Dietary intake is associated with risk of multiple myeloma and its precursor disease

Marianna Thordardottir1*, Ebba K. Lindqvist2, Sigrun H. Lund3, Rene Costello4, Debra Burton4, Laufey Steingrimsdottir5, Neha Korde6, Sham Mailankody6, Gudny Eiriksdottir7, Lenore J. Launer8, Vilmundur Gudnason1,7, Tamara B. Harris8, Ola Landgren6, Johanna E. Torfadottir3,9, Sigurdur Y. Kristinsson1,2*

1 Faculty of Medicine, University of Iceland, Reykjavik, Iceland, 2 Department of Medicine, Division of Hematology, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden, 3 Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavik, Iceland, 4 Multiple Myeloma Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, United States of America, 5 Faculty of Food Science and Human Nutrition, University of Iceland, Reykjavik, Iceland, 6 Myeloma Service, Division of Hematologic Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York, United States of America, 7 The Icelandic Heart Association, Kopavogur, Iceland, 8 Laboratory of Epidemiology and Population Sciences, Intramural Research Program, National Institute on Aging, Bethesda, Maryland, United States of America, 9 The Icelandic Cancer Society, Reykjavik, Iceland

These authors contributed equally to this work.

* mthordar@hi.is

Abstract

The etiology of monoclonal gammopathy of undetermined significance (MGUS), the precursor state of multiple myeloma (MM), is mostly unknown and no studies have been conducted on the effect of diet on MGUS or progression from MGUS to MM. We aimed to explore the association between common foods and MGUS and progression to MM. Data from the population-based AGES Study (N = 5,764) were utilized. Food frequency questionnaire was used to assess dietary intake during adolescence, midlife, and late life. Serum protein electrophoresis and serum free light-chain assay was performed to identify MGUS (n = 300) and LC-MGUS cases (n = 275). We cross linked our data with the Icelandic Cancer Registry to find cases of MM in the study group. We found that intake of fruit at least three times per week during adolescence was associated with lower risk of MGUS when compared to lower fruit consumption (OR = 0.62, 95% CI 0.41–0.95). We additionally found that intake of fruit at least three times per week during the late life period was associated with decreased risk of progressing from MGUS to MM (HR = 0.34, 95% CI 0.13–0.89) when compared to lower intake. Adolescent intake of fruit may reduce risk of MGUS, whereas fruit intake after MGUS onset may reduce risk of progressing to MM. Our findings suggest that diet might alter the risk of developing MGUS and progression to MM.

Introduction

All cases of the plasma cell malignancy multiple myeloma (MM) are preceded by monoclonal gammopathy of undetermined significance (MGUS) [1, 2], a premalignant asymptomatic
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may be sent to the AGES Reykjavik Study Executive Committee, contact: AGES data_request@hjarta.is, and the ICR (contact: Laufey Tryggvadottir, laufey@krabb.is) with approval from the Icelandic National Bioethics Committee (https://www.vsn.is/en/content/bioethics-committee-system, vsn@vsn.is).

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Materials and methods

Study population

For this study we used data from the Age, Gene/Environment Susceptibility–Reykjavik Study (AGES Study). The AGES Study is a continuation of the population-based Reykjavik Study, initiated in 1967 when all residents, born 1907–1935, of the Reykjavik metropolitan area were invited to participate in a prospective cohort study with the objective of examining risk factors...
for cardiovascular diseases. A total of 71% (n = 19,350) of the invited residents consented to participate during the years of 1967–1996 [30–32]. Of the 11,549 Reykjavik Study cohort members still alive in March 2002, when the AGES Study was initiated, 8,030 individuals were randomly chosen to take part in the study. By 2006, when the study ended, 5,764 (71.8%) had participated. Detailed description of the study and collection of data has been previously published [32], however in short, data were collected during three separate examinations using standardized protocols. The first visit included e.g. blood draw, anthropometry, electrocardiography, and extensive questionnaire including e.g. health history, lifestyle practices, and food history. The second examination included imaging protocols and the third examination included e.g. dementia assessments and vision screening [32].

At study entry the participants signed an informed consent form. The study was approved by the Icelandic Data Protection Authority, the Icelandic National Bioethics Committee (VSN-00-063-V35), and the Institutional Review Board of the National Institute on Aging in the USA.

Dietary habits across the lifespan
At AGES Study entry the participants provided retrospective information on dietary habits during adolescence (14–19 years old) and midlife (40–50 years old), as well as information on current dietary habits using a food frequency questionnaire. The questionnaire included a total of 63 questions (16 from the adolescent period, 17 from the midlife period, and 30 from the late life period) regarding intake of common foods and food groups i.e. total fish intake (and additional question on salted or smoked fish), fish oil, total meat intake (and additional question on salted or smoked meat), milk and milk products, fruit, vegetables (excluding potatoes), rye bread and flatbread, blood or liver sausage, oatmeal and muesli, potatoes, and whole wheat bread. Only foods and food groups that were included in the questionnaire from all three life stages were used for this study, except for whole wheat bread (midlife and late life only). The participants reported frequency of intake in each time period using the following response categories for meat, milk and milk products, fruit, vegetables, rye bread and flatbread, blood or liver sausage, oatmeal and muesli, potatoes, and whole wheat bread: never, less than once a week, 1–2 times a week, 3–4 times a week, 5–6 times a week, daily, and more than once a day. For fish oil the categories were the same except for: more than once a day. The categories for salted and smoked meat and fish were: never, less than once a month, 1–3 times a month, 1–2 times a week, 3–6 times a week, daily or more often. The food frequency questionnaire included three questions on fish consumption; frequency of consumption of fish in salad or as topping on bread, fish as main meal (including salted or smoked fish), and consumption of salted or smoked fish separately. Weekly intake of fish meals and fish in salad or as topping was combined into one variable and the daily total intake was converted into total fish portions per week, as has been previously described [33]. The validation study of the midlife diet took advantage of available data from a detailed nutrition study performed 18 years previously, using dietary history and the present diet was validated using a 3-day dietary history as a reference method. The AGES food frequency questionnaire was found suitable to rank individuals by their intake for most food groups from the midlife and late period [34, 35].

