely associated with obesity) may prevent progression from MGUS to myeloma (Fowler *et al*, 2011).

Abdominal obesity, as measured by waist circumference or waist-to-hip ratio, is associated with several types of cancer (Pischon *et al*, 2008). Waist circumference is positively correlated with visceral adipose tissue, which is more metabolically active than subcutaneous fat and produces much higher levels of adipokines (Pischon *et al*, 2008). In our study, waist circumference, but not waist-to-hip ratio, was an independent risk factor for multiple myeloma mortality. In contrast to our findings, two smaller multiple myeloma incidence studies (Britton *et al*, 2008; MacInnis *et al*, 2005) reported no association with waist circumference. However, both the EPIC (European Prospective Investigation into Cancer and Nutrition) study (n = 268 multiple myelomas; Britton *et al*, 2008) and the Melbourne Collaborative Cohort (n = 55 multiple myelomas, MacInnis *et al*, 2005) observed no association with BMI. Again, limited power may explain these results.

The mechanisms through which BMI and/or waist circumference might influence multiple myeloma aetiology are not yet established. Adipokines in the bone marrow microenvironment have been hypothesized to play a role (Mittleman, 2012). One such adipokine is the inflammatory cytokine interleukin-6 (IL6). IL6 is synthesized by adipocytes and IL6 concentrations are directly associated with obesity (Mittleman, 2012). In the blood, approximately 15–35% of total IL6 is produced by adipose tissue, and IL6 is considered a potent growth factor in multiple myeloma (Mittleman, 2012). Obesity can also lead to insulin resistance, which in turn results in elevated levels of bioavailable insulin-like growth factor 1 (IGF1); and more bioavailable IGF1 can increase myeloma cell proliferation and inhibit apoptosis (Ferlin *et al*, 2000). A recent study of prediagnosis plasma biomarkers of IGF-1, insulin, and IL6 (Birmann *et al*, 2012) reported statistically significant associations for both IGF binding protein-1 and soluble IL6 receptor concentrations with multiple myeloma

diagnosed within three and 6 years of blood draw respectively, suggesting that these pathways may play a role in multiple myeloma progression. Furthermore, a myeloma cell line study suggested a possible synergistic effect of IL6 and IGF1 in myeloma cells (Abroun *et al*, 2004). Another adipokine that has been recently linked to multiple myeloma is adiponectin, levels of which are lower in obese individuals (Roberts *et al*, 2010). Higher levels of circulating adiponectin were inversely associated with multiple myeloma risk in one recent study (Hofmann *et al*, 2012) and, as noted above, another showed that high adiponectin was associated with a lower risk of progression from MGUS to myeloma (Fowler *et al*, 2011). Reseland *et al* (2009) also reported an inverse association between plasma adiponectin and multiple myeloma, as well as a positive association with another adipokine associated with obesity, leptin. In addition, they measured gene expression profiles in two myeloma cell lines both with and without leptin, and found that leptin induced several genes involved in cell proliferation, apoptosis and signalling (Reseland *et al*, 2009). Metabolic pathways are complex, however, and further study is needed to disentangle the role of these factors in myeloma incidence and mortality, specifically the importance of the timing of these exposures in relation to the natural history of the disease. There are also novel hypotheses about how obesity may increase the risk of cancer, such as adipose tissue hypoxia, shared genetic susceptibility and migrating adipose stromal cells from white adipose tissue to tumour tissue (Roberts *et al*, 2010). Further research is warranted to explore these possibilities in relation to myelomagenesis.

The present study is the largest to date to examine the risk of multiple myeloma mortality with BMI both in early and later adulthood as well as with several other body size measures. Although two meta-analyses (Renehan *et al*, 2008; Wallin & Larsson, 2011) on BMI and multiple myeloma incidence had more cases (Renehan *et al* (2008): $n = 7937$ cases; Wallin and Larsson (2011): 8982 incident cases, 1845 deaths) neither of these studies examined anthropometric factors other than BMI at study entry. In addition, the varying referent groups and categories in a meta-analysis make the results more difficult to interpret. The present pooled dataset allowed us to create uniform exposure categories and examine a variety of potential effect modifiers. In addition, we were able to explore the change in BMI between early and later adulthood and the relative importance of these measures.

