

## **Adherence to the Western, Prudent, and Mediterranean dietary patterns and chronic lymphocytic leukemia in the MCC-Spain study.**

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**2-sentence summary:** Given that evidence on the role of diet in the etiology of chronic lymphocytic leukemia (CLL) is sparse, we evaluated the association between adherence to three dietary patterns (Western, Prudent and Mediterranean) and CLL in the MCC-Spain case-control study. Individuals with a higher adherence to a Western dietary pattern (i.e. high intakes of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, and convenience food) were more likely to have CLL, suggesting that a proportion of CLL cases could be prevented by modifying dietary habits.

**Conflict of interest** None

**Authorship Contribution**

Study conception and design: MP, MK, NA, GC, SS, PA

Acquisition of the data: SS, DC, YB, RMG, PA, EGL, LC, CR, EGB, EB, EA, MA, EC, EG, TDS, GFT, ROR

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## Abstract

Diet is a modifiable risk factor for several neoplasms but evidence for chronic lymphocytic leukemia is sparse. Previous studies examining the association between single-food items and chronic lymphocytic leukemia risk have yielded mixed results, while few studies have been conducted on overall diet, reporting inconclusive findings. This study aimed to evaluate the association between adherence to three dietary patterns and chronic lymphocytic leukemia in the MCC-Spain case-control study. Anthropometric, sociodemographic, medical and dietary information was collected for 369 chronic lymphocytic leukemia cases and 1,605 controls. Three validated dietary patterns –Western, Prudent and Mediterranean– were reconstructed in the MCC-Spain data. The association between adherence to each dietary pattern and chronic lymphocytic leukemia was assessed, overall and by Rai stage, using mixed logistic regression models adjusted for potential confounders. High adherence to a Western dietary pattern (i.e high intakes of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, and convenience food) was associated with chronic lymphocytic leukemia ( $OR_{Q4vs.Q1}=1.63$  (95%CI 1.11; 2.39);  $p\text{-trend}=0.02$ ; OR 1-SD increase=1.19 (95%CI 1.03; 1.37)), independently of Rai stages. No differences in the association were observed by sex, body mass index, energy intake, tobacco, physical activity, working on a farm and family history of hematologic malignancies. No associations were observed for Mediterranean and Prudent dietary patterns and chronic lymphocytic leukemia. This study provides the first evidence for an association between a Western dietary pattern and chronic lymphocytic leukemia, suggesting that a proportion of chronic lymphocytic leukemia cases could be prevented by modifying dietary habits. Further research, especially with a prospective design, is warranted to confirm these findings.

**Key words:** Chronic lymphocytic leukemia, dietary patterns, Western, Mediterranean, case-control study

## Introduction

Chronic lymphocytic leukemia (CLL) is the commonest leukemia among the adult population in western countries, with an annual incidence rate of around 5 per 100,000 person-years in Europe<sup>1</sup>, but its etiology is still poorly understood. A pooled analysis of 2,440 CLL cases and 15,186 controls from the InterLymph consortium showed significant inverse associations with atopic conditions, smoking, blood transfusion history, and recreational sun exposure, and positive associations with height, hepatitis C virus seropositivity, living or working in a farm, hairdresser occupation and family history of hematological malignancies<sup>2</sup>.

Diet is a modifiable risk factor for several neoplasms<sup>3</sup>, but evidence for CLL is inconclusive. Epidemiological data on the association of diet and CLL are heterogeneous, and mainly arise from studies on nutrients or single food items. While most prospective studies<sup>4–12</sup> did not find any association with a wide range of dietary factors, case-control studies<sup>13–25</sup> have yielded contradictory results for items such as meat, dairy or vegetables intake. Some authors argue that focusing on overall dietary patterns, instead of on individual foods or nutrients, may better capture dietary variability in the population's diet while allowing the evaluation of interactions between dietary factors<sup>26</sup>. However, the few studies that have been conducted on overall diet and CLL<sup>25,27,28</sup> reported inconclusive findings mainly due to small sample size.

A population-based multicase–control study (MCC-Spain) was launched to evaluate the influence of environmental exposures and their interaction with genetic factors in CLL, among other cancers<sup>29</sup>. The aim of the present study was to evaluate the association between adherence to three validated dietary patterns<sup>30</sup> – Western, Prudent and Mediterranean – and CLL in the MCC-Spain study.

## Methods

### *Study population*

MCC-Spain is a multicentric case–control study with population controls and cases with common tumors in Spain (prostate, breast, colorectal, gastroesophageal and CLL). Between 2010 and 2013, CLL cases aged 20 to 85 years were recruited in 11 Spanish hospitals from 5 Spanish provinces (Asturias, Barcelona, Cantabria, Girona and Granada). Simultaneously, population-based controls frequency-matched to cases, by age (5-year intervals), sex and province of recruitment were randomly selected from primary care centers within the hospitals' catchment areas. Participation rates were 87% in cases and 53% in controls with variability among geographical regions. After applying specific diet exclusion criteria (excluding participants with no dietary data or with missing or implausible energy intakes under 750 or over 4500 kcal/day), a total of 1,605 controls and 369 CLL cases were included. All participants signed an informed consent. Approval for the study was obtained from the ethical review boards of all recruiting centers. Additional information regarding the study design is provided elsewhere<sup>29</sup>.

### *Outcome definition*

CLL cases were diagnosed according the 'International Workshop on CLL criteria' (presence of an absolute count  $\geq 5 \times 10^9$  B-cells/L for 3 or more months in peripheral blood and a clonal population of B-cells CD5+, CD19+, and CD23+)<sup>31</sup>. All diagnoses were morphologically and immunologically confirmed using flow cytometry immunophenotype and complete blood cells count. CLL and small lymphocytic lymphoma were considered the same underlying disease. Given the indolent course of the disease, CLL cases were recruited and interviewed within 3 years from diagnosis. Disease severity at interview was evaluated using the Rai staging system obtained from medical records and verified by local hematologists. CLL subjects were then categorized into two groups based on Rai stage: (a) low-risk category including asymptomatic patients with lymphocytosis only (Rai 0) and (b) intermediate/high-risk category including patients with either lymphadenopathy, hepatomegaly, splenomegaly, anemia and/or thrombocytopenia (Rai I–IV).

### *Data collection*

Data on socio-demographic factors, lifestyle and personal/family medical history were collected through face-to-face interviews performed by trained personnel. Height and weight at different ages were self-reported. The questionnaire in Spanish is available at [www.mccspain.org](http://www.mccspain.org).

In addition, subjects were provided a semi-quantitative Food Frequency Questionnaire (FFQ), which was a modified version from a previously validated instrument in Spain to include regional products<sup>32</sup>. The FFQ was self-administered and returned by mail or filled out face to face. It included 140 food items with portion sizes specified for each item, and assessed usual dietary intake during the previous year. Cross-check questions on aggregated food group consumption were used to adjust the frequency of food consumption and reduce misreporting of food groups with large numbers of items<sup>33</sup>. Nutrient intakes were estimated using food composition tables published for Spain, and other sources<sup>34</sup>. The response rate of the FFQ was slightly lower in cases (82%) than in controls (87%). Overall, responsiveness was not associated with age and individuals from Granada were less likely to answer the FFQ than those from Barcelona. Those individuals who did not answer the diet questionnaire had a lower educational level and, in controls, were also more likely to be women.