Ascertainment of outcomes
As previously described [9, 36], a conventional agarose-gel serum protein electrophoresis (SPEP) was performed in 2013–2014 on all subjects from the AGES Study cohort to identify MGUS cases. A 0.5 mL serum sample, collected at study entry (2002–2006), was obtained for each study subject and samples with an equivocal or definite M-protein present on SPEP were...
then subjected to serum protein immunofixation for conformation and typing of the M-protein [6]. Serum free light chain (FLC) assay was performed on all samples [37]. The sensitivity and specificity of the laboratory tests have been previously published [38]. All testing was done by individuals blinded to all demographics and other details related to the samples.

MGUS cases were defined as having M-protein bands (detectable on SPEP or immunofixation) and an elevated M-protein concentration (\( \leq 30\text{g/L} \)) [39]. LC-MGUS cases were defined as having no visible M-protein, a pathological FLC ratio (\(<0.26\) or \(>1.65\)) on FLC analysis, and an increased free light-chain concentration (f-kappa \(>19.4\) mg/L, f-lambda \(>26.3\) mg/L) [40]. We ascertained MM diagnosis and diagnosis of other LP diseases through linkage with the nationwide Icelandic Cancer Registry [41]. The start date of follow-up was at AGES Study entry (March 2002-February 2006) until March 2014.

**Exclusion from analysis**

For this study we excluded a total of 40 (0.7%) subjects from analysis, 21 due to previous LP diseases, 16 due to missing blood sample, one due to absent consent form, and one subject had high M-protein concentration at baseline and therefore fulfilled criteria for smoldering MM. One subject was additionally excluded from the progression analysis due to lack of follow-up. Our analyses include individuals responding to the dietary questions, ranging from 5,270 to 5,304 from the adolescent period, from 5,279 to 5,301 from the midlife period, and from 507–511 from the late life period, depending on the question.

**Statistical analysis**

A total of 12 food items were analyzed for the adolescent period and 13 for both midlife and the late life period. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for MGUS and LC-MGUS according to adolescent and midlife diet. For each type of food or food group, participants were grouped according to their frequency of intake or portions per week (total fish consumption only). Each type of food or food group was analyzed in an age and sex adjusted model (Model 1) and additionally in a fully adjusted model where all the foods and food groups were simultaneously added to one model, including age and sex (Model 2). An additional adjustment was made for physical activity and BMI measured in midlife in the adolescent and midlife models, and since the adjustment did not affect our results physical activity and BMI were omitted from the models. Additionally, we cross-classified the intake from the adolescent and midlife periods by combining individuals with low adolescent intake and low midlife intake for each type of food and set them as a reference group for low and high, high and low, and high and high intake at these time periods. We then used logistic regression to test the association between the cross-classified categories of intake and MGUS and LC-MGUS combined. Models were adjusted for age and sex.

Cox proportional hazard regression was used to test whether diet at study entry was a associated with progression from MGUS/LC-MGUS to MM or other LP diseases. For this analysis only individuals with MGUS and LC-MGUS were used, and due to few cases of MM and other LP disease they were not analyzed separately. Results are presented as hazard ratios (HR) with 95% CI. All models were adjusted for sex and age at AGES Study entry. We further adjusted our models for BMI and physical activity and we tested the association in a model where all the foods were simultaneously added to one model. Due to few number of cases and therefore low statistical power, and no effect on results, these analyses were not included in our results. All analyses were performed in R version 3.3.3. [42]
Sensitivity analysis

As described in detail previously [9, 36], we had an unusually high prevalence of LC-MGUS in our cohort (4.8%), mainly due to a high prevalence of kappa cases (96%). The distribution of log-transformed kappa and lambda values was found to resembled the normal distribution, and therefore the cut-off for the involved chains was moved to the 97.5th percentile. A definition of LC-MGUS as a pathological FLC-ratio of < 0.26 and > 1.65, in combination with an increased concentration of more than 40.0 mg/L of the light-chain involved was used to perform sensitivity analysis on the association between diet and MGUS/LC-MGUS.

Results

The mean age of participants was 77 years (range 66–98) at study baseline. MGUS and LC-MGUS was identified in 300 (5.2%) and 275 (4.8%) subjects, respectively (Table 1). Using the modified definition of LC-MGUS resulted in 52 cases. By cross linking the AGES Study cohort to the Icelandic Cancer Registry we found that 18 participants progressed to MM, of which one from LC-MGUS during a median follow-up of 8 years. Additionally, 11 progressed to other LP diseases (Hodgkin’s, Non-Hodgkin’s lymphoma, Waldenström’s macroglobulinaemia, lymphoid leukemia, chronic lymphocytic leukemia, and acute lymphocytic leukemia), of which two from LC-MGUS.

