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ORIGINAL ARTICLE

Socioeconomic Position is Positively Associated with Monoclonal Gammopathy of Undetermined Significance in a Population-based Cohort Study

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Abstract
Knowledge of social inequalities in monoclonal gammopathy of undetermined significance (MGUS) will contribute to understanding multiple myeloma (MM) etiology, as MGUS consistently precedes MM. The aim of the present study was to examine whether socioeconomic position (SEP) is associated with MGUS in a population-based cohort including information on potential MGUS risk factors. Overall, 4787 study participants aged 45–75 years with information on MGUS were included. SEP indicators (education, income) and potential risk factors (i.e., body mass index, diabetes, smoking, dietary factors) were assessed at baseline. Overall, 260 MGUS cases were detected at baseline and prospectively over a 10-year follow-up. In age-adjusted logistic regression models, a lower chance of having MGUS at baseline or developing MGUS during 10 years of follow-up was indicated for groups of low SEP with odds ratios (OR) of 0.39 (95% confidence interval [95%-CI] 0.19–0.76) for women and 0.48 (95% CI 0.10–1.16) for men in the lowest compared to the highest educational group. After additionally including potential mediating risk factors in the regression models, the estimated ORs changed only slightly in magnitude. Similar results were obtained for income. Current smoking and low fruit consumption were associated with MGUS independently of SEP in women, but not in men. The present study indicates a lower MGUS risk in lower SEP groups. Supporting evidence is given that smoking and diet play a role in the development of MGUS independently of SEP, while it has to be assumed that risk factors unknown to date are responsible for the observed social inequalities in MGUS.

Keywords Health inequalities · Monoclonal gammopathy of undetermined significance · MGUS · Socioeconomic position · Multiple myeloma

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma (MM) [1, 2], a neoplasm of plasma cells indicated by an overproduction of monoclonal immunoglobulins. While MGUS also shows presence of a monoclonal immunoglobulin, it is characterized by a lack of other MM features such as lytic bone lesions, anemia, hypercalcemia, or renal insufficiency [3, 4]. The prevalence of MGUS in populations of European descent aged 50 years and older has been estimated at 3% to 4% [4, 5]. MGUS progresses to MM at a rate of approximately 1% per year [6, 7].

Next to ethnic differences in MM risk, previous studies have established male sex, increasing age and — given the strong familial clustering — genetic factors as risk factors contributing to the etiology of MM [8, 9]. However, preventable risk factors for MM are still largely unknown. Potential risk factors that have been discussed include obesity, diabetes, smoking, diet (such as fish, vegetable/fruit consumption), and other lifestyle factors as well as pesticide exposure and occupational factors [8, 10, 11]. Some studies have investigated whether discussed risk factors for MM are associated with MGUS with inconclusive results

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regarding the role of obesity, diabetes, and smoking [12–16]. As it is generally assumed that risk-related lifestyle and occupational factors may be unequally distributed across strata of socioeconomic position (SEP), investigating the relationship between SEP indicators and MGUS will contribute to the understanding of MM etiology. Studies including SEP as potential risk factor for MM have also shown inconclusive results with reports of increased MM risk in individuals of low SEP [17, 18], reports of higher MM mortality in individuals of high SEP [19], or lack of association [20]. In a study with women, low education was associated with higher MGUS risk, but decreased effect size estimates have been observed when adjusting for ethnic differences [13]. In another study in male pesticide applicators, the trend of effect size estimates across SEP strata also suggested a higher MGUS risk with lower education [14]. However, there is lack of studies investigating SEP effects in population-based study samples of both sexes covering the full range of the SEP distribution, while at the same time considering risk factors potentially mediating the SEP effect on MGUS.

In the present study, the association of SEP with MGUS was investigated in a population-based cohort separately for women and men, including potential risk factors that have been suggested to increase MM and MGUS risk and that were available for analysis in the study population (i.e., body mass index [BMI], diabetes, smoking, dietary factors such as fish, vegetable, and fruit consumption).

