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Review

# Body mass index and risk of multiple myeloma: A meta-analysis of prospective studies ☆

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ABSTRACT

Excess body weight has been identified as a risk factor for various cancer types. Since the publication of two meta-analyses indicating that body mass index (BMI) is positively associated with the risk of multiple myeloma, the evidence from prospective cohort studies on this issue has largely accumulated. We therefore conducted a meta-analysis to update and expand the previous results. We searched the PubMed and EMBASE databases through 26 January 2011 and reviewed the reference lists of retrieved articles. Prospective cohort studies were included if they reported relative risk (RR) estimates with 95% confidence intervals (CIs) for the association between BMI and multiple myeloma incidence or mortality. A random-effects model was used to combine study-specific results. A total of 15 cohort studies on multiple myeloma incidence and five studies on multiple myeloma mortality were included in the meta-analysis. Compared with subjects in the normal weight category, the risk of multiple myeloma was statistically significantly elevated among subjects categorised as overweight (RR, 1.12; 95% CI, 1.07–1.18) or obese (RR, 1.21; 95% CI, 1.08–1.35). For multiple myeloma mortality, the corresponding summary RR estimates were 1.15 (95% CI, 1.04–1.27) and 1.54 (95% CI, 1.35–1.76). Results from this meta-analysis are in line with the conclusions of the previous meta-analyses, and suggest that excess body weight is a risk factor for multiple myeloma.



## 1. Introduction

Multiple myeloma is a haematological cancer characterised by proliferation of malignant plasma cells. The disease is relatively rare and the prognosis is poor with a 5-year relative survival of 38.5%.[1] Other than increasing age, male gender, black race, family history of the disease and monoclonal gammopathy of undetermined significance, there are few established risk factors for multiple myeloma.[2] Therefore, identification of modifiable risk factors could provide an opportunity for primary prevention and have marked impact on morbidity and mortality from the disease.

The increasing prevalence of overweight and obesity is of great concern for public health, as excess body weight is known to be a major risk factor for cardiovascular disease, type 2 diabetes and certain cancer types.[3,4] Findings from individual epidemiological studies on excess body weight in relation to the risk of multiple myeloma have been inconsistent. However, when results were combined in a meta-analysis of nine cohort studies published through May 2007,

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overweight and obesity were associated with a 12% and 27% increase in risk of multiple myeloma, respectively. For case-control studies, the summary estimates were significantly higher.[5] Similarly, another meta-analysis of cohort studies published through November 2007 reported a risk increase of 11% per 5 kg/m$^2$ increase in body mass index (BMI).[4] Since 2007, eight prospective cohort studies have been published on the association between BMI and multiple myeloma incidence and/or mortality. The aim of this present meta-analysis was to update and expand the previous meta-analyses, to include all prospective studies on this issue published through 26 January 2011. Further, we separately assessed the influence of overweight and obesity on multiple myeloma mortality.

## 2. Materials and methods

### 2.1. Study selection

We identified eligible studies by searching the PubMed and EMBASE databases through 26 January 2011, using the keywords *myeloma*, *plasma cell neoplasms* or *haematopoietic cancer* in combination with *BMI*, *body mass index*, *obesity* or *overweight*. No language restrictions were imposed. Further, the reference lists of retrieved articles were examined for additional relevant studies. Studies with prospective cohort design were included in the meta-analysis if they reported relative risk (RR) estimates with corresponding 95% confidence intervals (CIs) for the association between BMI and incidence of, or mortality from, multiple myeloma. If results based on the same study population were reported in more than one study, we included the one with the largest number of cases.

### 2.2. Data extraction

From each study, we extracted the first author's last name, publication year, country where the study was performed, study period, sex and age of study participants, number of cases and cohort size, method for assessing height and weight, RR estimates with corresponding 95% CIs for each category of BMI in the overweight and obese range, and variables adjusted for in the analysis. When several risk estimates were presented, we used the ones adjusted for the largest number of potential confounders.

### 2.3. Statistical analysis

The RRs from individual studies and corresponding 95% CIs were transformed to their natural logarithms to stabilise the variance and to normalise the distributions. To examine the associations of overweight (BMI 25 to <30) and obesity (BMI $\geqslant$30) with multiple myeloma incidence and mortality, we pooled study-specific RRs for the category representing overweight or obesity versus the reference category. For five studies[6–10] that reported RRs for more than one BMI category within the overweight or obesity range, we pooled these RRs with inverse variance weight and used the pooled estimate. For one study[11] that reported RRs for black and white subjects separately, we also used a pooled estimate. When separate RR estimates for men and women were not available, we used the combined estimate. For each study, we also estimated a RR for a 5 kg/m$^2$ increase in BMI using the method proposed by Greenland and Longnecker and Orsini et al.[12,13] Summary RR estimates were calculated with the DerSimonian and Laird random-effects model,[14] which considers both within- and