Adolescent intake

We found, in Model 2, that intake of fruit at least three times per week during the adolescent period was associated with lower risk of MGUS when compared intake less than three times per week (OR = 0.62, 95% CI 0.41–0.95). Consumption of other food items during that period was not associated with MGUS (Table 2). Additionally, we found that intake of fish at least two times per week was associated with higher risk of LC-MGUS (OR = 1.33, 95% CI 1.02–1.73) when compared to intake less than two times per week. Adolescent consumption of other foods was not associated with LC-MGUS (Table 2). In our sensitivity analysis we did not find any association between fish intake and risk of LC-MGUS in Model 2 as we did in our primary analysis. No association was found between consumption of other food items and LC-MGUS in our sensitivity analysis.

Midlife intake

We found in Model 2 that intake of whole wheat bread at least five times per week was associated with lower risk of MGUS (OR = 0.75, 95% CI 0.57–0.99) when compared to participants without MGUS.

Table 1. Characteristics of study participants at AGES study entry.

| Without MGUS | MGUS | LC-MGUS | MM | LP |
|-------------|------|---------|----|----|
| n = 5,150 (90.0%) | n = 300 (5.2%) | n = 275 (4.8%) | n = 18 (3.1%)† | n = 11 (5.1%)† |
| Gender, n. (%) |
| Female | 3,046 (59.1) | 141 (47.0) | 119 (43.3) | 10 (55.6) | 13 (46.4) |
| Male | 2,104 (40.9) | 159 (53.0) | 156 (56.7) | 8 (44.4) | 15 (53.6) |
| Mean age, years (range) | 76.8 (66–98) | 78.3 (67–93) | 79.4 (66–97) | 77.8 (69–87) | 77.5 (68–87) |
| BMI, kg/m² (mean) | 27.0 | 26.7 | 27.0 | 27.2 | 26.5 |
| BMI midlife, kg/m² (mean) | 25.2 | 25.5 | 25.6 | 26.2 | 26.2 |

†Proportion of cases that progressed from MGUS or LC-MGUS.

Abbreviations: MGUS—Monoclonal gammopathy of undetermined significance, LC-MGUS—Light chain monoclonal gammopathy of undetermined significance, MM—Multiple myeloma, LP—Other lymphoproliferative diseases.

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Table 2. The association between diet in adolescence and MGUS and LC-MGUS.