### *Dietary patterns*

Three validated dietary patterns identified in a Spanish case-control study (EpiGEICAM)<sup>30</sup> were reconstructed in the MCC-study: a) a Western dietary pattern characterized by high intakes of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, convenience food and sauces, b) a Prudent pattern, with high intakes of low-fat dairy products, vegetables, fruits, whole grains and juices; and c) a Mediterranean pattern, defined by a high intake of fish, vegetables, legumes, boiled potatoes, fruits, olives and vegetable oil. Further information on the dietary patterns identification can be found elsewhere<sup>30</sup>. In brief, dietary information extracted from a semi-quantitative questionnaire in the EpiGEICAM study was converted to mean daily intake in grams and grouped into 26 food categories. Major existing dietary patterns were identified in the control population by applying principal components analysis (PCA) without rotation of the variance-covariance matrix over the 26 inter-correlated food groups. The obtained set of loadings represent the correlation between the consumption of each food group and the component/pattern score and can be used to apply such patterns in other populations<sup>35</sup>. In the MCC-study, we grouped the FFQ items into the same 26 food groups (**Supplementary material, Table S1**), and calculated the score of adherence to the Western, Prudent and Mediterranean dietary patterns as a linear combination of the loads described in the EpiGEICAM study and the log-transformed centered food group consumption reported by the participants of MCC-Spain study.

### *Statistical analyses*

As descriptive analyses, we compared anthropometric, socio-demographic and lifestyle characteristics between cases and controls. Chi-squared test was used to evaluate the level of significance of the differences observed in categorical variables, Student t-test for normally distributed continuous variables

and Wilcoxon rank-sum test for non-normally distributed continuous variables. In addition, we analyzed the distribution of each dietary pattern (continuous) across categories of descriptive variables. Student's t-test was used to assess differences observed in variables with 2 categories and ANOVA for those with more than two categories.

The association between the dietary patterns and CLL was evaluated using mixed logistic regression models with random province-specific intercepts. The exposure variables (adherence to Western, Prudent or Mediterranean patterns) were included in the model both as continuous variables (1-standard deviation (SD) increase of the controls' scores) and as categorical variables (according to the quartile distribution in all controls). All models were adjusted for age (years, continuous), sex, education (no formal education, primary school, secondary school, university), and energy intake (kcal/day, continuous) as fixed effects and province of residence as a random effect term. Height (cm, continuous), waist-to-hip ratio (continuous), body mass index (BMI in kg/m<sup>2</sup>, continuous), ever worked on a farm (yes, no), family history of hematologic malignancies (yes, no), alcohol consumption (g/day, continuous), smoking status (never, past, current), and physical activity (in the last 10 years, measured in Metabolic Equivalent of Task (METs)/week: inactive (0), low (0.1-8), moderate (8-15.9) and very active ( $\geq 16$ )) were examined as potential confounders, but were not included in the final models as they were not found alone, or in combination, to affect the estimates. Interaction terms were modeled between each of these separate variables and the dietary score (continuous), and tested using log-likelihood ratio tests. A possible effect modification of sex, BMI, energy intake, tobacco, physical activity, working on a farm and family history of hematologic malignancies was tested including an interaction term between each of the patterns and such variables. The estimation of the effects according to Rai stage (0 vs. I-IV) was calculated with multinomial logistic regression models adjusted by the set of variables described above plus province of residence as random effect term. Finally, sensitivity analyses were performed to examine how the inclusion of I) cases with longer period of time from diagnosis to recruitment (<1 year vs.  $\geq 1$  year) and II) cases treated before the interview affected the overall estimates. Odds ratios (OR) and 95% confidence intervals (CI) were also obtained with multinomial logistic regression models. The p for heterogeneity of effects across Rai stage and for sensitivity analyses was obtained with the Wald test. All analyses were performed using STATA/MP (version 14.1, 2015, StataCorp LP) and statistical significance was set at 2-sided  $p < 0.05$ .

## Results

Distribution of baseline characteristics between cases and controls is shown in **Table 1**. Compared with controls, cases were more adherent to the Western pattern, while no differences in level of adherence



to the Prudent and Mediterranean patterns were observed in bivariate analyses. CLL cases were also slightly older, had a higher waist-to-hip ratio, and were more likely to have a family history of hematological malignancy and to have ever worked in a farm. No other differences were observed for the rest of the pre-selected variables.

The distribution of key characteristics of controls according to level of adherence to each dietary pattern is shown in the Supplementary material (**Figure S1**). Controls with greater adherence to a Western pattern were more likely to be men, younger, taller, current smokers, less prone to have worked in farming or agriculture, had a lower BMI and waist-to-hip ratio, and a higher level of education, energy and alcohol intake. Those with a higher adherence to a Prudent pattern were more likely to be women, younger, taller, physically active, never/former smokers, more highly educated, less prone to have worked in farming or agriculture, and with a higher energy intake and lower alcohol consumption. Finally, controls with a greater adherence to a Mediterranean pattern were more likely to be men, physically active, showed a lower proportion of ever smokers and farming or agriculture ever workers, and a higher energy intake.

**Figure 1** summarizes the adjusted ORs for the association between CLL and level of adherence to the Western, Prudent and Mediterranean dietary patterns. Individuals in highest quartile of the Western score had an OR for CLL of 1.63 (95% CI 1.11; 2.39) compared with individuals with low adherence (p for trend 0.02). Each SD increment in the score was associated with a 19% higher OR of having CLL (95% CI 1.03; 1.37). No associations were observed for Mediterranean and Prudent diet patterns. The impact of each individual covariate (region, age, sex, education, and energy intake) in the association of the three dietary patterns and CLL is provided in Supplementary material (**Figure S2**).

Since CLL is more prevalent in men, who are also more likely to adhere to a Western dietary pattern (**Table 1** and **Figure S1**), all analyses were stratified by sex. No differences across sexes were observed for any of the dietary patterns (p-heterogeneity: Western (0.79), Prudent (0.11) and Mediterranean (0.17); data not shown). In addition, no differences were observed by BMI, energy intake, tobacco, physical activity, working on a farm and family history of hematologic malignancies (all p for interaction >0.05, data not shown).

Analyses by Rai-stage did not show significant heterogeneity of effects for the Western or Prudent dietary patterns (p-het = 0.50 and 0.17, respectively). However, weak opposite trends in relation to a Mediterranean diet pattern were observed; it was inversely associated (although not statistically significant) with Rai 0 CLL (OR 1-SD increase= 0.88 (95% CI 0.74; 1.04)) and positively related with Rai I-IV CLL (OR 1-SD increase= 1.15 (95% CI 0.93; 1.41)) (p-heterogeneity=0.04) (**Table 2**).