Methods

Study population

Data of the prospective population-based Heinz Nixdorf Recall Study were used for the present analysis. The study's design and rationale have been described in detail elsewhere [21]. Briefly, 4814 women and men aged 45–75 years were included in the study population using a random sample derived from mandatory citizen registries of three large cities (Bochum, Essen, Mülheim/Ruhr) in an urban region in the western part of Germany. Participants were recruited from 2000 to 2003 with a baseline response proportion of 55.8% [22]. The study was approved by the local ethics committee (99-69-1200) and informed consent was obtained from all participants. The study comprises extended quality management procedures including a certification according to DIN ISO 9001:2000.

Monoclonal gammopathy of undetermined significance (MGUS)

MGUS was assessed at baseline and prospectively at the 5-year and the 10-year follow-up examination using serum samples collected at each visit and stored at − 80 °C (details have been described previously [5]). For MGUS determination, standard serum electrophoresis was combined with parallel screening immunofixation electrophoresis (scIFE) using pentavalent antisera (Hydragel 12 IF, Penta-Kit, Sebia, Fulda, Germany). Confirmatory IFE using antisera against γ, α, μ, κ, and λ immunoglobulin chains was performed in samples showing a visible or suspected monoclonal band. Electrophoresis gels were evaluated by a trained physician. MGUS cases were defined according to the International Myeloma Working Group criteria [3], including information on the detectable monoclonal protein on SPE and/or IFE, monoclonal protein concentration, laboratory results, and disease history.

Free kappa (κ) and free lambda (λ) immunoglobulin light chains (FLC) were determined using a Dade Behring BNII automated nephelometer (Siemens, Germany) utilizing a commercially available kit (FREELITE, The Binding Site Ltd, Birmingham, UK). Published reference ranges for κ and λ FLC were used (3.3–19.4 mg/L and 5.7–26.3 mg/L, respectively) [23]. A pathological κ/λ FLC ratio was defined as < 0.26 or > 1.65 for participants with an estimated glomerular filtration rate (eGFR) of > 30 mL/min and as < 0.37 or > 3.1 for participants with an eGFR of < 30 mL/min [24].

Indicators of socioeconomic position

Information on the SEP indicators' education and income was assessed by standardized face-to-face interviews at baseline examination. Education was defined according to the International Standard Classification of Education as total years of formal education by combining school and vocational training [25]. It was then included into analyses either as continuous variable or categorized into three groups with the lowest educational group of ten and less years (equivalent to a basic school degree with no vocational training) and the highest educational group of 14 and more years of education (equivalent to vocational training including additional qualification or a university degree). Income was defined as the monthly household equivalent income by dividing the total household net income by a weighting factor for each household member [26]. It was included into analyses either as continuous variable or categorized into three groups using sex-specific tertiles. To account for different mechanisms in causing social inequalities in health both SEP indicators were analyzed separately [27, 28].

Potential risk factors

Information on the potential risk factors for MM and MGUS that were available for analysis (i.e., BMI, diabetes, smoking, dietary intake such as fish, vegetable, and fruit consumption) were assessed at study baseline. Diabetes mellitus was defined as either of the following criteria: reporting a history of diabetes mellitus, taking glucose-lowering drugs, having fasting blood glucose levels of greater than 125 mg/dL, or having non-fasting glucose levels of 200 mg/dL or greater. Current smoking was defined as smoking cigarettes during the past year, former smoking as having a history of smoking before the past year, and never smoking as never having smoked. BMI was computed from standardized measurements of height and weight (kg/m^2). Dietary intake was assessed by a validated food frequency questionnaire (FFQ) [29]. Frequency of consumption was assessed using a five-point scale with the categories daily, 4–6 times/week, 1–3 times/week, 1–3 times/month, and hardly ever/never for each food item. Based on the FFQ, information for fish, boiled vegetable, raw vegetable, and fruit consumption was dichotomized into low consumption (1–3 times/week or less) vs. high consumption (at least 4–6 times/week), except for fish consumption, which was dichotomized into low consumption (1–3 times/month) vs. high consumption (at least 1–3 times/week) [30].