|                | No MGUS | MGUS  | LC-MGUS | MGUS  | LC-MGUS | MGUS  | LC-MGUS |
|----------------|---------|-------|---------|-------|---------|-------|---------|
|                | n (%)   | n (%) | n (%)   | OR    | 95%CI   | OR    | 95%CI   |
| Fish           |         |       |         |       |         |       |         |
| ≤ 2 portions p/w | 2,335 (49.1) | 140 (52.2) | 99 (40.7) | 1.00  | 1.00 | 1.00 | 1.00 | 1.00 | 1.06–1.83 |
| > 2 portions p/w | 2,424 (50.9) | 128 (47.8) | 144 (59.3) | 0.85  | 0.66–1.09 | 1.33 | 1.02–1.73 | 0.88 | 0.68–1.14 | 1.39 | 1.06–1.83 |
| Fish oil       |         |       |         |       |         |       |         |
| less than weekly | 2,280 (47.6) | 119 (44.4) | 128 (52.7) | 1.00  | 1.00 | 1.00 | 1.00 |
| weekly or more  | 2,509 (52.4) | 149 (55.6) | 115 (47.3) | 1.13  | 0.88–1.45 | 0.82 | 0.63–1.06 | 1.14 | 0.89–1.48 | 0.87 | 0.66–1.14 |
| Salted fish    |         |       |         |       |         |       |         |
| 3 times a month or less | 2,210 (46.4) | 128 (47.8) | 114 (46.9) | 1.00  | 1.00 | 1.00 | 1.00 |
| once p/w or more | 2,555 (53.6) | 140 (52.2) | 129 (53.1) | 0.85  | 0.66–1.10 | 0.84 | 0.64–1.09 | 0.95 | 0.71–1.26 | 0.89 | 0.66–1.21 |
| Meat           |         |       |         |       |         |       |         |
| 2 times p/w or less | 1,689 (35.3) | 103 (38.6) | 91 (37.6) | 1.00  | 1.00 | 1.00 | 1.00 |
| 3 times p/w or more | 3,093 (64.7) | 164 (61.4) | 151 (62.4) | 0.87  | 0.67–1.12 | 0.89 | 0.68–1.17 | 0.89 | 0.68–1.15 | 0.86 | 0.62–1.14 |
| Smoked/salted meat |         |       |         |       |         |       |         |
| 3 times a month or less | 3,111 (65.2) | 184 (68.7) | 157 (64.9) | 1.00  | 1.00 | 1.00 | 1.00 |
| Once a week or more | 1,663 (34.8) | 84 (31.3) | 85 (35.1) | 0.79  | 0.60–1.03 | 0.90 | 0.68–1.18 | 0.82 | 0.61–1.10 | 0.94 | 0.69–1.28 |
| Milk and milk products |         |       |         |       |         |       |         |
| less than daily | 1,074 (22.4) | 65 (24.3) | 63 (25.9) | 1.00  | 1.00 | 1.00 | 1.00 |
| daily | 3,719 (77.6) | 203 (75.7) | 180 (74.1) | 0.87  | 0.65–1.17 | 0.79 | 0.59–1.07 | 0.91 | 0.67–1.24 | 0.85 | 0.62–1.17 |
| Fruit          |         |       |         |       |         |       |         |
| 2 times p/w or less | 4,077 (85.3) | 241 (89.9) | 217 (89.7) | 1.00  | 1.00 | 1.00 | 1.00 |
| 3 times p/w or more | 701 (14.7) | 27 (10.1) | 25 (10.3) | 0.71  | 0.47–1.06 | 0.75 | 0.49–1.15 | 0.62 | 0.41–0.95 | 0.81 | 0.52–1.26 |
| Vegetables     |         |       |         |       |         |       |         |
| 2 times p/w or less | 3,517 (73.5) | 197 (73.8) | 197 (81.1) | 1.00  | 1.00 | 1.00 | 1.00 |
| 3 times p/w or more | 1,265 (26.5) | 70 (26.2) | 46 (18.9) | 1.06  | 0.80–1.41 | 0.71 | 0.51–0.99 | 1.17 | 0.87–1.57 | 0.78 | 0.55–1.10 |
| Rye bread/flatbread |         |       |         |       |         |       |         |
| less than daily | 2,481 (52.0) | 141 (52.6) | 120 (49.4) | 1.00  | 1.00 | 1.00 | 1.00 |
| daily | 2,289 (48.0) | 127 (47.4) | 123 (50.6) | 0.88  | 0.68–1.14 | 0.94 | 0.72–1.22 | 0.94 | 0.71–1.23 | 1.00 | 0.75–1.34 |
| Sausage/liver  |         |       |         |       |         |       |         |
| less than weekly | 1,252 (26.1) | 74 (27.6) | 68 (28.0) | 1.00  | 1.00 | 1.00 | 1.00 |
| weekly or more  | 3,539 (73.9) | 194 (72.4) | 175 (72.0) | 0.84  | 0.63–1.11 | 0.78 | 0.58–1.04 | 0.86 | 0.65–1.18 | 0.85 | 0.61–1.18 |
| Oatmeal/muesli  |         |       |         |       |         |       |         |
| 2 times p/w or less | 2,119 (44.4) | 110 (41.4) | 108 (44.6) | 1.00  | 1.00 | 1.00 | 1.00 |
| 3 times p/w or more | 2,650 (55.7) | 156 (58.6) | 134 (55.4) | 1.02  | 0.79–1.31 | 0.84 | 0.64–1.09 | 1.09 | 0.83–1.44 | 0.93 | 0.70–1.24 |
| Potatoes       |         |       |         |       |         |       |         |
| less than daily | 483 (10.1) | 35 (13.1) | 25 (10.3) | 1.00  | 1.00 | 1.00 | 1.00 |
| daily | 4,300 (89.9) | 233 (86.9) | 217 (89.7) | 0.76  | 0.52–1.10 | 0.99 | 0.64–1.51 | 0.81 | 0.55–1.20 | 1.04 | 0.67–1.63 |

*Adjusted for age and sex.
*A Adjusted for age, sex and the other food groups.

Abbreviations: MGUS—Monoclonal gammopathy of undetermined significance, LC-MGUS—Light chain monoclonal gammopathy of undetermined significance, OR—Odds ratio, CI—confidence interval

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with intake of less than five times per week. Intake of other foods from midlife was not associated with MGUS (Table 3). Midlife intake of the tested food items was not associated with LC-MGUS (Table 3). In our sensitivity analysis we found in Model 2 that midlife intake of
Table 3. The association between midlife diet and MGUS and LC-MGUS.