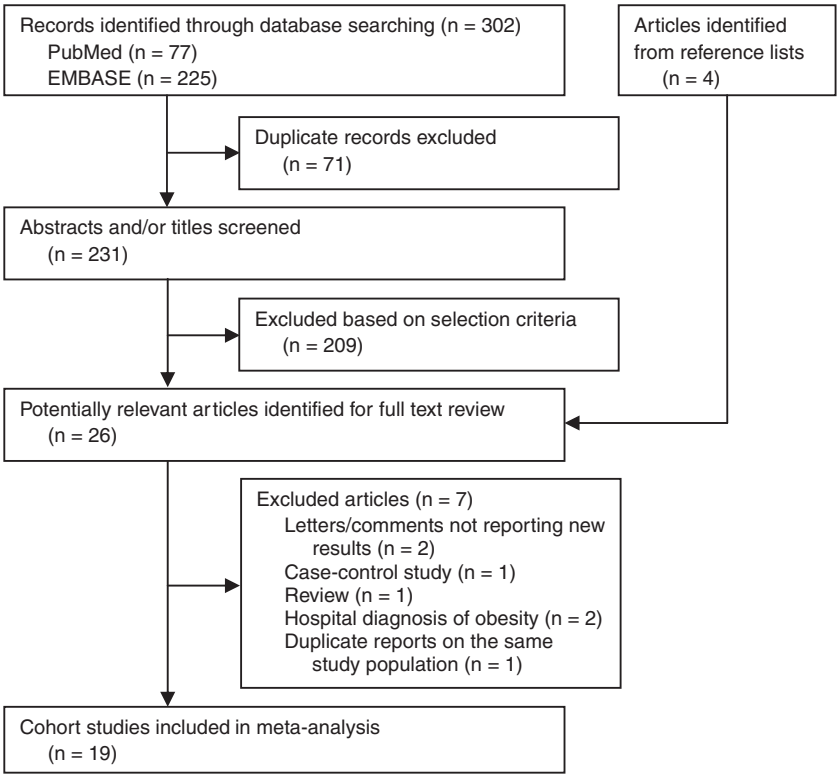


**Fig. 1 – Flowchart of selection of studies for inclusion in meta-analysis.**

**Table 1 – Prospective cohort studies of body mass index and multiple myeloma.**

| Study | Country (period) | Sex and age | Cases (cohort size) | Assessment of weight and height | BMI (kg/m$^2$) categories | | | Adjusted variables |
|---|---|---|---|---|---|---|---|---|
| | | | | | Reference | Overweight | Obesity | |
| *Incidence* | | | | | | | | |
| Friedman et al.[11] | United States (1964–1988) | Men and women aged 13–92 years | 167 (150,296) | Measured | ⩽23.1; ⩽21.0[a] | 25.2-27.3; 22.9–25.8[a] | ⩾27.3; ⩾25.8[a] | Age, sex |
| Blair et al.[26] | United States (1986–2001) | Women aged 55–69 years | 95 (37,083) | Self-reported | 18.5–22.9 | 25.0–29.9 | ⩾30.0 | Age |
| MacInnis et al.[19] | Australia (1990–2003) | Men and women aged 27–75 years | 55 (40,909) | Measured | <25.0 | 25.0–29.9 | ⩾30.0 | Age, sex, country of birth, education |
| Oh et al.[6] | Korea (1992–2001) | Men aged ⩾20 years | 103 (781,283) | Measured | 18.5–22.9 | 25.0–26.9 27.0–29.9 | – | Age, smoking, alcohol, exercise, family history of cancer, residency area |
| Birmann et al.[27] | United States (1980–2002) | Men aged 40–75 years and women aged 30-55 years | 215 (136,623) | Self-reported | <22.0 | 25.0–29.9 | ⩾30.0 | Age, sex, physical activity |
| Engeland et al.[7] | Norway (1963–2002) | Men and women aged 20–74 years | 6,115[b] (2,000,424) | Measured | 18.5–24.9 | 25.0–29.9 | ⩾30.0; 30.0–34.9; 35.0–39.9; ⩾40.0[a] | Age, sex, birth cohort |
| Fernberg et al.[28] | Sweden (1971–2004) | Men aged 14–72 years | 520 (336,381) | Self-reported | 18.5–25.0 | 25.1–30.0 | >30.0 | Age, tobacco use |
| Reeves et al.[8] | United Kingdom (1996–2004) | Women aged 50–64 years | 491 (1,222,630) | Self-reported | 22.5–24.9 | 25.0-27.4; 27.5–29.5 | ⩾30.0 | Age, geographical region, socioeconomic status, reproductive history, smoking, alcohol, physical activity |
| Britton et al.[29] | 10 European countries (1993–) | Men and women aged 25–70 years | 268 (371,983) | Measured | <25.0 | 25.0–29.9 | ⩾30.0 | Age, sex, study centre |
| Pylypchuk et al.[30] | Netherlands (1986–1999) | Men and women aged 55–69 years | 279 (120,852) | Self-reported | <24.9 | 25.0–29.9 | ⩾30.0 | Age, sex |
| Söderberg et al.[31] | Sweden and Finland (1969–2004) | Men and women aged 18–96 years | 140 (70,067) | Self-reported | 18.5–24.9 | 25.0–29.9 | ⩾30.0 | Age, sex, country |
| De Roos et al.[9] | United States (1994–2008) | Women aged 50–79 years | 92 (81,219) | Measured | <25.0 | 25.0–29.9 | 30.0–34.9; ⩾35.0 | Age, minority race, education, U.S. region, smoking |
| Kanda et al.[32] | Japan (1990–2006) | Men and women aged 40–69 years | 88 (94,547) | Self-reported | 23.0–24.9 | 25.0–29.9 | ⩾30.0 | Age, sex, study area, alcohol, smoking |
| Lu et al.[33] | United States (1995–2007) | Women aged 22–84 years | 111 (121,216) | Self-reported | 20.0–24.9 | 25.0–29.9 | ⩾30.0 | Age, race, height at cohort entry |
| Troy et al.[34] | United States (1993–2006) | Men and women aged 55–74 years | 243[b] (142,982) | Self-reported | 18.5–24.9 | 25.0–29.9 | ⩾30.0 | Age, sex, race/ethnicity, education |