Sensitivity analyses by time from diagnosis to recruitment yielded similar results for the three dietary patterns (Supplementary material, **Table S2**). Similarly, excluding cases treated prior to consent (N=79) did not materially modify the results (p-heterogeneity in trends: Western (0.25), Prudent (0.32) and Mediterranean (0.33)), but higher ORs for a Western dietary pattern were observed in cases treated prior to consent in comparison to those not treated (Supplementary material, **Table S3**).

## Discussion

This study provides, for the first time, evidence of an association between adherence to a Western dietary pattern and CLL. By contrast, no associations were found for a Prudent or Mediterranean pattern.

There is limited evidence linking extrinsic-risk factors, and particularly diet, with non-Hodgkin lymphoma (NHL). In the 2007 report by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)<sup>3</sup>, *the Panel* decided not to make any judgements regarding the causality of associations between specific dietary factors and NHL, but pointed out a suggestive inverse association with vegetables, fruits, and alcoholic beverages and a positive association with meat, total fat, body fatness, and dairy. Recent meta-analyses further support these associations<sup>36,37</sup>, but evidence is still sparse to establish a causal role. Similarly, data on the association of diet and CLL are inconclusive, and mainly arise from studies on nutrients or single food items. To our knowledge, 9 prospective studies<sup>4–12</sup> and 13 case-control studies<sup>13–25</sup> have been published on this topic. With the exception of few studies that found positive associations with consumption of processed meat and poultry<sup>4</sup>, total carbohydrate<sup>8</sup> or fat (in women)<sup>11</sup> intake, and inverse associations with isoflavones consumption<sup>10</sup>, generally large prospective studies found no associations between a wide range of dietary factors and CLL. By contrast, case-control studies have yielded contradictory results for meat<sup>13,14,16,24,25</sup>, dairy products<sup>13–17</sup>, fish<sup>15,18</sup> or vegetables and fruit<sup>14,16,19,22,23,25</sup> intake.

Inconsistencies in previous epidemiological nutritional studies in part reflect the difficulty in disentangling the influence of single food items that, when consumed in combination, may be highly correlated and exert synergistic or antagonistic effects on CLL risk. The examination of dietary patterns, which better reflect the complexity of dietary intake, has been used to address such limitations<sup>26</sup>. So far, only few studies have examined associations of dietary patterns and risk of CLL<sup>25,27,28</sup>, reporting inconclusive findings mainly due to small sample size. Ollberding *et al.*<sup>28</sup> pointed out that a high adherence to a 'Meat, Fat and Sweets' dietary pattern – characterized by high intakes of French fries, red meat, processed meat, pizza, salty snacks, sweets and desserts – was associated with an increased risk of overall NHL (OR<sub>Q4vs.Q1</sub>=3.6; 95% CI 1.9, 6.8) in a Nebraska case-control study. This association was

maintained when stratifying by lymphoma subtypes but sub-analyses did not include CLL cases due to sample size (n=25). By contrast, a large prospective cohort in the US did not find associations with a 'Fat and Meat' pattern and CLL etiology<sup>27</sup>. However, this pattern did not include sweets and deserts, sweetened beverages, or convenience foods, which may be important contributing factors of these associations. Thus, not only differences in the study design and setting, but also in food groups loaded in these data-driven analyses, should be carefully considered when comparing results. In line with our findings, no associations with overall NHL<sup>25,27,28</sup> or CLL<sup>25,27</sup> were detected for a 'healthy' dietary pattern characterized by high intakes of fruits and vegetables.

We observed opposite trends in relation to a Mediterranean diet pattern and Rai stages, with stronger adherence among cases with higher disease severity (p-heterogeneity=0.04). We hypothesize that reverse causality could be partly explaining these results. While Rai 0 patients are usually diagnosed in a routine blood test and present an indolent course, Rai I-IV are more prone to be symptomatic (e.g. night sweat, fatigue, weight loss or fever) and to receive active treatment. Thus, those patients with a more severe disease – and probably more concerned about their illness – would be more prone to shift towards a healthier-like dietary pattern. However, these results have to be taken with cautious since none of the trends showed statistical significant associations.

CLL is the most common leukemia in Western countries while its incidence is much lower in Eastern countries, where it accounts for only 1% to 3% of NHL in most series<sup>38</sup>. While genetic backgrounds may be responsible for part of the differences in the CLL incidence, some studies have suggested that environmental factors also play an important role. A dramatic increase in CLL incidence in Taiwan in the recent years was associated with a strong birth-cohort effect, that corresponded to the Westernization of lifestyle in Taiwan since 1960<sup>39</sup>. In addition, a higher incidence of CLL has been reported among US-born Asians compared to foreign-born Asians, pointing out the influence of environmental factors that change with immigration and acculturation to a Westernized lifestyle<sup>40</sup>. Our results further support that a Westernization of diet could partly explain these incidence patterns.

A Western diet has been associated with obesity phenotypes<sup>41</sup>, including a higher waist-to-hip ratio, which has in turn been recently linked to higher OR of CLL – particularly in women, in the MCC-Spain study<sup>42</sup>. Despite the fact that CLL cases showed a higher waist-to-hip ratio than controls in our study, waist-to-hip ratio and body mass index were not included as covariates in the final multiple-adjusted model since they did not change risk estimates. Hence, an independent effect of the Western dietary pattern may be contributing to CLL lymphomagenesis, which seems plausible from a mechanistic point of view. On one hand, it is well-established that dietary changes, and particularly switching from a low-fat,

plant polysaccharide-rich diet to a high-fat, high-sugar Western diet, can induce alterations in microbiota composition<sup>43</sup>. Beyond its role in the biosynthesis of key components (e.g. vitamins, essential amino acids or short chain fatty acid byproducts), several studies using germ-free mice suggest that microbiota also plays a fundamental role on the induction, training, and function of the host immune system<sup>44</sup>. Exposure to a Western diet may have selected for a microbiota that lack the resilience and diversity required to establish balanced immune responses, and this phenomenon is proposed to account for some of the dramatic rise in autoimmune and chronic inflammatory disorders found in high-income countries. On the other hand, a diet high in fat, refined grains, red and processed meats, and sweets has been largely associated with higher levels of inflammatory markers<sup>45</sup> and with inflammation-related chronic diseases<sup>46</sup>. In particular in CLL, the strong production of inflammatory cytokines and chemokines accompanied by activation of intra-cellular pro-inflammatory pathways, and the presence of somatic mutations that activate pro-inflammatory signaling pathways, suggest that chronic inflammation plays a pathophysiological role in this disease<sup>47</sup>. Thus, an inflammation-related mechanism may in part underlie the observed associations with CLL, although no research on the inflammatory potential of diet and CLL risk has been yet conducted.