Statistical analyses

For the main analyses, 4787 participants with non-missing information on MGUS were included (Figure S1). There was information missing on education (n = 13), income (n = 306), and on some of the potential risk factors leading to exclusion of these participants from the respective analyses. Participants with missing information on SEP did not differ in rates of MGUS and participants with missing information on MGUS did not differ in SEP.

To increase the precision of effect size estimates for detecting associations of SEP indicators with MGUS in the main analysis, prevalent MGUS cases at baseline were analyzed together with incident MGUS cases, corresponding to a lifetime MGUS prevalence (i.e., having MGUS at least at one of the three examination dates). Sex-stratified logistic regression models were fitted to calculate odds ratios (OR) and their corresponding 95% confidence intervals (95% CI) separately for education and income entered either as independent continuous variables or categorical with the group of highest education or income as reference. Different regression models were then calculated starting with age-adjusted models to control for confounding of the total SEP effect followed by age-adjusted models also including one additional potential mediating risk factor each and ending with an age-adjusted model including all potential mediating risk factors. For detecting associations of potential risk factors with MGUS, sex-stratified logistic regression models were fitted and adjusted for age and education to control for confounding. In addition, sensitivity analysis was performed by separately investigating incident MGUS cases over 10 years of follow-up only (Figure S1). Analyses were performed using the R statistical package version 3.3.0 [31]. For original data, please contact the corresponding author.

Results

Characteristics of the study population are shown in Table 1. The overall number of prevalent and incident MGUS cases

Table 1 Characteristics of study participants stratified by sex

	All	Women	Men
n	4787 (100%)	2402 (50.2%)	2385 (49.8%)
Age (years)[a]	59.6 (± 7.8)	59.6 (± 7.8)	59.7 (± 7.8)
MGUS[b]	260 (5.4%)	103 (4.3%)	157 (6.6%)
Education (years of training)[b]			
≤ 10 y	544 (11.4%)	424 (17.7%)	120 (5.0%)
11–13 y	2659 (55.7%)	1524 (63.5%)	1135 (47.8%)
≥ 14 y	1571 (32.9%)	451 (18.8%)	1120 (47.2%)
Income (€/month)[c]	1449 (1108–1875)	1313 (937–1875)	1520 (1108–2073)
Smoking[b]			
Never smoker	2000 (41.8%)	1335 (55.6%)	665 (27.9%)
Past smoker	1659 (34.7%)	555 (23.1%)	1104 (46.4%)
Current smoker	1121 (23.5%)	510 (21.3%)	611 (25.7%)
Diabetes mellitus[b]	649 (13.6%)	233 (9.7%)	416 (17.4%)
Body mass index (kg/m^2)[a]	27.9 (± 4.6)	27.6 (± 5.2)	28.2 (± 4.0)
Low fish consumption[b]	2984 (63.4%)	1462 (61.7%)	1522 (65.0%)
Low boiled vegetable consumption[b]	2962 (62.9%)	1322 (55.9%)	1640 (69.9%)
Low raw vegetable consumption[b]	3215 (68.3%)	1460 (61.8%)	1755 (74.9%)
Low fruit consumption[b]	1450 (30.8%)	534 (22.5%)	916 (39.1%)

[a] Mean (± sd)

[b] Number (%)

[c] Median (quartile range)

was 260 (5.4%) with women showing a lower risk of MGUS than men (for clinical characteristics of MGUS cases see Table S1). Out of these, 103 (3.5%) incident cases of MGUS were observed over a follow-up of 10 years (Table S2). Differences between women and men were also observed in the distribution of SEP indicators with women reporting less years of formal education and lower household income. SEP indicators stratified by MGUS status showed a higher proportion of high education in MGUS cases as well as a higher household income (Table S3).