(*continued on next page*)

**Table 1 – *continued***

| Study | Country (period) | Sex and age | Cases (cohort size) | Assessment of weight and height | BMI (kg/m$^2$) categories | | | Adjusted variables |
|---|---|---|---|---|---|---|---|---|
| | | | | | Reference | Overweight | Obesity | |
| *Mortality* | | | | | | | | |
| Calle et al.[10] | United States (1982–1998) | Men and women aged ⩾30 years | 1,328 (900,053) | Self-reported | 18.5–24.9 | 25.0–29.9 | 30.0–34.9; 35.0–39.9 | Age, sex, education, smoking, physical activity, alcohol, marital status, race, aspirin use, fat consumption, vegetable consumption, oestrogen replacement therapy (women) |
| Chiu et al.[35] | United States (1967–2002) | Men and women aged 15–90 years | 66 (35,420) | Measured | ⩽24.1; ⩽21.0[a] | 24.1–26.3; 26.3–28.6; 23.3–26.2[a] | ⩾28.6; ⩾26.2[a] | Age, sex, education, smoking, race, postload glucose level |
| Khan et al.[36] | Japan (1988–2003) | Men and women aged 40–79 years | 98 (109,698) | Self-reported | 18.5–25.0 | 25.0–30.0 | ⩾30.0 | Age, sex |
| Reeves et al.[8] | United Kingdom (1996–2005) | Women aged 50–64 years | 284 (1,222,630) | Self-reported | 22.5–24.9 | 25.0–27.4; 27.5–29.5 | ⩾30.0 | Age, geographical region, socioeconomic status, reproductive history, smoking, alcohol, physical activity |
| Parr et al.[20] | Asia-Pacific region (1961–) | Men and women aged 20–107 years | 69 (401,215) | –[c] | 18.5–24.9 | 25.0–29.9 | 30.0–60.0 | Age, sex, study, smoking |

[a] BMI categories for men and women, respectively.
[b] Plasma cell neoplasms.
[c] Methods used in the 39 individual cohorts not reported.

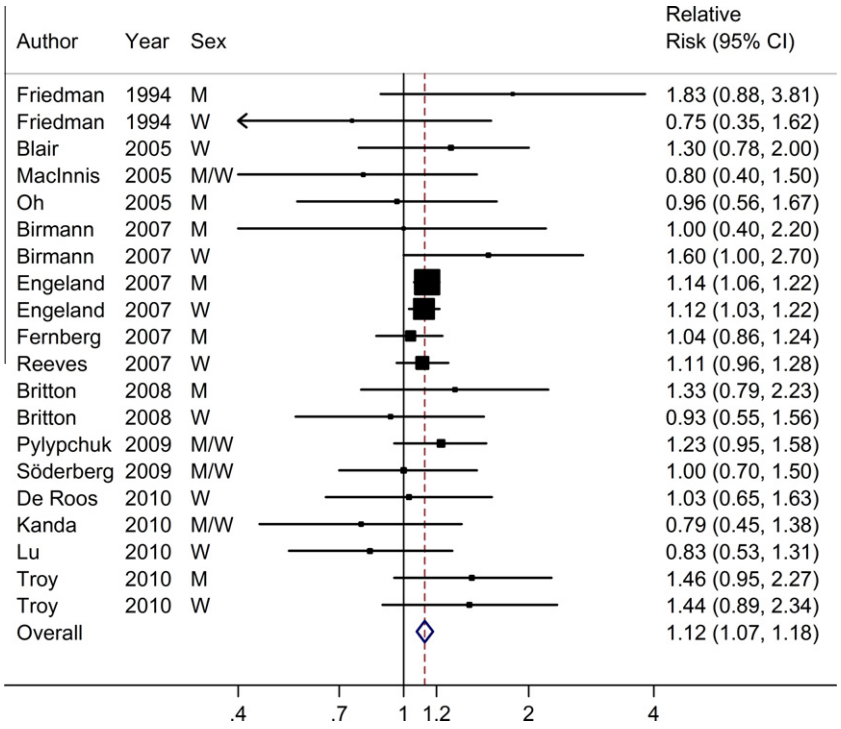


**Fig. 2 – Relative risk estimates of multiple myeloma incidence for overweight versus normal weight, for individual studies (men and women separately when available) and all studies combined. Squares indicate study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, i.e. the inverse of the variance); horizontal lines indicate 95% confidence intervals; diamond indicates the summary relative risk estimate with 95% confidence interval. Test for heterogeneity: Q = 14.87, $p = 0.73$, $I^2 = 0.0\%$. M = men; W = women.**