|                | No MGUS | MGUS | LC-MGUS | MGUS | LC-MGUS | MGUS | LC-MGUS |
|----------------|---------|------|---------|------|---------|------|---------|
|                | n (%)   | n (%)| n (%)   | OR   | 95% CI  | OR   | 95% CI  |
| Fish           |         |      |         |      |         |      |         |
| ≤ 2 portions p/w | 565 (11.8) | 35 (13.1) | 33 (13.6) | 1.00 | 1.00 | 1.00 | 1.00 |
| > 2 portions p/w | 4,204 (88.2) | 233 (86.9) | 209 (86.4) | 0.84 | 0.58–1.22 | 0.77 | 0.52–1.13 | 0.87 | 0.59–1.28 | 0.80 | 0.54–1.19 |
| Fish oil       |         |      |         |      |         |      |         |
| less than weekly | 1,852 (38.7) | 97 (36.3) | 97 (39.9) | 1.00 | 1.00 | 1.00 | 1.00 |
| weekly or more  | 2,931 (61.3) | 170 (63.7) | 146 (60.1) | 1.09 | 0.84–1.41 | 0.94 | 0.72–1.23 | 1.10 | 0.84–1.44 | 0.95 | 0.72–1.25 |
| Salted fish    |         |      |         |      |         |      |         |
| 3 times a month or less | 3,241 (67.8) | 187 (69.8) | 161 (66.3) | 1.00 | 1.00 | 1.00 | 1.00 |
| once p/w or more | 1,541 (32.2) | 81 (30.2) | 82 (33.7) | 0.81 | 0.62–1.07 | 0.91 | 0.67–1.20 | 0.82 | 0.60–1.13 | 0.90 | 0.65–1.25 |
| Meat           |         |      |         |      |         |      |         |
| 2 times p/w or less | 1,809 (37.8) | 106 (39.6) | 93 (38.3) | 1.00 | 1.00 | 1.00 | 1.00 |
| 3 times p/w or more | 2,977 (62.2) | 162 (60.4) | 150 (61.7) | 0.94 | 0.73–1.21 | 1.03 | 0.78–1.35 | 0.93 | 0.72–1.21 | 1.00 | 0.76–1.32 |
| Smoked/salted meat |         |      |         |      |         |      |         |
| 3 times a month or less | 3,530 (73.8) | 199 (74.3) | 170 (70.2) | 1.00 | 1.00 | 1.00 | 1.00 |
| Once a week or more | 1,252 (26.2) | 69 (25.7) | 72 (29.8) | 0.89 | 0.67–1.18 | 1.05 | 0.79–1.40 | 0.95 | 0.68–1.32 | 1.12 | 0.80–1.56 |
| Milk and milk products |         |      |         |      |         |      |         |
| less than daily | 1,957 (40.9) | 99 (37.1) | 90 (37.2) | 1.00 | 1.00 | 1.00 | 1.00 |
| daily          | 2,823 (59.1) | 168 (62.9) | 152 (62.8) | 1.11 | 0.86–1.43 | 1.08 | 0.82–1.41 | 1.17 | 0.89–1.53 | 1.15 | 0.87–1.53 |
| Fruit          |         |      |         |      |         |      |         |
| 2 times p/w or less | 3,271 (68.4) | 185 (69.0) | 181 (74.5) | 1.00 | 1.00 | 1.00 | 1.00 |
| 3 times p/w or more | 1,512 (31.6) | 83 (31.0) | 62 (25.5) | 1.10 | 0.84–1.44 | 0.88 | 0.65–1.19 | 1.19 | 0.87–1.62 | 0.84 | 0.60–1.18 |
| Vegetables     |         |      |         |      |         |      |         |
| 2 times p/w or less | 3,081 (64.6) | 182 (68.2) | 162 (66.7) | 1.00 | 1.00 | 1.00 | 1.00 |
| 3 times p/w or more | 1,692 (35.4) | 85 (31.8) | 81 (33.3) | 0.92 | 0.70–1.20 | 1.02 | 0.77–1.34 | 0.84 | 0.62–1.14 | 1.11 | 0.81–1.52 |
| Rye bread/flatbread |         |      |         |      |         |      |         |
| less than daily | 3,264 (68.1) | 185 (69.0) | 166 (68.3) | 1.00 | 1.00 | 1.00 | 1.00 |
| daily          | 1,526 (31.9) | 83 (31.0) | 77 (31.7) | 0.86 | 0.66–1.13 | 0.83 | 0.62–1.10 | 0.91 | 0.68–1.22 | 0.84 | 0.62–1.15 |
| Sausage/liver  |         |      |         |      |         |      |         |
| less than weekly | 2,322 (48.5) | 123 (45.9) | 112 (46.1) | 1.00 | 1.00 | 1.00 | 1.00 |
| weekly or more  | 2,466 (51.5) | 145 (54.1) | 131 (53.9) | 1.05 | 0.82–1.35 | 1.00 | 0.77–1.30 | 1.07 | 0.82–1.39 | 1.00 | 0.76–1.33 |
| Oatmeal/muesli |         |      |         |      |         |      |         |
| 2 times p/w or less | 2,910 (60.9) | 147 (55.1) | 140 (57.9) | 1.00 | 1.00 | 1.00 | 1.00 |
| 3 times p/w or more | 1,869 (39.1) | 120 (44.9) | 102 (42.1) | 1.18 | 0.92–1.52 | 1.01 | 0.77–1.31 | 1.27 | 0.94–1.60 | 1.05 | 0.80–1.40 |
| Potatoes       |         |      |         |      |         |      |         |
| less than daily | 742 (15.5) | 48 (17.9) | 40 (16.5) | 1.00 | 1.00 | 1.00 | 1.00 |
| daily          | 4,046 (84.5) | 220 (82.1) | 203 (83.5) | 0.80 | 0.58–1.11 | 0.86 | 0.60–1.22 | 0.82 | 0.58–1.16 | 0.88 | 0.61–1.28 |
| Whole wheat bread |         |      |         |      |         |      |         |
| 4 times p/w or less | 1,489 (31.2) | 101 (38.1) | 87 (36.1) | 1.00 | 1.00 | 1.00 | 1.00 |
| 5 times p/w or more | 3,291 (68.8) | 164 (61.9) | 154 (63.9) | 0.76 | 0.59–0.98 | 0.83 | 0.64–1.09 | 0.75 | 0.57–0.99 | 0.86 | 0.64–1.15 |

*aAdjusted for age and sex.  
*bAdjusted for age, sex and the other food groups.  
Abbreviations: MGUS—Monoclonal gammopathy of undetermined significance, LC-MGUS—Light chain monoclonal gammopathy of undetermined significance, OR—Odds ratio, CI—confidence interval.