In age-adjusted regression models both SEP indicators were associated with MGUS in women and men with study participants in the lowest education or income group showing a substantially lower MGUS risk compared to participants in the highest education or income group (Table 2). The strongest age-adjusted effect size estimate was observed for women with ten and less years of education showing an OR of 0.39 (95% CI 0.19–0.76), indicating that the chance of having MGUS at baseline or developing MGUS during 10 years of follow-up was approximately 60% lower compared to women with 14 and more years of education. For men, the strongest age-adjusted effect size estimate was also observed in the group with ten and less years of education showing an OR of 0.48 (95% CI 0.10–1.16). For study participants in the middle education or income groups, indication for a lower risk of MGUS was also observed, leading to a positive trend in the magnitude of effect size estimates across SEP groups. This was supported by using education and income as continuous variables in age-adjusted logistic regression models, showing ORs of 1.12 (95% CI 1.02–1.23; $p = 0.01$) and 1.11 (95% CI 1.04–1.20; $p = 0.004$) per year of education for women and men and ORs of 1.22 (95% CI 0.89–1.64; $p = 0.20$) and 1.34 (95% CI 1.07–1.68; $p = 0.01$) per 1000€ income, respectively. After additionally including potential mediating risk factors in the regression models, the estimated ORs changed only slightly in magnitude for both SEP indicators, even in the regression models including all potential mediating risk factors simultaneously (Table 2). In the sensitivity analyses considering only incident MGUS cases, direction and magnitude of ORs were similar to those obtained in the main analysis population (Table S4). Exceptions with ORs less strong in magnitude were noted for the middle educational group in men, the middle-income tertile in women and the low-income tertile in men. Overall, 95% CIs were wider in the sensitivity analysis (i.e., estimation of effects was less precise).

In women, current smoking and low fruit consumption showed the strongest indication of association with MGUS independently of the SEP association (Table 3). While in women, ORs > 1 were observed for all dietary factors as well as for diabetes, effect size estimates were substantially less strong in men. BMI did not show any indication of association in women neither in men. In the sensitivity analyses considering only incident MGUS cases, similar results were observed (Table S5).

Discussion

In the present study, associations of education and income with MGUS were observed in women and men of a population-based cohort, indicating a substantially lower MGUS risk in lower SEP groups. The associations were present across all SEP groups and did not change after adjustment for potential mediating risk factors such as BMI, diabetes, smoking, and dietary factors. While the covariates included in the analysis did not seem to mediate the association of SEP with MGUS, associations of current smoking and low fruit consumption with MGUS independent of the SEP were detected in women.

Associations of education and income with MGUS have been investigated previously in a study population of women aged 40–79 years [13]. Direction of effect size estimates for both SEP indicators gave some indication for a higher MGUS risk in lower SEP groups, while ethnic differences were partly responsible for the observed association. In a study of male pesticide applicators aged 30–94 years, direction of effect size estimates have also suggested a higher MGUS risk with lower education [14]. However, in the present study, the opposite direction of SEP effects was observed showing a positive association between SEP and MGUS across SEP categories as well as in regression models including continuous SEP variables. This discrepancy may be explained as follows: (1) compared to the present study the number of MGUS cases was much smaller in both previous studies leading to less precise effect size estimates; (2) SEP indicators in both previous studies were either categorical or dichotomized potentially leading to loss of statistical power and biased results [32]; (3) next to methodological differences there may be one or more yet unknown MGUS risk factors with different social distributions in different populations responsible for the diverging direction of SEP effect size estimates. However, it is not clear which underlying factors are causing a lower MGUS risk in groups of low SEP in the present study as all potential mediating risk factors included in the analysis did not alter the SEP effect observed.

In a study on time trends in MM mortality, higher mortality rates in groups of higher SEP have been reported for women and men [19]. The authors have argued that under-ascertainment bias may be the main explanation for the positive association observed, since under-ascertainment of MM as cause of death has been hypothesized to be related to low SEP. However, higher MGUS risk in higher SEP groups as observed in the present study cannot be explained by under-ascertainment, as all study participants underwent the same screening steps to detect MGUS irrespective of their SEP status.

