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Original Research Article

Long-term adherence to the Mediterranean diet and risk of rheumatoid arthritis and psoriasis: 20-y follow-up of the Seguimiento Universidad de Navarra Project

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A B S T R A C T

Background: The role of dietary patterns in the primary prevention of specific autoimmune conditions remains poorly understood.
Objectives: This study aimed to evaluate the association between Mediterranean diet (MedDiet) adherence and risk of incident rheumatoid arthritis and psoriasis.
Methods: We conducted a prospective analysis of 15,874 immune-mediated inflammatory disease–free participants from the Seguimiento Universidad de Navarra Project cohort (median follow-up: 15.1 y). The outcomes were the incidence of rheumatoid arthritis and psoriasis. Adherence to the MedDiet was repeatedly assessed using validated food frequency questionnaires with the MedDiet score and classified into energy-adjusted tertiles. Incident cases were identified through biennial questionnaires. Primary analyses used Cox proportional hazards models with cumulative mean dietary exposure. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from multivariable models, stratified by age and follow-up period and adjusted for sociodemographic, lifestyle, and clinical confounders.
Results: During follow-up, we identified 165 incident cases of psoriasis (0.73 per 1000 person-years) and 119 incident cases of rheumatoid arthritis (0.53 per 1000 person-years). High MedDiet adherence (T3 compared with T1) was inversely associated with rheumatoid arthritis risk (HR = 0.53; 95% CI: 0.32, 0.89; *P*-trend = 0.020). For psoriasis, higher adherence showed a nonsignificant inverse association (HR = 0.86; 95% CI: 0.57, 1.32; *P*-trend = 0.491). In exploratory item-by-item analyses for rheumatoid arthritis, lower meat intake and higher fruit/nut intake were associated with lower disease risk (HR = 0.41; 95% CI: 0.27, 0.61; HR = 0.64; 95% CI: 0.43, 0.95, respectively).
Conclusions: High MedDiet adherence was inversely associated with risk of incident rheumatoid arthritis among Spanish university graduates, whereas the association for psoriasis remained inconclusive.
This trial was registered at clinicaltrials.gov as NCT02669602 (https://clinicaltrials.gov/study/NCT02669602).

Keywords: Mediterranean diet, autoimmune disease, rheumatoid arthritis, psoriasis, prospective cohort, nutrition

Abbreviations: ASMD, absolute standardized mean difference; CI, confidence interval; FFQ, food frequency questionnaire; HR, hazard ratio; IMID, immune-mediated inflammatory disease; IPW, inverse probability weighting; MDS, Mediterranean diet score; MedDiet, Mediterranean diet; OR, odds ratio; SHR, subdistribution hazard ratio; SUN, Seguimiento Universidad de Navarra.

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Introduction

Immune-mediated inflammatory diseases (IMIDs), including psoriasis and rheumatoid arthritis, represent a heterogeneous group of chronic conditions characterized by immune regulation disruption leading to autologous tissue damage [1]. Over recent decades, the global incidence of IMIDs has increased significantly, imposing a substantial burden on healthcare systems and patient quality of life [2]. Although genetic susceptibility provides a baseline risk, environmental and lifestyle factors, particularly dietary habits, are increasingly recognized as essential modulators of systemic immune tolerance [3].

Chronic low-grade inflammation, oxidative stress, and shared cytokine cascades (such as TNF-α and IL-23/IL-17 pathways) are pathophysiological features across these conditions [4]. Diets rich in ultraprocessed foods, saturated fats, and refined sugars have been associated with proinflammatory states mediated by gut microbiota dysbiosis and impaired mucosal integrity [5,6]. Such nutritional profiles contrast sharply with the anti-inflammatory nature of the Mediterranean diet (MedDiet), which exerts potent anti-inflammatory effects by modulating biomarkers of inflammation [7,8]. Conversely, the MedDiet provides a rich array of anti-inflammatory nutrients, bioactive compounds, and antioxidants that modulate inflammatory signaling cascades and cellular stress responses [7,8].

Epidemiological studies suggest that high adherence to the MedDiet is associated with a lower incidence of chronic specific inflammatory conditions, such as rheumatoid arthritis [9], whereas dietary interventions showed potential to attenuate disease severity in psoriasis [10]. However, significant knowledge gaps remain. Most existing prospective research has evaluated single-disease outcomes, rather than composite IMIDs sharing systemic inflammatory pathways, and long-term dynamic cohort data remain limited [9,11–14]. Second, although the MedDiet is analyzed as a holistic pattern, the specific contribution of its individual constituent dietary components to systemic immune protection remains incompletely understood.