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meat at least three times per week and daily intake of rye bread and flatbread was associated with lower risk of LC-MGUS (OR = 0.44, 95% CI 0.23–0.84 and OR = 0.32, 95% CI 0.14–0.78, respectively) when compared to lower intake. No association was found between consumption of other food items from the midlife periods and LC-MGUS in our sensitivity analysis.

**Cross-classification across two time points**

Looking at both the adolescent and midlife period together, no association was found between any of the food items and MGUS/LC-MGUS (S1 Table). However, in our sensitivity analysis (S2 Table) we found that daily intake of rye bread and flatbread and potatoes during both the adolescent and midlife periods was associated with lower risk of MGUS/LC-MGUS when compared to less than daily intake at both periods (OR = 0.70, 95% CI 0.55–0.95 and OR = 0.63, 95% CI 0.45–0.96, respectively).

**Progression to multiple myeloma and other lymphoproliferative diseases**

We found, in a sex and age adjusted model, that fruit intake at least three times per week was inversely associated with risk of progression to MM (HR = 0.34, 95% CI 0.13–0.89) when compared to intake less than three times per week. The association remained statistically significant when cases of other LP diseases were combined with MM cases (HR = 0.45, 95% CI 0.21–0.96). Intake of other food items was not associated with risk of progression to MM and other LP diseases (Table 4). Similar results were found when analyzing risk of progression in MGUS cases only.

**Discussion**

In this population-based study we found, using a food frequency questionnaire for evaluation of dietary intake during three separate time periods, that food intake may affect risk of MGUS, and specifically that intake of fruit at least three times per week during adolescence and midlife intake of whole wheat bread at least five times per week, was associated with lower risk of MGUS when compared to lower intakes. Additionally, we found, albeit based on few cases, that late life intake of fruit at least three times per week in individuals with MGUS or LC-MGUS was associated with lower risk of progressing to MM and other LP diseases. Adjusting for BMI and physical activity did not change the results. These findings suggest that dietary habits might influence the etiology of MGUS and progression to MM and other LP diseases.

We found that intake of fruit at least three times per week during the adolescent period was inversely associated with risk of MGUS later in life when compared to lower intake, and, based on a small number of cases, we found that late life intake of fruit at least three times per week in patients with MGUS or LC-MGUS was associated with lower risk of progression. The findings are in accordance with other studies consistently showing high intake of fruit and other plant foods to be inversely associated with different types of cancer [43, 44]. A review of findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) from 2014 reported an inverse association between fruit intake and cancer risk at some sites [43]. The literature regarding fruit and risk of MM is scarce. To date, only two studies have examined the role of fruit in the etiology of MM. Both are US-based case-control studies on adults already diagnosed with MM, with no association reported [21, 23]. Major differences in the amount (intake levels) and time of exposure (period of life) and time of assessment (exposure assessed after MM diagnosis) could explain the discrepancy with regards to our study. A potential biologic mechanism for our finding is perhaps the anti-carcinogenic effect of vitamin C as it traps free radicals and protects against oxidation [45]. Nevertheless, very few participants reported daily or more than daily fruit intake in present study. Therefore, the cut-off for
A high intake of fruit in our study was three times per week or more. This would normally be considered low intake, but due to the low frequency of fruit consumption the cut-off could not be adjusted. Table 4 shows the association between late life diet and risk of progression from MGUS and LC-MGUS to multiple myeloma and other lymphoproliferative diseases.