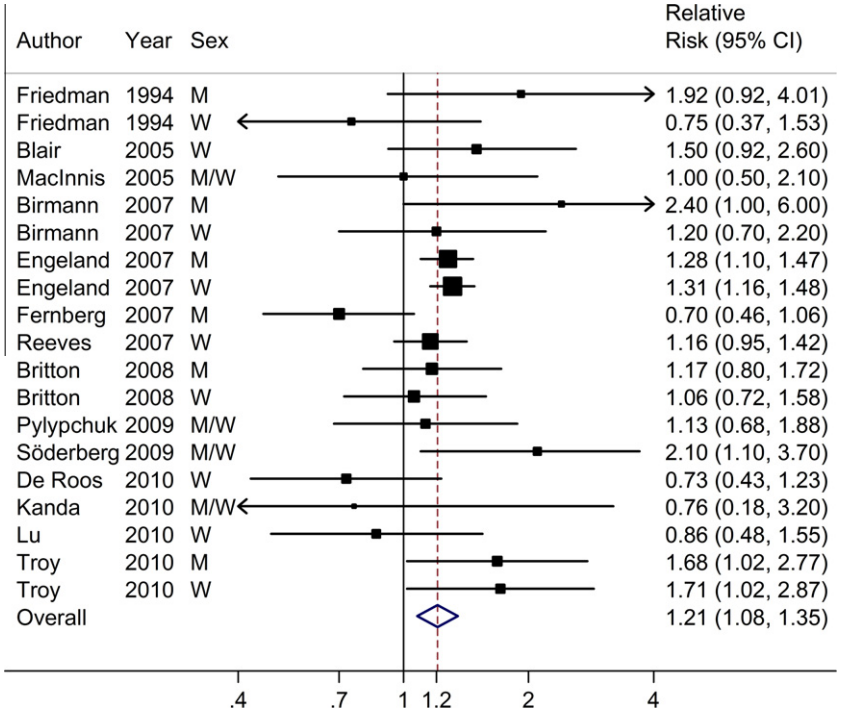


**Fig. 3 – Relative risk estimates of multiple myeloma incidence for obesity versus normal weight, for individual studies (men and women separately when available) and all studies combined. Squares indicate study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, i.e. the inverse of the variance); horizontal lines indicate 95% confidence intervals; diamond indicates the summary relative risk estimate with 95% confidence interval. Test for heterogeneity: Q = 27.31, $p = 0.07$, $I^2 = 34.1\%$. M = men; W = women.**

between-study variability. We checked for nonlinearity of the dose-response relationship between BMI and multiple myeloma by estimating polynomial models. This was done by using the 'pool-first' method described by Greenland and Longnecker.[12] We found that the best-fitting model was a linear model.

Statistical heterogeneity among studies was evaluated by using the Q and $I^2$ statistics.[15] Potential publication bias was assessed with the Egger regression asymmetry test.[16] All statistical analyses were performed with Stata software, version 10 (StataCorp, College Station, Texas). $P < 0.05$ was considered statistically significant.

## 3. Results

A flowchart of the identification of relevant studies is shown in Fig. 1. Briefly, a total of 302 articles were identified by

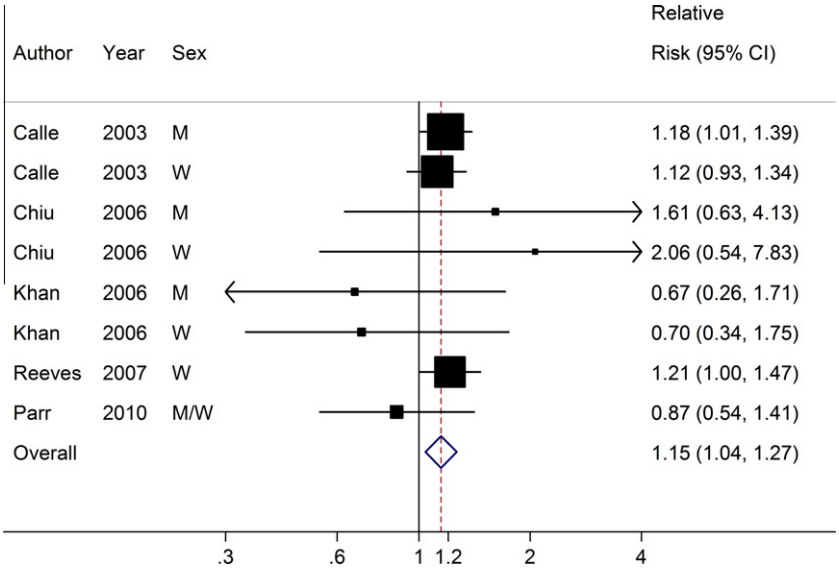


**Fig. 4 – Relative risk estimates of multiple myeloma mortality for overweight versus normal weight, for individual studies (men and women separately when available) and all studies combined. Squares indicate study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, i.e. the inverse of the variance); horizontal lines indicate 95% confidence intervals; diamond indicates the summary relative risk estimate with 95% confidence interval. Test for heterogeneity: Q = 5.67, $p = 0.58$, $I^2 = 0.0\%$. M = men; W = women.**