The present study gave indication for a higher MGUS risk associated with current smoking and low fruit

Table 2 Odds ratios (OR) and 95% confidence intervals (95% CI) for the association of education and income with monoclonal gammopathy of undetermined significance (MGUS) in women and men adjusted for age and potential mediating risk factors (with highest educational group/income tertile as reference)

Education	Women									Men							
			Education ≤ 10 years			Education 11–13 years					Education ≤ 10 years			Education 11–13 years		
Model	*n*	*n* case	OR	(95% CI)	*p*	OR	(95% CI)	*p*	*n*	*n* case	OR	(95% CI)	*p*	OR	(95% CI)	*p*
Age	2399	103	0.39	(0.19–0.76)	0.01	0.62	(0.38–1.06)	0.07	2375	156	0.48	(0.10–1.16)	0.12	0.67	(0.47–0.94)	0.02
Age + body mass index (BMI)	2386	103	0.39	(0.20–0.78)	0.01	0.63	(0.38–1.07)	0.08	2365	155	0.45	(0.16–1.05)	0.10	0.65	(0.46–0.91)	0.01
Age + smoking	2399	103	0.42	(0.21–0.84)	0.01	0.66	(0.40–1.13)	0.12	2375	156	0.46	(0.16–1.06)	0.10	0.65	(0.46–0.92)	0.01
Age + diabetes mellitus	2399	103	0.37	(0.18–0.73)	0.01	0.61	(0.37–1.04)	0.06	2375	156	0.48	(0.16–1.10)	0.12	0.67	(0.47–0.93)	0.02
Age + fish consumption	2367	100	0.37	(0.18–0.75)	0.01	0.64	(0.39–1.10)	0.09	2335	156	0.49	(0.17–1.13)	0.13	0.67	(0.48–0.95)	0.02
Age + boiled vegetable consumption	2365	100	0.39	(0.19–0.77)	0.01	0.64	(0.39–1.10)	0.09	2338	156	0.48	(0.17–1.11)	0.12	0.67	(0.47–0.94)	0.02
Age + raw vegetable consumption	2363	99	0.39	(0.19–0.77)	0.01	0.63	(0.38–1.08)	0.08	2336	156	0.49	(0.17–1.14)	0.14	0.68	(0.48–0.95)	0.02
Age + fruit consumption	2368	100	0.37	(0.18–0.74)	0.01	0.62	(0.38–1.08)	0.08	2337	156	0.49	(0.17–1.14)	0.14	0.67	(0.48–0.95)	0.02
Age + all risk factors (full model)	2344	99	0.37	(0.18–0.76)	0.01	0.65	(0.38–1.13)	0.11	2323	155	0.46	(0.15–1.02)	0.09	0.64	(0.45–0.90)	0.01
Income	Women								Men							
			Low-income tertile			Middle-income tertile					Low-income tertile			Middle-income tertile		
Model	*n*	*n*		case	OR	(95-	% CI)	*p*	OR	(95-		% CI)	*p*	*n*	*n* case	OR
(95% CI)	*p*	OR	(95-	% CI)	*p*											
Age	2195	92	0.60	(0.35–1.02)	0.06	0.79	(0.47–1.32)	0.36	2286	150	0.54	(0.35–0.83)	0.01	0.79	(0.53–1.20)	0.27
Age + body mass index (BMI)	2184	92	0.60	(0.35–1.03)	0.06	0.79	(0.47–1.32)	0.36	2276	149	0.53	(0.34–0.82)	0.004	0.78	(0.51–1.18)	0.24
Age + smoking	2195	92	0.61	(0.36–1.04)	0.07	0.82	(0.49–1.38)	0.45	2286	150	0.54	(0.35–0.83)	0.01	0.79	(0.53–1.20)	0.27
Age + diabetes mellitus	2195	92	0.59	(0.35–1.01)	0.05	0.77	(0.46–1.30)	0.33	2286	150	0.54	(0.35–0.83)	0.005	0.79	(0.53–1.21)	0.28
Age + fish consumption	2171	91	0.61	(0.36–1.03)	0.06	0.76	(0.45–1.29)	0.31	2253	150	0.54	(0.35–0.83)	0.01	0.79	(0.52–1.20)	0.26
Age + boiled vegetable consumption	2170	91	0.61	(0.36–1.03)	0.06	0.77	(0.45–1.30)	0.32	2254	150	0.54	(0.35–0.83)	0.005	0.79	(0.52–1.20)	0.26
Age + raw vegetable consumption	2167	90	0.61	(0.36–1.03)	0.07	0.74	(0.43–1.25)	0.26	2253	150	0.54	(0.35–0.84)	0.01	0.79	(0.53–1.21)	0.28
Age + fruit consumption	2172	91	0.59	(0.35–0.99)	0.05	0.76	(0.45–1.29)	0.31	2255	150	0.54	(0.35–0.83)	0.01	0.79	(0.52–1.20)	0.26
Age + all risk factors (full model)	2151	90	0.61	(0.35–1.04)	0.07	0.75	(0.44–1.28)	0.29	2241	149	0.53	(0.34–0.82)	0.004	0.79	(0.52–1.19)	0.26