|                  | Total | Multiple myeloma | Multiple myeloma and other LP | Multiple myeloma | Multiple myeloma and other LP |
|------------------|-------|------------------|-------------------------------|-----------------|-------------------------------|
|                  | n (%) | n (%)            | n (%)                        | HR 95%CI        | HR 95%CI                      |
| Fish             |       |                  |                               |                 |                               |
| ≤ 2 portions p/w | 149 (29.2) | 7 (41.2)        | 10 (35.7)                    | 1.00            | 1.00                          |
| > 2 portions p/w | 361 (70.8) | 10 (58.8)       | 18 (64.3)                    | 0.62            | 0.24–1.64                     |
| Fish oil         |       |                  |                               |                 |                               |
| less than weekly | 152 (29.9) | 6 (35.3)        | 9 (32.1)                     | 1.00            | 1.00                          |
| weekly or more   | 357 (70.1) | 11 (64.7)       | 19 (64.9)                    | 0.81            | 0.30–2.22                     |
| Salted fish      |       |                  |                               |                 |                               |
| less than once a month | 371 (72.7) | 13 (76.5)  | 21 (75.0)                    | 1.00            | 1.00                          |
| once a month or more | 139 (27.3) | 4 (23.5)    | 7 (25.0)                     | 0.95            | 0.30–2.95                     |
| Meat             |       |                  |                               |                 |                               |
| 2 times p/w or less | 186 (36.4) | 5 (29.4)    | 6 (21.4)                     | 1.00            | 1.00                          |
| 3 times p/w or more | 325 (63.6) | 12 (70.6)   | 22 (78.6)                    | 1.47            | 0.51–4.21                     |
| Smoked/salted meat |       |                  |                               |                 |                               |
| less than once a month | 341 (66.7) | 14 (82.4)  | 20 (71.4)                    | 1.00            | 1.00                          |
| once a month or more | 170 (33.3) | 3 (17.6)    | 8 (28.6)                     | 0.47            | 0.13–1.68                     |
| Milk and milk products |       |                  |                               |                 |                               |
| less than daily  | 223 (43.7) | 8 (47.1)     | 10 (35.7)                    | 1.00            | 1.00                          |
| daily            | 287 (56.3) | 9 (52.9)      | 18 (64.3)                    | 0.96            | 0.37–2.50                     |
| Fruits           |       |                  |                               |                 |                               |
| 2 times p/w or less | 151 (29.5) | 9 (52.9)     | 13 (46.4)                    | 1.00            | 1.00                          |
| 3 times p/w or more | 360 (70.5) | 8 (47.1)     | 15 (53.6)                    | 0.34            | 0.13–0.89                     |
| Vegetables       |       |                  |                               |                 |                               |
| 2 times p/w or less | 270 (52.9) | 11 (64.7)    | 16 (57.1)                    | 1.00            | 1.00                          |
| 3 times p/w or more | 240 (47.1) | 6 (35.3)     | 12 (42.9)                    | 0.54            | 0.20–1.49                     |
| Rye bread/flatbread |       |                  |                               |                 |                               |
| 2 times p/w or less | 225 (44.4) | 10 (58.8)    | 15 (53.6)                    | 1.00            | 1.00                          |
| 3 times p/w or more | 282 (55.6) | 7 (41.2)     | 13 (46.4)                    | 0.57            | 0.22–1.52                     |
| Sausage/liver    |       |                  |                               |                 |                               |
| never            | 111 (21.8) | 3 (17.6)     | 6 (21.4)                     | 1.00            | 1.00                          |
| ever             | 398 (78.2) | 14 (82.4)    | 22 (78.6)                    | 1.40            | 0.40–4.88                     |
| Oatmeal/muesli   |       |                  |                               |                 |                               |
| 2 times p/w or less | 265 (51.9) | 9 (52.9)     | 17 (60.7)                    | 1.00            | 1.00                          |
| 3 times p/w or more | 246 (48.1) | 8 (47.1)     | 11 (39.3)                    | 0.96            | 0.36–2.51                     |
| Potatoes         |       |                  |                               |                 |                               |
| less than daily  | 220 (43.1) | 7 (41.2)     | 12 (42.9)                    | 1.00            | 1.00                          |
| daily            | 290 (56.9) | 10 (58.8)    | 16 (57.1)                    | 1.12            | 0.42–2.96                     |
| Whole wheat bread |       |                  |                               |                 |                               |
| 4 times p/w or less | 130 (25.5) | 4 (23.5)     | 4 (14.3)                     | 1.00            | 1.00                          |
| 5 times p/w or more | 380 (74.5) | 13 (76.5)    | 24 (85.7)                    | 1.02            | 0.33–3.15                     |

*Models adjusted for age and sex.

Abbreviations: MGUS—Monoclonal gammopathy of undetermined significance, LC-MGUS—Light chain monoclonal gammopathy of undetermined significance, LP—lymphoproliferative, OR—Odds ratio, CI—confidence interval.

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be higher. The beneficial threshold for both risk of MGUS and progression to MM may therefore be low. Since access to fruit was limited in Iceland, especially during the adolescent period for this population and in rural areas, it is possible that fruit intake was an indicator of higher social status or overall healthier life-style, and therefore the higher intake individuals were at lower risk for multiple health outcomes, including MGUS and MM.

Interestingly, we did not find an association between intakes of fish and fish liver oil and MGUS or progression to MM. Although not significant, the point estimates in the progression analysis were in the same direction as previous studies on the association between fish intake and risk of MM have reported. A few case-control studies have reported an inverse association between fish intake and risk of MM [21, 24–26], including two that have found a dose-response relationship [21, 25]. Both of these studies report much lower fish intake than reported in our study. A suggested mechanism for the association is the cancer preventive effect of the polyunsaturated omega-3 essential fatty acid (n-3) [46]. Fish intake is a common indicator for social status [47]. However, for the Icelandic population, fish was widely available and the diet was characterized by a very high fish intake. Due to the high intake we do not have a non-exposed reference group in our fish intake analysis. Although our population has a uniquely high intake of fish, the most common types were lean fish, low in n-3. Nevertheless, the Icelandic population has high levels of the marine derived n-3 in both diet and plasma, even those with low intake of fish liver oil, a common supplement in Iceland, rich in n-3 [48]. Therefore, we cannot rule out the option that a possible beneficial threshold of n-3 might already have been reached by our low intake fish and fish liver oil reference groups. Another reason for not finding an association between fish consumption and MM in our study could be the lack of a reference group in the study that did not consume fish.

We found that intake of whole wheat bread at least five time per week was inversely associated with MGUS when compared to lower intake. To date, only one study has analyzed the association between whole grain intake and risk of MM. A case-control study based on 120 MM cases below the age of 75 years reported that high intake of whole grain foods was inversely associated with MM risk in women (OR = 0.5, p < 0.05) but not in men [49]. Potential mechanisms that could mediate the effect of whole grains on MM risk have not been sufficiently explored. However, whole grains have been suggested to have positive effects on long-term insulin secretion [50] which could be of importance regarding MM since increased availability of IGF-1 can increase MM cell proliferation and prevent apoptosis [51].