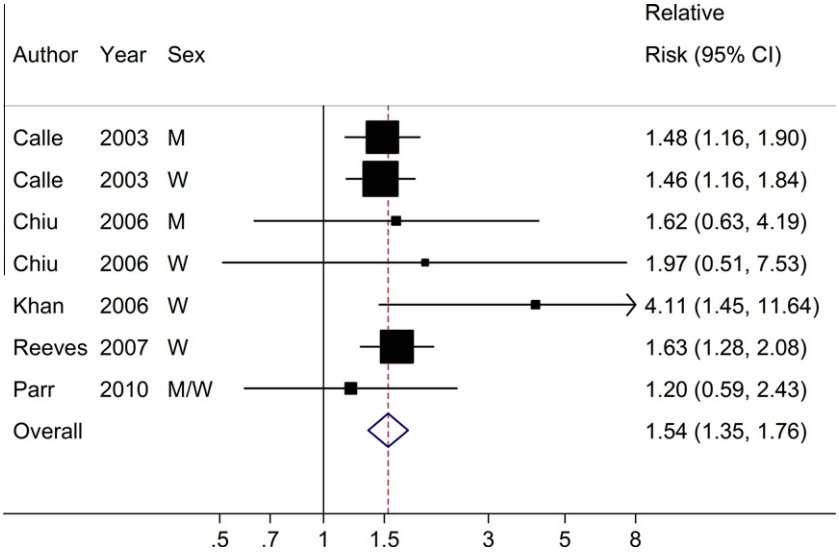


**Fig. 5 – Relative risk estimates of multiple myeloma mortality for obesity versus normal weight, for individual studies (men and women separately when available) and all studies combined. Squares indicate study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, i.e. the inverse of the variance); horizontal lines indicate 95% confidence intervals; diamond indicates the summary relative risk estimate with 95% confidence interval. Test for heterogeneity: Q = 4.53, $p = 0.61$, $I^2 = 0.0\%$. M = men; W = women.**

searching the databases, 71 duplicated articles in the two databases and 209 articles that did not meet the selection criteria were excluded after screening of abstract and/or title. The remaining 22 articles and four additional articles[17–20] identified from reference lists were obtained for full-text review. Among these, two were letters or comments not reporting new results,[21,22] and one was a letter reporting results from a case-control study.[23] In addition, one review article,[24] two articles that defined obesity based on hospital diagnosis and thus did not determine BMI,[17,25] and one article reporting results from the same study population as another study[18] were excluded. The remaining 19 prospective cohort studies were included in the meta-analysis.[6–11,19,20,26–36]

The included studies were published between 1994 and 2010 and involved a total of 7,154,881 participants, 8,982 incident multiple myeloma cases, and 1,845 multiple myeloma deaths (Table 1). The outcome was incidence of multiple myeloma in 14 studies[6,7,9,11,19,26–34] and mortality from multiple myeloma in four studies.[10,20,35,36] One study reported results for incidence of and mortality from multiple myeloma separately.[8] Eight studies were conducted in the United States,[9–11,26,27,33–35] six in Europe,[7,8,28–31] three in Asia[6,32,36] and one in Australia.[19] In addition, one study was a pooling project involving 39 cohorts in the Asia-Pacific region.[20] All studies reported RRs adjusted for age and sex, eight for smoking/tobacco use,[6,8–10,20,28,32,35] six for education or socioeconomic status,[8–10,19,34,35] five for race/ethnicity,[9,10,33–35] four for alcohol[6,8,10,32] and four for physical activity/exercise.[6,8,10,27] Weight and height were assessed by direct measurements in seven studies[6,7,9,11,19,29,35] and by self-report in eleven studies.[8,10,26–28,30–34,36] Assessment methods used in the individual cohorts included in the Asia-Pacific pooling project were not reported in the article.[20] All but two studies[11,35] used BMI categories matching the World Health Organization (WHO) definitions of overweight and/or obesity (i.e. BMI 25.0–29.9 and BMI $\geqslant$30). For the reference category, seven studies used the WHO definition of normal weight (i.e. BMI 18.5–24.9),[7,10,20,28,31,34,36] whereas other studies used a narrower BMI range[6,8,26,32,33] or an open-ended BMI category potentially including underweight.[9,11,19,27,29,30,35]

Overall, both overweight and obesity were statistically significantly associated with elevated multiple myeloma incidence and mortality. Figs. 2 and 3 show study-specific (for men and women separately when available) and summary RR estimates of multiple myeloma incidence for overweight and obesity compared to normal weight (overweight: summary RR, 1.12; 95% CI, 1.07–1.18; obesity: summary RR, 1.21; 95% CI, 1.08–1.35). Figs. 4 and 5 show the corresponding RR estimates of multiple myeloma mortality (overweight: summary RR, 1.15; 95% CI, 1.04–1.27; obesity: summary RR, 1.54; 95% CI, 1.35–1.76). There was indication of heterogeneity only among results for obesity in relation to multiple myeloma incidence, although not statistically significant ($p = 0.07$, $I^2 = 34.1\%$). Summary RR estimates of multiple myeloma incidence remained statistically significant after exclusion of the large study by Engeland et al.[7] (overweight: RR, 1.11; 95% CI, 1.02–1.20; obesity: RR, 1.17; 95% CI, 1.01–1.37).