Limitations of this study include the self-reported anthropometric data from all but one of the contributing cohorts. However we expect any resulting measurement error to be non-differential and bias towards the null. Although mortality, rather than incidence, was the end-point in this study, this is a highly fatal cancer and we expect the difference between associations with incidence and mortality to be minimal. BMI and multiple myeloma incidence studies from cohorts included in our pooled study reported results consistent with our mortality findings (Birmann *et al*, 2007; Blair *et al*, 2005; Hofmann *et al*, 2013; Troy *et al*, 2010) with two exceptions (Patel *et al*, 2013) (Wang *et al*, 2013). Furthermore, two recent analyses reported no association between high BMI and prognosis for multiple myeloma patients, and one (Beason & Colditz, 2012) reported that a higher BMI was associated with *better* survival, supporting the idea that the associations we observed represent an influence of adiposity on myeloma incidence rather than survival (Kumar *et al*, 2012; Vogl *et al*, 2011). Another potential limitation of using death certificate data is the accuracy of the diagnosis information. However, a 2011 study (German *et al*, 2011) comparing cancer registry records to death certificate data found that multiple myeloma was coded correctly on death certificates more than 95% of the time. Furthermore we expect any myeloma misclassification to be independent of body size and, therefore, would expect a bias towards the null. An additional limitation is that although the pooled dataset included information on several potential confounders, we did not have information on all risk factors for myeloma mortality, including family history of myeloma, occupational exposures to chemicals and myeloma treatment data. However we have included all covariates that, to our knowledge, are strongly associated with both body size and myeloma and would, therefore, expect any resulting bias from missing potential confounders to be small. Another limitation is that our results may not be generalizable beyond white, non-Hispanic populations due to the small percentage of non-white participants. Finally, although this study is much bigger than any individual study, some categories still have relatively small numbers due to the rarity of this cancer. Although our statistical power was not robust for detecting statistical significant associations for every category in isolation, our analyses, modelling anthropometric measures as continuous variables, had excellent power.

In conclusion, our results suggest that overall, and possibly also central, adiposity are risk factors for multiple myeloma mortality, and that BMI early in adulthood plays an important role - particularly for women who remain heavy throughout adulthood. These findings underscore the important public health message to maintain a healthy body weight throughout adulthood, and offer a potential opportunity for prevention of a highly fatal malignancy with a mostly unknown aetiology. Further exploration to understand the mechanisms of the relationship between excess adiposity and multiple myeloma is warranted.

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Authorship

All authors (LRT, CMK, BMB, PAH, SSW, KR, AVP, HOA, EW, GGG, PNS, MA, LBF, LB, JEB, GAC, GEF, SMG, JMG, EG, JNH, MSL, GN, YP, UP, PSR, CS, HDS, MJS, KV, EW, AW, AZJ, ABG, MPP) contributed data from their respective cohorts. LRT and MPP developed the analytic plan and led the data analysis and interpretation with significant contributions from CMK and PAH. LRT and MPP drafted the manuscript with input from the writing team (CMK, BMB, PAH, SSW, KR, AVP, HOA, EW, GGG, AND PNS); all other authors (MA, LBF, LB, JEB, GAC, GEF, SMG, JMG, EG, JNH, MSL, GN, YP, UP, PSR, CS, HDS, MJS, KV, EW, AW, AZJ, ABG) provided critical revisions. All authors approved the final version of this manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1A. Cohort-specific hazard ratio per 5 kg/m^2 of body mass index (BMI) and multiple myeloma mortality in men.

Fig. S1B. Cohort-specific hazard ratio per 5 kg/m^2 of body mass index (BMI) and multiple myeloma mortality in women.

Appendix S1. Funding for each cohort.

Table S1. Availability of body size data according to prospective cohort study.

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