We found inconsistency in LC-MGUS risk between our primary and sensitivity analyses when analyzing associations with fish, meat, and rye bread and flatbread intake and additionally when analyzing the association between rye bread and flatbread and potatoes and MGUS (MGUS and LC-combined) in our cross-classification analysis. The prevalence of LC-MGUS was 4.8% in our cohort, which is considerably higher than has been noted in previous studies [4, 5]. Although this is an elderly population the difference is substantial. It is therefore difficult to draw conclusions from the results.

The strength of our study is the well-established population-based cohort design with limited threat to both internal and external validity. Another major strength is the ability to study dietary intake throughout the lifespan, as studying early life exposures is challenging yet also important since many diseases originate early in life. Few studies have been able to provide data on adolescent or midlife diet combined with detailed ascertainment of later life health outcomes and we believe our study is unique in that aspect. Additionally, a major strength is the utilization of a validated food frequency questionnaire since majority of the questions had an acceptable correlation and the questionnaire was found suitable to rank individuals by their intake for most food groups when compared to a reference method [34, 35].
The mean age of our study population is 77 years and our cohort might represent a selection of participants that are healthier than the general population. Participants had to recall their dietary habits many decades back in time which could result in a misclassification of intake. Although, a previous study showed that food-related memory from childhood can be as accurate as from current diet, particularly for foods items eaten daily or rarely [52]. However, participants did not know their MGUS status at the time of questioning, and we therefore assume that the misclassification is non-differential. We did not have data on family history of hematologic cancers or information on total energy intake and were therefore unable to adjust for these factors. We do not know the true time of MGUS onset and therefore a misclassification of follow-up times could be present in our progression analysis, however, the prevalence of MGUS increases with age and by adjusting all our models for age we try to reduce the effect of this misclassification. Another limitation is lack of correlation to the reference method for midlife and late life intake of few food groups when the questionnaire was validated, possibly due to the inability of the food record used as reference method to adequately reflect individual intake of food items that are consumed less than four times a week [34, 35]. Validating early diet does pose great challenges and it is expected that such studies are unable to follow ideal procedures. Interpretation of our results are therefore limited by the results of the validation studies. Adolescent diet has not and cannot be validated, however, the data show similar frequency of intake according to residence in rural and coastal fishing areas, as documented in an Icelandic household study from 1939 [28, 53]. We cannot truly distinguish what could be smoldering multiple myeloma as we do not have bone marrow samples. Lastly, we cannot rule out the option that our findings are due to chance. Some of our results from the adolescent and midlife periods are limited by few number of MGUS or LC-MGUS cases in some categories, our progression analyses are additionally limited by few number of cases. Little is known about the relationship between diet and MGUS/LC-MGUS and progression to MM and this study can therefore be considered a hypothesis-generating study. Adjusting for multiple comparison is thought of as an insurance policy against mistakenly rejecting a null hypothesis, given that the null hypothesis is correct [54]. Due to the number of tests performed in the study the chances of rejecting a null hypothesis and obtaining positive results is high. However, the nature of our study is to seek potential risk factors for MGUS/LC-MGUS and progression to MM and we did not adjust for multiple testing in order not to increase the risk of missing out on possible risk factors.

To conclude, in this population-based screening study we found that high intake of fruit during the adolescent period and whole wheat bread during the midlife period may reduce the risk of MGUS later in life and that high fruit intake in late life may reduce the risk of progressing from MGUS/LC-MGUS to MM. Our findings suggest that food intake might alter the risk of developing MGUS and progressing to MM. Future studies should focus on clarifying the possible role of dietary habits in the pathogenesis of MGUS and MM.

Supporting information

S1 Table. Longitudinal effect of adolescent and midlife consumption of selected types of food on MGUS.

S2 Table. Longitudinal effect of adolescent and midlife consumption of selected types of food on risk of MGUS using higher cutoff values for involved light chains in LC-MGUS cases.
S1 File. Survey questionnaire.
(PDF)

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Author Contributions
Data curation: Gudny Eiriksdottir, Lenore J. Launer, Vilmundur Gudnason, Tamara B. Harris.
Formal analysis: Marianna Thordardottir.
Funding acquisition: Sigurdur Y. Kristinsson.
Investigation: Rene Costello, Debra Burton.
Methodology: Marianna Thordardottir, Ebba K. Lindqvist, Sigrun H. Lund, Laufey Stein-gimsdottir, Johanna E. Torfadottir, Sigurdur Y. Kristinsson.
Project administration: Sigurdur Y. Kristinsson.
Resources: Rene Costello, Debra Burton.
Supervision: Johanna E. Torfadottir, Sigurdur Y. Kristinsson.
Writing – original draft: Marianna Thordardottir.
Writing – review & editing: Ebba K. Lindqvist, Sigrun H. Lund, Rene Costello, Laufey Stein-gimsdottir, Neha Korde, Sham Mailankody, Gudny Eiriksdottir, Vilmundur Gudnason, Ola Landgren, Johanna E. Torfadottir, Sigurdur Y. Kristinsson.

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