consumption in women. In men, substantially less strong effect size estimates were observed, although direction of effects was consistent to those found in women. There were several studies with inconsistent results on the association of dietary factors such as fish and vegetable consumption with MM [8, 10, 11], while in the present study only a weak indication for an association of fish and vegetable consumption with MGUS was detected in women. However, in a study exploring the impact of 13 food items on MGUS risk, only intake of fruit at least three times per week was associated with lower risk of MGUS when compared to lower fruit consumption [33]. This is in line with the present results showing effect size estimates of the same magnitude.

In a case-control study in women and men aged 16–91 years, a higher MGUS risk was found in heavy smokers (defined as having smoked > 20 cigarettes/day for at least 5 years), showing a stronger effect compared to light smokers [16]. The present study adds further evidence, as stronger effects were observed for current smokers compared to past smokers suggesting that next to the dose-response effects reported before also smoking cessation seems to play a role in MGUS etiology. In a previous study of men, no association of smoking with MGUS was found [14], which is in line with the present results.

No indication for associations of BMI and diabetes mellitus with MGUS was observed. A previous study on the association between metabolic factors and MGUS has raised the possibility of detection bias as an explanation for previously reported associations between obesity, diabetes, and MGUS [15]. This was supported by the lack of association in the present study for both women and men, as well as in a previous longitudinal study exploring the impact different obesity measures on MGUS [12].

Table 3 Odds ratios (OR) and 95% confidence intervals (95%-CI) for the association of potential risk factors with monoclonal gammopathy of undetermined significance (MGUS) in women and men adjusted for age and education

Variable	*n*	*n* case	OR	(95% CI)	*p*
Women					
Body mass index (BMI)	2386	103	0.99	(0.95–1.04)	0.82
Smoking past	2399	103	1.47	(0.88–2.39)	0.13
Smoking current	2399	103	2.19	(1.29–3.65)	0.003
Diabetes mellitus	2399	103	1.45	(0.79–2.49)	0.20
Low fish consumption	2367	100	1.39	(0.91–2.15)	0.13
Low boiled vegetable consumption	2365	100	1.34	(0.89–2.04)	0.16
Low raw vegetable consumption	2363	99	1.18	(0.77–1.85)	0.44
Low fruit consumption	2368	100	1.82	(1.14–2.84)	0.01
Men					
Body mass index (BMI)	2365	155	1.03	(0.99–1.08)	0.11
Smoking past	2375	156	0.89	(0.61–1.33)	0.56
Smoking current	2375	156	1.20	(0.75–1.91)	0.44
Diabetes mellitus	2375	156	1.02	(0.66–1.53)	0.92
Low fish consumption	2335	156	1.08	(0.77–1.53)	0.67
Low boiled vegetable consumption	2238	156	1.25	(0.87–1.81)	0.23
Low raw vegetable consumption	2336	156	0.99	(0.68–1.45)	0.94
Low fruit consumption	2337	156	1.08	(0.76–1.53)	0.65

The strengths of the present study are its population-based study design, the assessment of prevalent as well as incident MGUS cases over a 10-year follow-up period using a sensitive screening approach including immunofixation, the inclusion of two different SEP indicators as well as the range of potential MGUS risk factors available for analysis. A limitation of the study is that urine samples were not analyzed and imaging as well as bone marrow biopsy results were not available for giving more detailed information on MGUS diagnosis and its severity. Therefore, a small fraction of MGUS cases and rare plasma cell dyscrasias might have been missed [34].