In the present study, we analyzed data from the Seguimiento Universidad de Navarra (SUN) Project, a prospective dynamic cohort of Spanish university graduates followed for >20 y [15]. We aimed to prospectively evaluate the longitudinal association between Mediterranean diet score (MDS) adherence and risk of incident rheumatoid arthritis and psoriasis in the SUN Project. We hypothesized that higher adherence to the MedDiet would be inversely associated with the risk of developing rheumatoid arthritis and psoriasis. In addition, we conducted item-by-item and leave-one-out analyses to evaluate the individual contributions of specific MDS items.

Methods

Study design

The SUN Project is a prospective, dynamic cohort consisting of Spanish university graduates, established to investigate the impact of nutrition and lifestyle on chronic disease development. Since its inception in December 1999, the study has utilized a rolling recruitment strategy, inviting alumni from the University of Navarra and other Spanish institutions via digital or postal mail [15,16]. Participation is entirely voluntary, and no financial incentives are provided.

The study protocol received approval from the Institutional Review Board of the University of Navarra (protocol: 091/2008), and the return of the completed baseline questionnaire (Q0) serves as informed consent. This cohort is registered at clinicaltrials.gov (NCT02669602) and follows the ethical guidelines of the Declaration of Helsinki.

At enrollment, participants provide detailed information regarding their sociodemographic profile, medical background, habits, and diet. Subsequent follow-up questionnaires are administered every 2 y to monitor changes in lifestyle and the emergence of new clinical diagnoses. Supplemental Figure 1 details the exclusion process. Of 23,321 individuals recruited through April 2024, 186 individuals were excluded because of having <2 y of follow-up. We further excluded 2755 participants with prevalent rheumatoid arthritis, psoriasis, or vitiligo at baseline and 1889 individuals with implausible caloric intake (<800 or >4000 kcal/d for males; <500 or >3500 kcal/d for females). In addition, 911 participants with a history of cancer, diabetes, or cardiovascular disease were removed, along with 15 individuals who developed rheumatoid arthritis or psoriasis within the first 2 y of follow-up to address potential reverse causality. After accounting for 1691 participants lost to follow-up (90.4% retention rate), the final analytical sample included 15,874 participants.

Sample size and statistical power

The SUN Project is a dynamic, open-enrollment prospective cohort; thus, the sample size was not fixed a priori and comprised all eligible participants enrolled up to the censoring date (N = 15,874; 224,161 person-years). Post hoc statistical power was evaluated for Cox proportional hazards regression models using the power cox procedure in Stata (power cox). Calculations were based on the observed sample size, total number of incident events, and default SD for binary exposure comparisons, assuming a 2-sided significance level (α) of 0.05.

Outcome: IMID incidence

This research primarily investigated the self-reported incidence of 2 selected IMIDs: rheumatoid arthritis and psoriasis, which are the IMIDs prospectively tracked within the SUN Project's longitudinal protocols. Although vitiligo is also evaluated within the cohort's questionnaires, it was excluded from the present analysis because of its low incidence during follow-up (n = 24), which conferred insufficient statistical power for robust multivariable analyses. Incident cases were ascertained through biennial follow-up questionnaires (self-reported), in which participants reported whether they had received a formal medical diagnosis of any of these conditions. For every positive response, participants provided the specific month and year of the diagnosis.

Dietary assessment

Dietary intake was evaluated at baseline and repeatedly assessed during follow-up at 10 and 20 y, using the same semiquantitative food frequency questionnaire (FFQ) containing 136 items, which was previously validated for the Spanish population [17]. Participants reported their mean consumption frequency over the preceding year across 9 possible categories, ranging from "never" to "≥6 times per day." Nutrient and total energy intakes were estimated using the Spanish Food Composition Tables (Tablas de composición de alimentos) and the Food Composition Database of the University of Granada (Tabla de composición de alimentos españoles) [18,19].