On a continuous scale, a 5 kg/m$^2$ increase in BMI was associated with a 12% and 21% increased risk of multiple myeloma incidence and mortality, respectively (Table 2). The summary RR did not differ appreciably between men and women, between studies conducted in different geographic regions, between studies based on self-report and direct measurements of weight and height, or between studies with different follow-up periods (Table 2). For the five studies that included only participants aged $\geqslant$50 years at baseline,[8,9,26,30,34] the summary RR for multiple myeloma incidence was 1.13 (95% CI, 1.02–1.26). Analysis limited to the seven studies[9,29–34] on multiple myeloma incidence published after the two previous meta-analyses resulted in a summary RR of 1.09 (95% CI,

**Table 2 – Summary relative risks of multiple myeloma incidence and mortality for an increment of 5 kg/m$^2$ in body mass index.**

| | Multiple myeloma incidence | | | Multiple myeloma mortality | | |
|---|---|---|---|---|---|---|
| | Studies (*n*) | RR (95% CI) | *P* for heterogeneity | Studies (*n*) | RR (95% CI) | *P* for heterogeneity |
| All studies | 15 | 1.12 (1.08–1.16) | 0.41 | 5 | 1.21 (1.13–1.30) | 0.72 |
| Sex | | | | | | |
| Men | 8 | 1.15 (1.05–1.25) | 0.29 | 2 | 1.23 (1.09–1.39) | 0.60 |
| Women | 10 | 1.10 (1.05–1.15) | 0.45 | 3 | 1.22 (1.13–1.32) | 0.37 |
| Geographic region[a] | | | | | | |
| United States | 6 | 1.14 (1.02–1.27) | 0.26 | 2 | 1.20 (1.11–1.29) | 0.86 |
| Europe | 6 | 1.12 (1.07–1.16) | 0.39 | 1 | 1.33 (1.15–1.52) | – |
| Asia | 2 | 1.02 (0.67–1.57) | 0.26 | 2 | 1.08 (0.85–1.36) | 0.62 |
| Assessment of weight and height | | | | | | |
| Self-reported | 9 | 1.13 (1.04–1.23) | 0.19 | 1 | 1.38 (0.90–2.13) | – |
| Measured | 6 | 1.12 (1.08–1.16) | 0.61 | 4 | 1.21 (1.13–1.29) | 0.51 |
| Follow-up time | | | | | | |
| <10 years | 2 | 1.07 (0.98–1.18) | 0.90 | 2 | 1.20 (0.95–1.54) | 0.12 |
| 10–19 years | 9 | 1.12 (1.01–1.25) | 0.19 | 2 | 1.19 (1.10–1.29) | 0.87 |
| $\geqslant$20 years | 4 | 1.12 (1.07–1.18) | 0.39 | 1 | 1.38 (0.89–2.13) | – |

[a] One study from Australia was excluded from the stratified analysis.

0.98–1.22). The Egger test showed no evidence of publication bias for multiple myeloma incidence ($p = 0.77$) or mortality ($p = 0.34$).

## 4. Discussion

Findings of this meta-analysis of prospective cohort studies are consistent with results from previous meta-analyses, supporting the suggested positive association of overweight and obesity with multiple myeloma. In addition, this is the first meta-analysis of the relationship between BMI and multiple myeloma mortality, suggesting a positive association of larger magnitude than that of the association between BMI and multiple myeloma incidence. However, the small number of studies of multiple myeloma mortality is insufficient to confirm a stronger association for mortality than for incidence. The associations did not differ substantially by sex, geographical region, assessment of height and weight, follow-up time or age. Compared to the two previously published meta-analyses,[4,5] meta-analysis limited to the seven subsequently published studies on multiple myeloma incidence resulted in a somewhat weaker association.

Strength of this meta-analysis is that the assessment was based on data from prospective cohort studies only, which are less susceptible to recall and selection bias than retrospective case-control studies. There are also potential limitations of our findings. First, a meta-analysis of observational studies cannot solve potential problems with confounding in the individual studies, which may introduce bias. For multiple myeloma mortality, the included studies covered a large period of time, and improved treatment strategies for multiple myeloma over time may have affected the results. In fact, none of the studies was adjusted for treatment. Because few risk factors for multiple myeloma have been established, there is also the potential of unknown confounding. Adjustment for variables other than age and sex varied considerably among the included studies. We assessed how unknown confounding could have affected the results[37] by using the Stata command by Orsini et al.[38] Assuming that the prevalence of the confounder was 30% among those who were obese and 20% among normal weight individuals and that the confounder is associated with 50% increased risk of multiple myeloma, the RR for the association between obesity and multiple myeloma would be attenuated from 1.21 to 1.16. Hence, the unknown confounder must be both strongly correlated with the exposure (in this case excess body weight) and with the outcome (multiple myeloma) to produce a spurious association. Second, non-differential misclassification of BMI, due to reliance on a single assessment of weight, may have attenuated risk estimates. Only one study regularly updated information on weight.[27] In addition, reliance on self-reported height and weight in a majority of the studies may also have attenuated the estimates, as self-report tends to underestimate BMI.[39] Third, heterogeneity among results may have been introduced because the individual studies used different cut points for BMI categories, particularly the cut points for the reference category differed among studies. Further, depending on the influence of underweight on multiple myeloma risk, the different reference categories could potentially have an impact on the observed associations. However, none of the studies that included a BMI category in the underweight range below the reference category found statistically significant associations between underweight and multiple myeloma incidence or mortality.[6–8,17,29,30,33] In addition, the association between increasing BMI and multiple myeloma was supported using a dose-response approach, which is not dependent on cut-points. Finally, because studies with null results and small sample sizes tend not to be published, publication bias, which may overestimate the summary RR, could be of concern. However, we found no evidence of publication bias in this meta-analysis.