The dietary patterns used in this study were identified using the control population of a multicentric case-control study on female breast cancer in Spain<sup>30</sup>. By contrast, the MCC-Spain study included male participants, which may have different dietary habits. However, this difference does not preclude the application of the original scoring system over the current sample. Scores of adherence to dietary patterns can be calculated following the exact same rules over different populations, resulting in different levels of adherence but still being valid, as has been recently proved<sup>35</sup>. As a matter of fact, the current dietary patterns have been previously constructed in the MCC-study and a Western dietary pattern was positively associated with gastric<sup>48</sup>, breast<sup>49</sup> and colorectal<sup>50</sup> cancers.

One of the main limitations is the study design since case-control studies are prone to selection and recall biases. Measurement errors in the estimation of food intake due to the use of self-reported FFQ are also of some concern. However, the FFQ was validated in the Spanish population and included regional products<sup>32</sup>. Moreover, some questions about general dietary habits were included in the questionnaire and were used to adjust the responses to the FFQ following the methodology described in Calvert *et al.*<sup>33</sup>. The inclusion of prevalent cases might be another cause for concern since patients who survived might have a very different etiology than those who died rapidly after diagnosis. In addition, diet can be influenced by many external factors and patients with longer survival period might have substantially modified their diet. However, results of the sensitivity analysis suggested that the use of

prevalent cases might not have introduced selective survival bias or reverse causation. We may have been limited by the small sample size and lack of statistical power to detect significant associations when evaluating certain subgroups. Finally, although we adjusted for a range of potential confounders, residual confounding cannot be totally ruled out.

Strengths of the study include the substantial sample size of CLL cases, with specific information on clinical presentation. We were able to collect detailed information on demographics and disease stage and statistically adjust for a number of potential confounding factors. This allowed the evaluation of potential interactions of diet with numerous covariates and the exploration of the associations by stage. Finally, the multi-centric nature of the study, with rural and urban areas included, allowed a wide geographic variability of dietary intake data.

In conclusion, in this Spanish population-based case-control study greater adherence to a Western dietary pattern was associated with CLL. These novel results suggest that a proportion of CLL cases could be prevented by modifying dietary patterns. Further research, especially with a prospective design, is warranted to confirm these findings.

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**Table 1.** Baseline characteristics of chronic lymphocytic leukemia for cases and controls in the MCC-Spain study.

|   | <b>Controls<br/>(n=1,605)</b> | <b>Cases<br/>(n=369)</b> | <b>P-value<sup>1</sup></b> |
|---|-------------------------------|--------------------------|----------------------------|
| <b>Western, mean (SD)</b>                                 | 5.88 (1.46)                   | 6.06 (1.40)              | <b>0.03</b>                |
| <b>Prudent, mean (SD)</b>                                 | 6.55 (1.12)                   | 6.66 (1.03)              | 0.07                       |
| <b>Mediterranean, mean (SD)</b>                           | 7.08 (1.00)                   | 7.16 (0.88)              | 0.20                       |
| Province, n(%)  |                               |                          | <b>&lt;0.001</b>           |
| Barcelona   | 900 (56)                      | 242 (66)                 |                            |
| Asturias  | 211 (13)                      | 51 (14)                  |                            |
| Cantabria   | 281 (18)                      | 21 (6)                   |                            |
| Granada   | 144 (9)                       | 27 (7)                   |                            |
| Girona  | 69 (4)                        | 28 (8)                   |                            |
| Age (years), mean (SD)                                    | 64.30 (10.54)                 | 66.19 (10.12)            | <b>0.002</b>               |
| Sex, n(%)   |                               |                          | 0.95                       |
| Male  | 936 (58)                      | 217 (59)                 |                            |
| Female  | 669 (42)                      | 152 (41)                 |                            |
| Energy intake (kcal/day), mean (SD)                       | 1901.15 (585.88)              | 1937.91 (612.06)         | 0.28                       |
| Current alcohol intake (g/day), median (IQR) <sup>2</sup> | 8.80 (0.58;27.32)             | 8.82 (0.83;24.47)        | 0.75                       |
| BMI (kg/m <sup>2</sup> ), mean (SD) <sup>2</sup>          | 26.99 (4.50)                  | 27.32 (4.43)             | 0.21                       |
| Height (cm), mean(SD) <sup>2</sup>                        | 165.63 (8.51)                 | 165.97 (9.11)            | 0.50                       |
| Waist-to-hip ratio <sup>3</sup> , n(%)                    |                               |                          | <b>0.004</b>               |
| Low   | 460 (29)                      | 77 (21)                  |                            |
| Moderate  | 449 (28)                      | 98 (27)                  |                            |
| High  | 682 (42)                      | 192 (52)                 |                            |
| Unknown   | 14 (1)                        | 2 (1)                    |                            |
| Smoking status, n(%)                                      |                               |                          | 0.39                       |
| Never   | 696 (43)                      | 165 (45)                 |                            |
| Former  | 602 (38)                      | 134 (36)                 |                            |
| Current   | 303 (19)                      | 67 (18)                  |                            |
| Unknown   | 4 (0)                         | 3 (1)                    |                            |
| Education, n(%)   |                               |                          | 0.54                       |
| No formal education                                       | 357 (22)                      | 94 (25)                  |                            |
| Primary   | 502 (31)                      | 106 (29)                 |                            |
| Secondary   | 461 (29)                      | 107 (29)                 |                            |
| University  | 285 (18)                      | 62 (17)                  |                            |
| Physical activity <sup>4</sup> , n(%)                     |                               |                          | 0.50                       |
| Inactive  | 656 (41)                      | 136 (37)                 |                            |
| Low   | 219 (14)                      | 55 (15)                  |                            |
| Moderate  | 190 (12)                      | 47 (13)                  |                            |
| Very active   | 502 (31)                      | 118 (32)                 |                            |
| Unknown   | 38 (2)                        | 13 (4)                   |                            |
| Ever worked in farming or agriculture, n(%)               |                               |                          | <b>&lt;0.001</b>           |
| No  | 1257 (78)                     | 258 (70)                 |                            |
| Yes   | 323 (20)                      | 108 (29)                 |                            |
| Unknown   | 25 (2)                        | 3 (1)                    |                            |
| Family history of hematological malignancy, n(%)          |                               |                          | <b>&lt;0.001</b>           |
| No  | 1551 (97)                     | 333 (90)                 |                            |
| Yes   | 54 (3)                        | 36 (10)                  |                            |
| Rai stage   |                               |                          |                            |
| 0   | -                             | 199 (54)                 |                            |
| I-IV  | -                             | 150 (41)                 |                            |
| Unknown   | -                             | 20 (5)                   |                            |

SD, standard deviation; IQR, interquartile interval; BMI, body mass index.

<sup>1</sup>P value for heterogeneity calculated with the Student t-test for comparison of normally distributed continuous variables, with the Wilcoxon rank-sum test for comparison of non-normally distributed continuous variables (alcohol intake), and with the Chi-square test for categorical variables. <sup>2</sup>% of missing values in continuous variables: alcohol intake (2%), BMI (4%), height (3%).