Mediterranean diet score

Adherence to the MedDiet was quantified using the MDS, as originally proposed by Trichopoulou et al. [20]. This 9-point scale

assigns a value of 1 for high consumption (above the sex-specific median) of 6 cardioprotective components: vegetables, legumes, fruits and nuts, cereal, fish, and the ratio of MUFA to SFA (MUFA: SFA). Conversely, 1 point is assigned for low consumption (below the median) of 2 components: dairy products and meat/meat products. For alcohol consumption, 1 point is granted to males consuming between 10 and 50 g/d and females consuming between 5 and 25 g/d. The total score ranges from 0 to 9, with higher values indicating greater adherence to the MedDiet pattern. The MDS was adjusted for total energy intake using the residual method and subsequently classified into approximate tertiles (T1, T2, and T3). They were not equally sized due to ties in the score, but we selected the cutoff points (<4 and >5) closest to the tertiles, and we have kept the name "tertiles."

Covariates

Potential confounders were recorded at baseline through a self-administered questionnaire. Sociodemographic variables included age (years), sex, and university education (years). Lifestyle factors encompassed smoking status (never, current, or former) and physical activity, quantified in metabolic equivalent of task hours per week [21]. Sedentary behavior was assessed via daily television viewing (high if ≥2 h/d) [22] and sleep patterns were analyzed by nocturnal duration (<6, 6–8, or >8 h/d) [23]. BMI (kg/m^2) was calculated from self-reported height and weight and categorized according to WHO criteria [24]. Dietary covariates included alcohol consumption (g/d), total energy intake (kcal/d), following a special diet (yes/no), and the habit of snacking between meals (yes/no).

To account for specific environmental triggers of skin and immune-related disorders, we evaluated daily sunlight exposure, calculated as the mean time spent sunbathing across both summer and winter (h/d), as well as medical history of stress, anxiety, or depression, and other prevalent chronic conditions at baseline.

Statistical analysis

Cox proportional hazards regression (with age as the underlying time variable) was employed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to estimate the association between MedDiet adherence and rheumatoid arthritis and psoriasis as individual outcomes. Primary analyses incorporated repeated dietary assessments updated at 10- and 20-y follow-ups using the cumulative mean of the energy-adjusted MDS from baseline up to the beginning of each follow-up interval to account for long-term dietary habits and minimize measurement error. Time-to-event was calculated as the interval from recruitment (baseline) to the date of the outcome of interest, or the end of follow-up, whichever occurred first. The multivariable models were stratified by age and follow-up period, and further adjusted for sex, education, smoking status, BMI, special diet, snacking, physical activity, television viewing, and sleep duration. To minimize potential reverse causality driven by preclinical disease or subclinical inflammation, our primary analyses excluded all incident cases diagnosed during the first 2 y of follow-up. Furthermore, to account for slowly developing conditions, we conducted a sensitivity analysis extending this lag period to 5 y by excluding all cases occurring within the first 5 y of follow-up. The proportional hazards assumption was confirmed using Schoenfeld residuals (estat phtest), log-negative-log plot inspections (stphplot), and by comparing observed Kaplan–Meier survival curves against Cox-predicted curves (stcoxkm).

Adjusted cumulative incidence curves were visualized using Nelson–Aalen curves weighted by inverse probability weighting (IPW) via sts graph. Because standard nonparametric Nelson–Aalen estimators cannot directly accommodate time-varying exposures, these curves were modeled using baseline dietary adherence. Propensity scores for tertiles were derived from a multinomial logistic regression model (mlogit) conditioned on the full set of potential confounders. To improve precision, stabilized weights were computed as the ratio of the marginal probability of exposure to the conditional propensity score. Extreme weights were truncated at the 1st and 99th percentiles (_pctile) to avoid influential outliers, and weights were subsequently recentered to a mean of 1. Covariate balance across exposure groups was evaluated using absolute standardized mean differences (ASMD), considering an ASMD <0.10 as indicative of negligible imbalance (Supplemental Figure 2). Dose–response relationships were examined using restricted cubic splines with 3 knots (mkspline/xrspline) modeled with repeated measures.

To evaluate the consistency and robustness of our findings, we conducted several additional analyses, all based on the primary repeated-measures cumulative mean framework. First, we performed stratified analyses for the individual disease types (psoriasis and rheumatoid arthritis) by sex, median age, follow-up duration, BMI, physical activity, and smoking status, using likelihood ratio tests to assess potential multiplicative interactions. Second, a series of sensitivity analyses was conducted by systematically excluding participants who could potentially contribute to introducing confounding or misclassification in the assessed associations; these included individuals with missing data in some FFQ items, those with baseline dyslipidemia, hypertension, or depression, participants following special diets or using dietary supplements, and pregnant women. We also excluded users with medications that might interfere with immune or inflammatory pathways, such as paracetamol, aspirin, β-blockers, antiobesity drugs, antidepressants, and anxiolytics. Furthermore, we performed further adjustments to our main model to account for potential disease triggers, including mean sun exposure and baseline psychological distress, defined as a self-reported medical diagnosis of depression, anxiety, or stress at recruitment. Finally, to address potential informative censoring, competing risks regression models were fitted using the Fine–Gray method (stcrreg), treating all-cause mortality as a competing event; these competing risk models were restricted to baseline MDS adherence because of analytical constraints in fitting subdistribution hazards with time-varying covariates.