The mechanisms explaining the observed association between excess body weight and multiple myeloma are not yet established. Most stages of the disease occur within the bone marrow, and the bone marrow microenvironment is required for its development.[40] The tumour cells are dependent on various types of surrounding cells, and the importance of adipocytes has become increasingly clear.[41] A plausible explanation is that overweight and obese individuals have elevated levels of the pro-inflammatory cytokine interleukin-6 (IL-6), which is in part produced by adipocytes.[42] IL-6 is known to be a potent myeloma cell growth factor, and IL-6 levels have also been shown to predict disease severity in multiple myeloma patients.[43] Levels of adiponectin, another inflammatory mediator secreted by adipocytes, are decreased with increasing overweight[44] and have been associated with a lower risk of multiple myeloma.[45] Further, elevated levels of insulin-like growth factor 1 (IGF-1), associated with the chronic hyperinsulinemic state in obesity, have been shown to stimulate myeloma cell proliferation and inhibit apoptosis.[46]

BMI is a limited measure, as it does not provide information about fat distribution. Many of the complications associated with obesity have been shown to be closely related to central obesity, whereas peripheral obesity is much less harmful.[47] Four of the studies included in this meta-analysis examined the relationship of central obesity, measured by waist circumference and waist-to-hip ratio, with risk of multiple myeloma.[19,26,29,33] One study observed a twofold higher risk among subjects in the highest tertile of waist circumference.[26] Conversely, three studies observed no association with waist circumference, and none of the studies observed any association with waist-to-hip ratio.

Early adult BMI may represent lifetime body size better than measurements at cohort entry. Three of the four studies that reported on the relationship between self-reported BMI at different ages prior to baseline and risk of multiple myeloma observed no associations.[9,30,33] One study observed a larger increase in multiple myeloma risk associated with obesity at age 20 than with obesity at baseline.[34] In addition, four studies reported on the association between weight change and multiple myeloma.[9,11,30,34] One observed a weak positive association with weight gain of least 4 kg per 10 years,[34] whereas one observed a reduction in risk associated with a weight gain of at least 0.3 kg per year among black women. Other associations were not statistically significant.[9,30]

In conclusion, results from this meta-analysis are in line with previous evidence of a positive association between excess body weight and risk of multiple myeloma. These findings suggest that multiple myeloma incidence and mortality

may in part be prevented by maintaining a healthy body weight.

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The study sponsors had no role in the design of the study; collection, analysis, and interpretation of the data; or in the preparation, review or approval of the manuscript.

## Conflict of interest statement

None declared.