<sup>3</sup>Waist to hip ratio risk categories according to WHO criteria. <sup>4</sup>Physical activity, in the last 10 years, measured in METs/week: inactive (0), low (0.1-8), moderate (8-15.9) and very active (≥16). **In bold:** p value <0.05

**Table 2:** Association between adherence to dietary patterns and chronic lymphocytic leukemia by severity of the disease, in the MCC-Spain study.

|                      | Controls<br>N(%)<br>(n=1,605) | Cases<br>N(%)<br>(n=199) | Rai 0                    |                  | Rai I-IV                 |  | p-het <sup>2</sup> |
|----------------------|-------------------------------|--------------------------|--------------------------|------------------|--------------------------|--|--------------------|
|                      |                               |                          | OR <sup>1</sup> (95% CI) | Cases<br>(n=150) | OR <sup>1</sup> (95% CI) |  |                    |
| <b>Western</b>       |                               |                          |                          |                  |                          |  |                    |
| Q1                   | 402 (25)                      | 45 (23)                  | 1                        | 26 (17)          | 1                        |  |                    |
| Q2                   | 401 (25)                      | 47 (24)                  | 1.11 (0.71;1.74)         | 39 (26)          | 1.40 (0.82;2.38)         |  |                    |
| Q3                   | 401 (25)                      | 47 (24)                  | 1.17 (0.73;1.87)         | 37 (25)          | 1.32 (0.76;2.30)         |  |                    |
| Q4                   | 401 (25)                      | 60 (30)                  | 1.60 (0.97;2.65)         | 48 (32)          | 1.71 (0.95;3.06)         |  |                    |
| p-trend              |                               |                          | 0.07                     |                  | 0.11                     |  |                    |
| 1-SD increase        |                               |                          | 1.15 (0.95;1.39)         |                  | 1.26 (1.02;1.56)         |  | 0.50               |
| <b>Prudent</b>       |                               |                          |                          |                  |                          |  |                    |
| Q1                   | 402 (25)                      | 42 (21)                  | 1                        | 30 (20)          | 1                        |  |                    |
| Q2                   | 401 (25)                      | 53 (27)                  | 1.09 (0.70;1.70)         | 37 (25)          | 1.16 (0.69;1.93)         |  |                    |
| Q3                   | 401 (25)                      | 52 (26)                  | 1.07 (0.68;1.69)         | 32 (21)          | 0.97 (0.56;1.66)         |  |                    |
| Q4                   | 401 (25)                      | 52 (26)                  | 1.01 (0.62;1.64)         | 51 (34)          | 1.47 (0.86;2.51)         |  |                    |
| p-trend              |                               |                          | 0.98                     |                  | 0.23                     |  |                    |
| 1-SD increase        |                               |                          | 0.99 (0.83;1.18)         |                  | 1.18 (0.96;1.45)         |  | 0.17               |
| <b>Mediterranean</b> |                               |                          |                          |                  |                          |  |                    |
| Q1                   | 402 (25)                      | 48 (24)                  | 1                        | 29 (19)          | 1                        |  |                    |
| Q2                   | 401 (25)                      | 51 (26)                  | 0.88 (0.57;1.36)         | 29 (19)          | 0.94 (0.55;1.62)         |  |                    |
| Q3                   | 401 (25)                      | 55 (28)                  | 0.88 (0.57;1.37)         | 46 (31)          | 1.39 (0.83;2.30)         |  |                    |
| Q4                   | 401 (25)                      | 45 (23)                  | 0.65 (0.40;1.06)         | 46 (31)          | 1.32 (0.76;2.27)         |  |                    |
| p-trend              |                               |                          | 0.11                     |                  | 0.17                     |  |                    |
| 1-SD increase        |                               |                          | 0.88 (0.74;1.04)         |                  | 1.15 (0.93;1.41)         |  | <b>0.04</b>        |

OR, odds ratio; 95% CI, 95% confidence interval; Q, quartile; SD, standard deviation.

<sup>1</sup> Multinomial logistic regression models adjusted for age, sex, education, energy intake (kcal/day) with province of residence as a random effect.

<sup>2</sup> P-value for the heterogeneity of effects

**In bold:** P-value<0.05

[FIGURE 1]

OR, odds ratio; 95% CI, 95% confidence interval; Q, quartile; SD, standard deviation. Black squares indicate OR and horizontal lines represent 95% CI<sup>†</sup> Logistic regression models adjusted for age, sex, education, energy intake (kcal/day) with province of residence as random effect.

**Figure 1.** Association between adherence to dietary patterns and chronic lymphocytic leukemia in the MCC-Spain study

**Control N(%)**  
N= 1,605

**Cases N(%)**  
N= 369

**OR<sup>1</sup> & 95%CI**

**P-trend**

**Western**

|               |          |          |                     |
|---------------|----------|----------|---------------------|
| Q1            | 402 (25) | 77 (21)  | ref                 |
| Q2            | 401 (25) | 90 (24)  | 1.19 (0.84 to 1.69) |
| Q3            | 401 (25) | 88 (24)  | 1.19 (0.83 to 1.72) |
| Q4            | 401 (25) | 114 (31) | 1.63 (1.11 to 2.39) |
| 1-SD increase |          |          | 1.19 (1.03 to 1.37) |

0.02

**Prudent**

|               |          |          |                     |
|---------------|----------|----------|---------------------|
| Q1            | 402 (25) | 80 (22)  | ref                 |
| Q2            | 401 (25) | 92 (25)  | 1.04 (0.74 to 1.47) |
| Q3            | 401 (25) | 89 (24)  | 1.00 (0.70 to 1.42) |
| Q4            | 401 (25) | 108 (29) | 1.16 (0.80 to 1.67) |
| 1-SD increase |          |          | 1.06 (0.92 to 1.21) |