To determine the contribution of individual MDS components according to each selected IMID, a 3-step analytical strategy was implemented within the repeated-measures framework. First, an item-by-item analysis was performed, with each component evaluated as the primary exposure, adjusted for the remaining elements of the score (total MDS minus the evaluated item) and all other covariates. Furthermore, a minus-one (leave-one-out) analysis was conducted, with 1 component systematically removed at a time to create "reduced" scores. To maintain comparability with the original 9-point scale, coefficients were rescaled by the ratio of the reduced score's range to the original range and expressed per 2-unit increment. Finally, a sequential analysis was performed with the components removed successively based on their statistical importance (ordered by *Z*-scores), starting with those showing the strongest inverse associations. This last analysis was aimed at identifying the specific items whose removal attenuated or eliminated the overall inverse association. Multicollinearity was assessed using Pearson correlation matrices.

To control for potential type I errors arising from multiple testing across individual components, subgroup interactions, and secondary endpoints, false discovery rate adjustments were applied using the Simes (Benjamini–Hochberg) procedure via the qqvalue package within each specific analytical family. Finally, to handle missing data in baseline covariates, we performed imputation using chained equations via Stata's mi suite (mi set, mi register, mi impute chained) under the missing-at-random assumption. Imputation models incorporated baseline sociodemographic, lifestyle, and clinical variables, using predictive mean matching ($k = 5$ nearest neighbors) for continuous parameters and logistic (logit) or multinomial regression (mlogit) for categorical parameters. The imputed dataset was extracted (mi extract 1) for the analytical workflow. Also, a sensitivity analysis according to the missing scenario (excluding imputed data) was performed.

All statistical analyses were conducted using Stata/MP version 18.0 (StataCorp LLC).

Results

Study population and follow-up

The final study population consisted of 15,874 participants after the application of exclusion criteria, totaling 225,086 person-years of follow-up for rheumatoid arthritis and 224,584 person-years for psoriasis (median of 15.1 y). During this period, psoriasis had the highest incidence (0.73 per 1000 person-years), followed by rheumatoid arthritis (0.53). Participants in the highest adherence tertile of the MDS (T3) presented lower adjusted incidence rates for both psoriasis and rheumatoid arthritis compared with lower tertiles (Supplemental Figure 3).

Baseline characteristics of the study population according to tertiles of MedDiet adherence are shown in Table 1. Participants in the highest tertile of adherence (T3) were older (mean age = 40.3 ± 12.2 y), more physically active, and consumed more alcohol than those in the lowest tertile (T1). Participants in T3 of the MedDiet were less

TABLE 1
Baseline characteristics of participants according to baseline tertiles of adherence to the MDS (The SUN Project)