In conclusion, results of the present study indicate an association of education and income with MGUS in women and men of a population-based study sample, showing a lower MGUS risk in lower SEP groups. It has to be assumed that one or more unknown risk factors for MGUS not included in the present analysis are responsible for the observed social inequalities in MGUS risk. In addition, there is supporting evidence that smoking and fruit intake as modifiable risk factors play a role in the development of MGUS, giving the potential for prevention strategies for MM. However, further population-based studies are needed to investigate the direction of the SEP effect on MGUS and to identify the MGUS risk factors involved.

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Authorship contributions KHJ, RE, SM, ND, LE, JD, UD, and BS contributed to the conception, study design, and data acquisition. ED, MA, MF, and BS conducted the statistical analyses. All authors contributed to the interpretation of results, manuscript preparation, and read and approved the final manuscript.

Compliance with ethical standards

Disclosures LE is now an employee of Janssen-Cilag, Germany.

References

1. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, Dispenzieri A, Kumar S, Clark RJ, Baris D, Hoover R, Rajkumar SV (2009) Monoclonal gammopathy of undetermined

significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 113(22):5412–5417
2. Weiss BM, Abadie J, Verma P, Howard RS, Kuehl WM (2009) A monoclonal gammopathy precedes multiple myeloma in most patients. Blood. 113(22):5418–5422
3. International Myeloma Working Group (2003) Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 121(5):749–757
4. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, Dispenzieri A, Katzmann JA, Melton LJ 3rd (2006) Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med 354(13):1362–1369
5. Eisele L, Dürig J, Hüttmann A, Dührsen U, Assert R, Bokhof B, Erbel R, Mann K, Jöckel KH, Moebus S, Heinz Nixdorf Recall Study Investigative Group (2012) Prevalence and progression of monoclonal gammopathy of undetermined significance and light-chain MGUS in Germany. Ann Hematol 91(2):243–248
6. Bladé J, Rosiñol L, Cibeira MT (2008) de Larrea, C F. Pathogenesis and progression of monoclonal gammopathy of undetermined significance. Leukemia. 22(9):1651–1657
7. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, Melton LJ 3rd (2002) A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 346(8):564–569
8. Alexander DD, Mink PJ, Adami H et al (2007) Multiple myeloma: a review of the epidemiologic literature. Int J Cancer 120(S12):40–61
9. Mitchell JS, Li N, Weinhold N et al (2016) Genome-wide association study identifies multiple susceptibility loci for multiple myeloma. Nat Comms 7:12050
10. Caini S, Masala G, Gnagnarella P, Ermini I, Russell-Edu W, Palli D, Gandini S (2016) Food of animal origin and risk of non-Hodgkin lymphoma and multiple myeloma: a review of the literature and meta-analysis. Crit Rev Oncol Hematol 100:16–24
11. Wang Y, Wu Q, Zhu J, Wu L (2015) Fish consumption and risk of myeloma: a meta-analysis of epidemiological studies. Cancer Causes Control 26(9):1307–1314
12. Thordardottir M, Lindqvist EK, Lund SH et al (2017) Obesity and risk of monoclonal gammopathy of undetermined significance and progression to multiple myeloma: a population-based study. Blood advances 1(24):2186–2192
13. Landgren O, Rajkumar SV, Pfeiffer RM, Kyle RA, Katzmann JA, Dispenzieri A, Cai Q, Goldin LR, Caporaso NE, Fraumeni JF, Blot WJ, Signorello LB (2010) Obesity is associated with an increased risk of monoclonal gammopathy of undetermined significance among black and white women. Blood. 116(7):1056–1059
14. Landgren O, Kyle RA, Hoppin JA et al (2009) Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. Blood. 113(25):6386–6391
15. Boursi B, Weiss BM, Haynes K, Mamtani R, Yang Y (2016) Reappraisal of risk factors for monoclonal gammopathy of undetermined significance. Am J Hematol 91(6):581–584