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## REFERENCES

1. Altekruse SF, Kosary CL, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2007. Bethesda, MD: National Cancer Institute, 2010. Available at: http://seer.cancer.gov/csr/1975_2007/(Accessed December 3, 2010), 2010.
2. Alexander DD, Mink PJ, Adami HO, et al. Multiple myeloma: a review of the epidemiologic literature. *Int J Cancer* 2007;**120**(Suppl 12):40–61.
3. Perez Perez A, Ybarra Munoz J, Blay Cortes V, de Pablos Velasco P. Obesity and cardiovascular disease. *Public Health Nutr* 2007;**10**:1156–63.
4. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;**371**:569–78.
5. Larsson SC, Wolk A. Body mass index and risk of multiple myeloma: a meta-analysis. *Int J Cancer* 2007;**121**:2512–6.
6. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. *J Clin Oncol* 2005;**23**:4742–54.
7. Engeland A, Tretli S, Hansen S, Bjorge T. Height and body mass index and risk of lymphohematopoietic malignancies in two million Norwegian men and women. *Am J Epidemiol* 2007;**165**:44–52.
8. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ* 2007;**335**:1134.
9. De Roos AJ, Ulrich CM, Ray RM, et al. Intentional weight loss and risk of lymphohematopoietic cancers. *Cancer Causes Control* 2010;**21**:223–36.
10. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity and mortality from cancer in a prospectively studied cohort of US adults. *N Engl J Med* 2003;**348**:1625–38.
11. Friedman GD, Herrinton LJ. Obesity and multiple myeloma. *Cancer Causes Control* 1994;**5**:479–83.
12. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992;**135**:1301–9.
13. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stat J* 2006;**6**:40–57.
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88.
15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–58.
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.
17. Wolk A, Gridley G, Svensson M, et al. A prospective study of obesity and cancer risk (Sweden). *Cancer Causes Control* 2001;**12**:13–21.
18. Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni Jr JF. Relation of body mass index to cancer risk in 362, 552 Swedish men. *Cancer Causes Control* 2006;**17**:901–9.
19. MacInnis RJ, English DR, Hopper JL, Giles GG. Body size and composition and the risk of lymphohematopoietic malignancies. *J Natl Cancer Inst* 2005;**97**:1154–7.
20. Parr CL, Batty GD, Lam TH, et al. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424, 519 participants. *Lancet Oncol* 2010;**11**:741–52.
21. Larsson SC, Wolk A. Excess body fatness: an important cause of most cancers. *The Lancet* 2008;**371**:536–7.
22. Islam R, Altundag K, Kurt M, Altundag O, Turen S. Association between obesity and multiple myeloma in postmenopausal women may be attributed to increased aromatization of androgen in adipose tissue. *Med Hypotheses* 2005;**65**:1001–2.
23. Bosetti C, Negri E, Gallus S, et al. Anthropometry and multiple myeloma 2. *Epidemiology* 2006;**17**:340–1.
24. Lichtman MA. Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma. *Oncologist* 2010;**15**:1083–101.
25. Samanic C, Gridley G, Chow WH, et al. Obesity and cancer risk among white and black United States veterans. *Cancer Causes Control* 2004;**15**:35–43.
26. Blair CK, Cerhan JR, Folsom AR, Ross JA. Anthropometric characteristics and risk of multiple myeloma. *Epidemiology* 2005;**16**:691–4.
27. Birmann BM, Giovannucci E, Rosner B, Anderson KC, Colditz GA. Body mass index, physical activity, and risk of multiple myeloma. *Cancer Epidemiol Biomarkers Prev* 2007;**16**:1474–8.
28. Fernberg P, Odenbro A, Bellocco R, et al. Tobacco use, body mass index, and the risk of leukemia and multiple myeloma: a nationwide cohort study in Sweden. *Cancer Res* 2007;**67**:5983–6.
29. Britton JA, Khan AE, Rohrmann S, et al. Anthropometric characteristics and non-Hodgkin's lymphoma and multiple myeloma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Haematologica* 2008;**93**:1666–77.
30. Pylypchuk RD, Schouten LJ, Goldbohm RA, Schouten HC, van den Brandt PA. Body mass index, height, and risk of lymphatic malignancies: a prospective cohort study. *Am J Epidemiol* 2009;**170**:297–307.
31. Soderberg KC, Kaprio J, Verkasalo PK, et al. Overweight, obesity and risk of haematological malignancies: a cohort study of Swedish and Finnish twins. *Eur J Cancer* 2009;**45**:1232–8.
32. Kanda J, Matsuo K, Inoue M, et al. Association of anthropometric characteristics with the risk of malignant lymphoma and plasma cell myeloma in a Japanese population: a population-based cohort study. *Cancer Epidemiol Biomarkers Prev* 2010;**19**:1623–31.

33. Lu Y, Sullivan-Halley J, Henderson KD, et al. Anthropometric characteristics and multiple myeloma risk. *Epidemiology* 2010;**21**:272–3.
34. Troy JD, Hartge P, Weissfeld JL, et al. Associations between anthropometry, cigarette smoking, alcohol consumption, and non-Hodgkin lymphoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Am J Epidemiol* 2010;**171**:1270–81.
35. Chiu BC, Gapstur SM, Greenland P, Wang R, Dyer A. Body mass index, abnormal glucose metabolism, and mortality from hematopoietic cancer. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:2348–54.
36. Khan MM, Mori M, Sakauchi F, et al. Risk factors for multiple myeloma: evidence from the Japan Collaborative Cohort (JACC) study. *Asian Pac J Cancer Prev* 2006;**7**:575–81.
37. Greenland S. Basic methods for sensitivity analysis of biases. *Int J Epidemiol* 1996;**25**:1107–16.
38. Orsini N, Bellocco R, Greenland S. EPISENSRRI: Stata module for basic sensitivity analysis for unmeasured confounders, Statistical Software Components S456793, Boston College Department of Economics 2006.
39. Kuczmarski MF, Kuczmarski RJ, Najjar M. Effects of age on validity of self-reported height, weight, and body mass index: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Am Diet Assoc 2001;101:28–34; quiz 35–6.
40. Zipori D. The hemopoietic stem cell niche versus the microenvironment of the multiple myeloma-tumor initiating cell. *Cancer Microenviron* 2010;**3**:15–28.
41. Caers J, Deleu S, Belaid Z, et al. Neighboring adipocytes participate in the bone marrow microenvironment of multiple myeloma cells. *Leukemia* 2007;**21**:1580–4.
42. Mohamed-Ali V, Goodrick S, Rawesh A, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, *in vivo*. *J Clin Endocrinol Metab* 1997;**82**:4196–200.
43. Lauta VM. A review of the cytokine network in multiple myeloma: diagnostic, prognostic, and therapeutic implications. *Cancer* 2003;**97**:2440–52.
44. Arita Y, Kihara S, Ouchi N, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999;**257**:79–83.
45. Dalamaga M, Karmaniolas K, Panagiotou A, et al. Low circulating adiponectin and resistin, but not leptin, levels are associated with multiple myeloma risk: a case-control study. *Cancer Causes Control* 2009;**20**:193–9.
46. Ferlin M, Noraz N, Hertogh C, et al. Insulin-like growth factor induces the survival and proliferation of myeloma cells through an interleukin-6-independent transduction pathway. *Br J Haematol* 2000;**111**:626–34.
47. Arner P. Regional adipocity in man. *J Endocrinol* 1997;**155**:191–2.