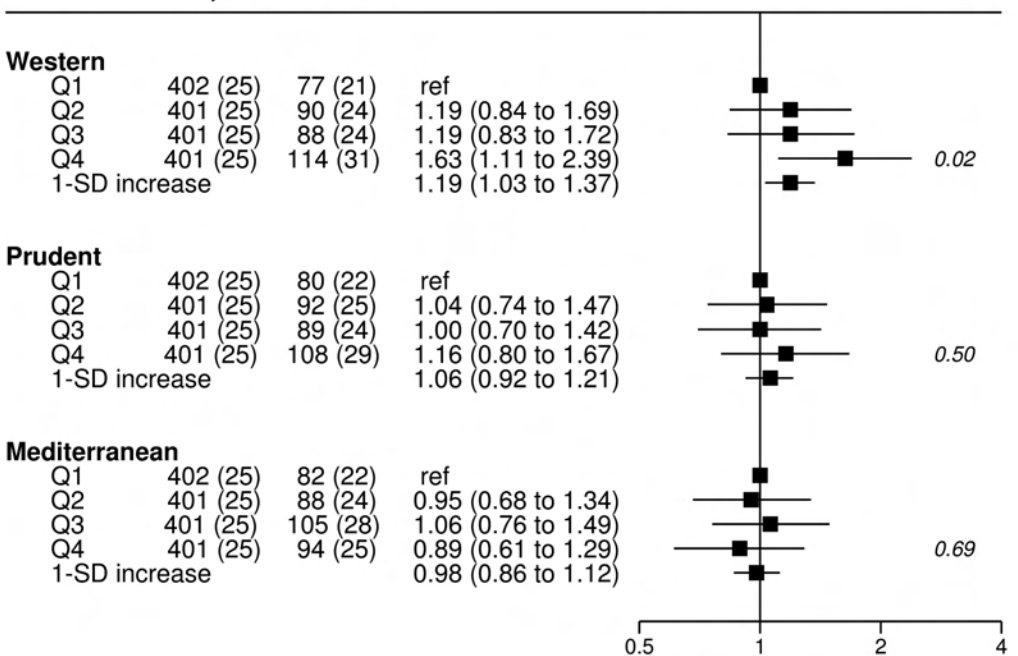
0.50

**Mediterranean**

|               |          |          |                     |
|---------------|----------|----------|---------------------|
| Q1            | 402 (25) | 82 (22)  | ref                 |
| Q2            | 401 (25) | 88 (24)  | 0.95 (0.68 to 1.34) |
| Q3            | 401 (25) | 105 (28) | 1.06 (0.76 to 1.49) |
| Q4            | 401 (25) | 94 (25)  | 0.89 (0.61 to 1.29) |
| 1-SD increase |          |          | 0.98 (0.86 to 1.12) |

0.69

0.5 1 2 4



## Supplementary material

**Table S1.** Composition of food groups on the food frequency questionnaire of the MCC-Spain study and component loading for each pattern identified in the EpiGEICAM study [30].

| Food group                 | Food   | L <sub>W</sub> <sup>1</sup> | L <sub>P</sub> <sup>1</sup> | L <sub>M</sub> <sup>1</sup> |
|----------------------------|--|-----------------------------|-----------------------------|-----------------------------|
| <b>High-fat dairy</b>      | Whole-fat milk, condensed milk, whole-fat yogurt, semi-cured, cured, or creamy cheese, blue cheese, custard, milk shake, ice-cream, double cream.                                    | 0.60                        | -0.11                       | 0.20                        |
| <b>Low-fat dairy</b>       | Semi-skimmed and skimmed milk, soy milk, skimmed yogurt, curd, cottage or fresh white cheese.  | -0.49                       | 0.60                        | -0.01                       |
| <b>Eggs</b>                | Eggs.  | 0.19                        | 0.08                        | 0.16                        |
| <b>White meat</b>          | Chicken, rabbit and duck.  | 0.08                        | 0.17                        | 0.18                        |
| <b>Red meat</b>            | Pork, beef, lamb, liver (beef, pork or chicken), entrails, hamburgers (pork or beef) and meatballs (pork or beef).   | 0.27                        | 0.09                        | 0.22                        |
| <b>Processed meat</b>      | Sausages, serrano ham and other cold meat, bacon, pâté, foie-gras.   | 0.36                        | 0.10                        | 0.26                        |
| <b>White fish</b>          | Fresh or frozen white fish (hake, sea bass, sea bream), ½-salted fish and ½-smoked fish.   | 0.01                        | 0.24                        | 0.34                        |
| <b>Oily fish</b>           | Fresh or frozen blue fish (tuna, swordfish, sardines, anchovies, salmon), canned fish, ½-salted fish and ½-smoked fish.  | 0.05                        | 0.24                        | 0.44                        |
| <b>Seafood/shellfish</b>   | Clams, mussels, oysters, squid, cuttlefish, octopus, prawn, crab, shrimp and similar products.   | 0.17                        | 0.27                        | 0.35                        |
| <b>Leafy vegetables</b>    | Spinach, chard, lettuce and other leafy vegetables.  | -0.11                       | 0.34                        | 0.40                        |
| <b>Fruiting vegetables</b> | Tomato, eggplant, zucchini, cucumber, pepper, artichoke and avocado.   | 0.00                        | 0.36                        | 0.45                        |
| <b>Root vegetables</b>     | Carrot, pumpkin and radish.  | 0.05                        | 0.35                        | 0.44                        |
| <b>Other vegetables</b>    | Cooked cabbage, cauliflower or broccoli, onion, green beans, asparagus, mushrooms, corn, garlic, gazpacho, vegetable soup and other vegetables.                                      | -0.04                       | 0.40                        | 0.42                        |
| <b>Legumes</b>             | Peas, lentils, chickpeas, beans and broad beans.   | 0.21                        | 0.15                        | 0.34                        |
| <b>Potatoes</b>            | Roasted or boiled potatoes and sweet potatoes.   | 0.17                        | 0.25                        | 0.40                        |
| <b>Fruits</b>              | Orange, grapefruit, mandarin, banana, apple, pear, grapes, kiwi, strawberries, cherries, peach, figs, melon or watermelon, prunes, mango and papaya and other fresh or dried fruits. | -0.07                       | 0.31                        | 0.31                        |
| <b>Nuts</b>                | Almonds, peanuts, pine nuts, hazelnut  | 0.18                        | 0.22                        | 0.29                        |
| <b>Refined grains</b>      | White-flour bread, rice, pasta   | 0.37                        | 0.15                        | 0.23                        |

|                                    |   |       |      |       |
|------------------------------------|---|-------|------|-------|
| <b>Whole grains</b>                | Whole-grain bread and breakfast cereals   | -0.43 | 0.47 | -0.06 |
| <b>Olives and vegetable oil</b>    | Olives, added olive oil to salads, bread and dishes, other vegetable oils (sunflower, corn, and soybean).   | 0.12  | 0.19 | 0.34  |
| <b>Other edible fats</b>           | Margarine, butter and lard.   | 0.22  | 0.02 | 0.11  |
| <b>Sweets</b>                      | Chocolate and other sweets, cocoa powder, plain cookies, chocolate cookies, pastries (croissant, donut, cake, pie or similar)                         | 0.35  | 0.18 | 0.05  |
| <b>Sugary</b>                      | Jam, honey, sugar and fruit in sugar syrup.   | 0.24  | 0.05 | 0.00  |
| <b>Juices</b>                      | Tomato juice, freshly squeezed orange juice, juice (other than freshly squeezed)  | 0.25  | 0.67 | -0.39 |
| <b>Caloric drinks</b>              | Sugar-sweetened soft drinks and nut milk.   | 0.74  | 0.21 | -0.25 |
| <b>Convenience food and sauces</b> | Croquette, fish sticks, dumplings, kebab, fried potatoes, crisps, pizza, instant soup, mayonnaise, tomato sauce, hot sauce, ketchup and other sauces. | 0.47  | 0.12 | 0.24  |

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<sup>1</sup>Component loadings for the W: Western; P: Prudent; M: Mediterranean dietary patterns.