16. Pasqualetti P, Festuccia V, Acitelli P, Collacciani A, Giusti A, Casale R (1997) Tobacco smoking and risk of haematological malignancies in adults: a case-control study. Br J Haematol 97(3):659–662
17. Baris D, Brown LM, Silverman DT, Hayes R, Hoover RN, Swanson GM, Dosemeci M, Schwartz AG, Liff JM, Schoenberg JB, Pottern LM, Lubin J, Greenberg RS, Fraumeni JF Jr (2000) Socioeconomic status and multiple myeloma among US blacks and whites. Am J Public Health 90(8):1277–1281
18. Boffetta P, Stellman SD, Garfinkel L (1989) A case-control study of multiple myeloma nested in the American Cancer Society prospective study. Int J Cancer 43(4):554–559
19. Velez R, Beral V, Cuzick J (1982) Increasing trends of multiple myeloma mortality in England and Wales; 1950-79: are the changes real? J Natl Cancer Inst 69(2):387–392
20. Vågerö D, Norell SE (1989) Mortality and social class in Sweden–exploring a new epidemiological tool. Scand J Soc Med 17(1):49–58
21. Schmermund A, Möhlenkamp S, Stang A et al (2002) Assessment of clinically silent atherosclerotic disease and established and novel risk factors for predicting myocardial infarction and cardiac death in healthy middle-aged subjects: rationale and design of the Heinz Nixdorf RECALL Study. Risk Factors, Evaluation of Coronary Calcium and Lifestyle. Am. Heart J 144(2):212–218
22. Stang A, Moebus S, Dragano N, Beck EM, Möhlenkamp S, Schmermund A, Siegrist J, Erbel R, Jöckel KH, Heinz Nixdorf Recall Study Investigation Group (2005) Baseline recruitment and analyses of nonresponse of the Heinz Nixdorf Recall Study: identifiability of phone numbers as the major determinant of response. Eur J Epidemiol 20(6):489–496
23. Katzmann JA, Clark RJ, Abraham RS et al (2002) Serum reference intervals and diagnostic ranges for free kappa and free lambda immunoglobulin light chains: relative sensitivity for detection of monoclonal light chains. Clin Chem 48(9):1437–1444
24. Hutchison CA, Plant T, Drayson M et al (2008) Serum free light chain measurement aids the diagnosis of myeloma in patients with severe renal failure. BMC Nephrol 9(1):101
25. UNESCO. International standard classification of education: ISCED 1997. http://www.uis.unesco.org/Library/Documents/isced97-en.pdf. Updated January 30, 2011.
26. Hagenaars AJ, Zaidi MA, de Vos K Poverty statistics in the late 1980s: research base on micro-date. Luxembourg: EUR-OP; 1994. Theme 3: population and social conditions (yellow). Series C: Accounts and surveys
27. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey SG (2006) Indicators of socioeconomic position (part 1). J Epidemiol Community Health 60(1):7–12
28. Geyer S (2006) Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. J Epidemiol Community Health 60(9):804–810
29. Winkler G, Döring A (1998) Validation of a short qualitative food frequency list used in several German large scale surveys. Z Ernahrungswiss 37(3):234–241
30. Muff C, Dragano N, Jöckel K, Moebus S, Möhlenkamp S, Erbel R, Mann K, Siegrist J (2010) Is the co-occurrence of smoking and poor consumption of fruits and vegetables confounded by socioeconomic conditions? Int J Public Health 55(4):339–346
31. R Development Core Team. R: a language and environment for statistical computing. http://www.R-project.org/.
32. Royston P, Altman DG, Sauerbrei W (2006) Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med 25(1):127–141
33. Thordardottir M, Lindqvist EK, Lund SH, Costello R, Burton D, Steingrimsdottir L, Korde N, Mailankody S, Eiriksdottir G, Launer LJ, Gudnason V, Harris TB, Landgren O, Torfadottir JE, Kristinsson SY (2018) Dietary intake is associated with risk of multiple myeloma and its precursor disease. PLoS One 13(11):e0206047
34. Katzmann JA, Kyle RA, Benson J, Larson DR, Snyder MR, Lust JA, Rajkumar SV, Dispenzieri A (2009) Screening panels for detection of monoclonal gammopathies. Clin Chem 55(8):1517–1522