**Table S2:** Association between adherence to dietary patterns and risk of chronic lymphocytic leukemia by time from diagnosis to interview, in the MCC-Spain study.

|                      | Controls<br>N(%)<br>(n=1.543) | <1 year from diagnosis  |                          | ≥ 1 year from diagnosis  |                          | p-het <sup>2</sup> |
|----------------------|-------------------------------|-------------------------|--------------------------|--------------------------|--------------------------|--------------------|
|                      |                               | Cases<br>N(%)<br>(n=98) | OR <sup>1</sup> (95% CI) | Cases<br>N(%)<br>(n=271) | OR <sup>1</sup> (95% CI) |                    |
| <b>Western</b>       |                               |                         |                          |                          |                          |                    |
| Q1                   | 402 (25)                      | 23 (23)                 | 1                        | 54 (20)                  | 1                        |                    |
| Q2                   | 401 (25)                      | 20 (20)                 | 0.89 (0.48;1.66)         | 70 (26)                  | 1.30 (0.88;1.93)         |                    |
| Q3                   | 401 (25)                      | 18 (18)                 | 0.78 (0.41;1.49)         | 70 (26)                  | 1.36 (0.92;2.02)         |                    |
| Q4                   | 401 (25)                      | 37 (38)                 | 1.69 (0.96;3.00)         | 77 (28)                  | 1.56 (1.05;2.31)         |                    |
| p-trend              |                               |                         | 0.073                    |                          | 0.03                     |                    |
| 1-SD increase        |                               |                         | 1.16 (0.93;1.45)         |                          | 1.18 (1.03;1.36)         | 0.90               |
| <b>Prudent</b>       |                               |                         |                          |                          |                          |                    |
| Q1                   | 402 (25)                      | 26 (27)                 | 1                        | 54 (20)                  | 1                        |                    |
| Q2                   | 401 (25)                      | 26 (27)                 | 0.90 (0.51;1.60)         | 66 (24)                  | 1.13 (0.76;1.67)         |                    |
| Q3                   | 401 (25)                      | 20 (20)                 | 0.67 (0.37;1.24)         | 69 (25)                  | 1.20 (0.81;1.77)         |                    |
| Q4                   | 401 (25)                      | 26 (27)                 | 0.84 (0.47;1.49)         | 82 (30)                  | 1.42 (0.96;2.08)         |                    |
| p-trend              |                               |                         | 0.402                    |                          | 0.07                     |                    |
| 1-SD increase        |                               |                         | 0.94 (0.76;1.16)         |                          | 1.14 (0.99;1.32)         | 0.11               |
| <b>Mediterranean</b> |                               |                         |                          |                          |                          |                    |
| Q1                   | 402 (25)                      | 23 (23)                 | 1                        | 59 (22)                  | 1                        |                    |
| Q2                   | 401 (25)                      | 24 (24)                 | 0.92 (0.51;1.67)         | 64 (24)                  | 0.99 (0.67;1.46)         |                    |
| Q3                   | 401 (25)                      | 32 (33)                 | 1.13 (0.65;1.99)         | 73 (27)                  | 1.10 (0.75;1.61)         |                    |
| Q4                   | 401 (25)                      | 19 (19)                 | 0.65 (0.35;1.22)         | 75 (28)                  | 1.13 (0.77;1.65)         |                    |
| p-trend              |                               |                         | 0.313                    |                          | 0.43                     |                    |
| 1-SD increase        |                               |                         | 0.94 (0.76;1.15)         |                          | 1.05 (0.92;1.21)         | 0.33               |

OR, odds ratio; 95% CI, 95% confidence interval; Q, quartile; SD, standard deviation.

<sup>1</sup>Multinomial-logistic regression models adjusted for age, sex, level of education, energy intake (kcal/day), body mass index (kg/m<sup>2</sup>) with province of residence as a random effect.

<sup>2</sup>P-value for the heterogeneity of effects

**In bold:** P-trend < 0.05

**Table S3:** Association between adherence to dietary patterns and risk of chronic lymphocytic leukemia according to treatment prior to interview, in the MCC-Spain study.

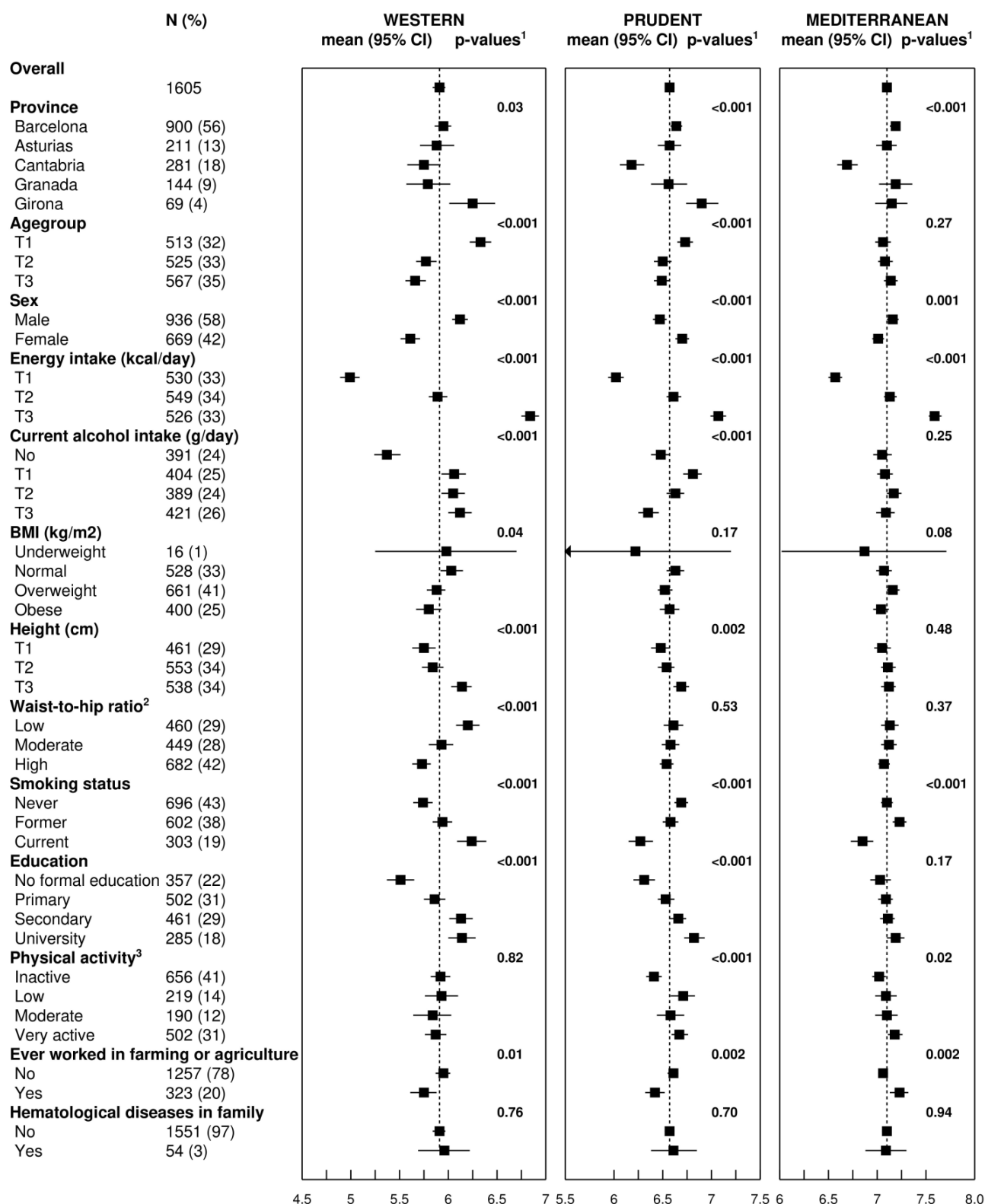
|                      | Controls<br>N(%)<br>(n=1,605) | Cases not treated before<br>the interview |                          | Cases treated before the<br>interview |                          | p-het <sup>2</sup> |
|----------------------|-------------------------------|---|--------------------------|---------------------------------------|--------------------------|--------------------|
|                      |                               | Cases<br>N(%)<br>(n=288)                  | OR <sup>1</sup> (95% CI) | Cases<br>N(%)<br>(n=79)               | OR <sup>1</sup> (95% CI) |                    |
| <b>Western</b>       |                               |   |                          |                                       |                          |                    |
| Q1                   | 402 (25)                      | 66 (23)                                   | 1                        | 11 (14)                               | 1                        |                    |
| Q2                   | 401 (25)                      | 71 (25)                                   | 1.11 (0.76;1.62)         | 18 (23)                               | 1.54 (0.71;3.36)         |                    |
| Q3                   | 401 (25)                      | 66 (23)                                   | 1.07 (0.72;1.60)         | 22 (28)                               | 1.85 (0.85;4.03)         |                    |
| Q4                   | 401 (25)                      | 85 (30)                                   | 1.47 (0.96;2.26)         | 28 (35)                               | <b>2.35 (1.04;5.31)</b>  |                    |
| p-trend              |                               |   | 0.11                     |                                       | <b>0.04</b>              |                    |
| 1-SD increase        |                               |   | 1.13 (0.96;1.33)         |                                       | 1.37 (1.02;1.82)         | 0.25               |
| <b>Prudent</b>       |                               |   |                          |                                       |                          |                    |
| Q1                   | 402 (25)                      | 62 (22)                                   | 1                        | 17 (22)                               | 1                        |                    |
| Q2                   | 401 (25)                      | 72 (25)                                   | 1.02 (0.70;1.50)         | 19 (24)                               | 1.06 (0.54;2.11)         |                    |
| Q3                   | 401 (25)                      | 75 (26)                                   | 1.07 (0.72;1.57)         | 14 (18)                               | 0.75 (0.35;1.59)         |                    |
| Q4                   | 401 (25)                      | 79 (27)                                   | 1.08 (0.71;1.63)         | 29 (37)                               | 1.45 (0.72;2.92)         |                    |
| p-trend              |                               |   | 0.69                     |                                       | 0.41                     |                    |
| 1-SD increase        |                               |   | 1.02 (0.88;1.19)         |                                       | 1.20 (0.91;1.58)         | 0.32               |
| <b>Mediterranean</b> |                               |   |                          |                                       |                          |                    |
| Q1                   | 402 (25)                      | 64 (22)                                   | 1                        | 18 (23)                               | 1                        |                    |
| Q2                   | 401 (25)                      | 74 (26)                                   | 0.99 (0.68;1.44)         | 13 (16)                               | 0.70 (0.34;1.46)         |                    |
| Q3                   | 401 (25)                      | 83 (29)                                   | 1.04 (0.72;1.52)         | 22 (28)                               | 1.06 (0.54;2.06)         |                    |
| Q4                   | 401 (25)                      | 67 (23)                                   | 0.79 (0.52;1.20)         | 26 (33)                               | 1.15 (0.57;2.32)         |                    |
| p-trend              |                               |   | 0.34                     |                                       | 0.47                     |                    |
| 1-SD increase        |                               |   | 0.94 (0.81;1.09)         |                                       | 1.10 (0.83;1.45)         | 0.33               |

OR, odds ratio; 95% CI, 95% confidence interval; Q, quartile; SD, standard deviation.

<sup>1</sup>Multinomial-logistic regression models adjusted for age, sex, level of education, energy intake (kcal/day), body mass index (kg/m<sup>2</sup>) with province of residence as a random effect.

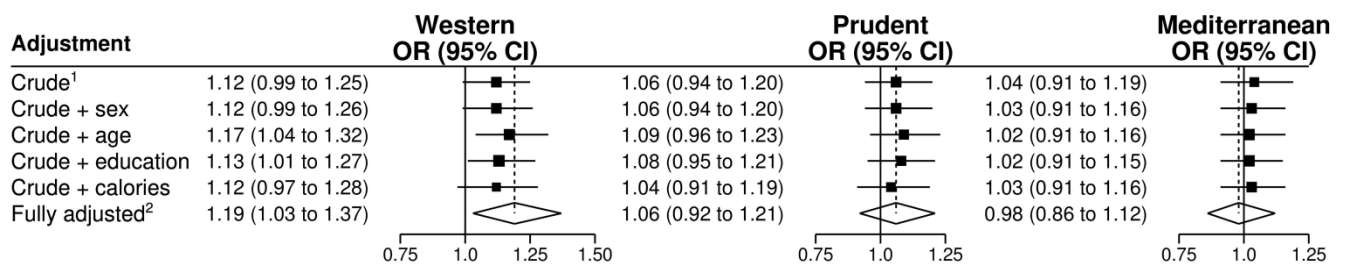
<sup>2</sup>P-value for the heterogeneity of effects

**In bold:** P-trend < 0.05



T, tertile; BMI, body mass index. Numbers do not always add up due to missing data <sup>1</sup>P value for heterogeneity <sup>2</sup>Waist to hip ratio <sup>3</sup>Waist to hip ratio risk categories according to WHO criteria. <sup>4</sup>Physical activity, in the last 10 years, measured in METs/week: inactive (0), low (0.1-8), moderate (8-15.9) and very active ( $\geq 16$ ).

**Figure S1.** Means and 95% confidence intervals (CI) of levels of adherence to the dietary patterns according to characteristics of controls of the MCC-Spain study.



OR, odds ratio; CI, confidence interval. <sup>1</sup>Crude model includes only province as random effects. <sup>2</sup>Model adjusted for age, sex, education, energy intake with province of residence as random effects.

**Figure S2.** Odds ratios of chronic lymphocytic leukemia for a 1-SD increase in dietary patterns adjusted for one factor at a time covariate of the final model, in the MCC-Spain study.

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