Variables	Total	MDS		
		T1 (0–3 points)	T2 (4–5 points)	T3 (6–9 points)
Sociodemographic	15,874	5900	6259	3715
Age (y)	36.62 ± 11.27	33.90 ± 9.90	36.97 ± 11.21	40.33 ± 12.22
Sex (female), *n* (%)	9839 (62.0)	3638 (61.7)	3914 (62.5)	2287 (61.6)
University education (y)	5.06 ± 1.50	5.04 ± 1.49	5.07 ± 1.49	5.09 ± 1.53
Health and lifestyle				
Normoweight (BMI < 25 kg/m^2), *n* (%)	10,788 (68.0)	4139 (70.2)	4225 (67.5)	2424 (65.2)
Physical activity, METs-h/wk	22.2 ± 23.2	19.7 ± 21.2	22.2 ± 22.9	26.1 ± 25.9
Hypertension diagnosis, *n* (%)	1347 (8.5)	392 (6.6)	541 (8.6)	414 (11.1)
Dyslipidemia diagnosis, *n* (%)	2474 (15.6)	672 (11.4)	987 (15.8)	815 (21.9)
Depression diagnosis, *n* (%)	1701 (10.7)	573 (9.7)	687 (11.0)	441 (11.9)
High psychological distress, *n* (%)	1792 (11.3)	602 (10.2)	726 (11.6)	464 (12.5)
Never smoking, *n* (%)	7991 (50.3)	3210 (54.4)	3097 (49.5)	1684 (45.3)
Short sleep duration (<6 h/d), *n* (%)	818 (5.2)	280 (4.7)	318 (5.1)	220 (5.9)
Long sleep duration (>8 h/d), *n* (%)	2143 (13.5)	875 (14.8)	836 (13.4)	432 (11.6)
Television viewing (≥2 h/d), *n* (%)	5503 (34.7)	2074 (35.2)	2212 (35.3)	1217 (32.8)
Sun exposure (h/d)	0.67 ± 0.76	0.67 ± 0.75	0.68 ± 0.76	0.67 ± 0.76
Paracetamol or aspirin use, *n* (%)	1687 (10.6)	602 (10.2)	679 (10.8)	406 (10.9)
Dietary intake				
Total energy intake (kcal/d)	2351.19 ± 611.78	2325.97 ± 611.70	2339.45 ± 635.25	2411.01 ± 566.12
Carbohydrates (g/d)	256.69 ± 83.36	244.16 ± 81.11	256.54 ± 84.82	276.82 ± 80.45
Proteins (g/d)	105.62 ± 27.75	104.27 ± 26.98	105.39 ± 29.35	108.17 ± 25.97
Total fats (g/d)	95.26 ± 30.75	99.67 ± 30.77	93.99 ± 31.27	90.39 ± 28.87
Saturated fats (g/d)	32.84 ± 12.21	37.30 ± 12.43	31.85 ± 11.75	27.43 ± 9.83
Monounsaturated fats (g/d)	41.32 ± 14.44	41.84 ± 13.85	41.14 ± 14.97	40.81 ± 14.44
Polyunsaturated fats (g/d)	13.73 ± 5.85	13.98 ± 6.01	13.56 ± 5.87	13.61 ± 5.52
Following a special diet, *n* (%)	1181 (7.4)	277 (4.7)	500 (8.0)	404 (10.9)
Snacking between meals, *n* (%)	5458 (34.4)	2322 (39.4)	2110 (33.7)	1026 (27.6)
Supplement use, *n* (%)	2964 (18.7)	997 (16.9)	1210 (19.3)	757 (20.4)
MDS components				
Monounsaturated/saturated ratio	1.23 ± 0.34	1.11 ± 0.21	1.27 ± 0.34	1.45 ± 0.38
Fruit consumption (g/d)	276.03 ± 294.46	194.48 ± 218.52	295.45 ± 280.01	429.83 ± 344.09
Vegetable consumption (g/d)	465.05 ± 338.83	347.98 ± 235.67	491.10 ± 330.74	650.65 ± 382.32
Cereal consumption (g/d)	81.51 ± 71.25	74.61 ± 67.04	85.74 ± 71.97	107.16 ± 71.70
Legume consumption (g/d)	20.64 ± 17.87	16.62 ± 16.95	20.64 ± 17.87	25.20 ± 18.20
Fish consumption (g/d)	85.12 ± 59.28	65.67 ± 46.76	92.50 ± 61.34	119.97 ± 59.42
Meat consumption (g/d)	170.48 ± 78.49	192.02 ± 77.78	166.32 ± 78.04	144.55 ± 71.54
Dairy consumption (g/d)	131.11 ± 196.94	233.02 ± 220.17	112.97 ± 179.71	62.92 ± 114.48
Alcohol intake (g/d)	6.37 ± 9.54	5.03 ± 9.65	6.54 ± 9.31	8.22 ± 9.41

Values are presented as mean ± SD for continuous variables and as frequencies *n* (%) for categorical variables. T1, T2, and T3 represent, respectively, the first, second, and third tertiles of adherence in MDS. High psychological distress was defined as a self-reported medical diagnosis of depression, anxiety, or stress at recruitment.
Abbreviations: MDS, Mediterranean diet score; MET, metabolic equivalent of task; SUN, Seguimiento Universidad de Navarra.

likely to be never-smokers (45.3%) or engage in snacking between meals (27.6%) as compared with those in T1. Notably, individuals in T3 showed a higher prevalence of hypertension (11.1%), dyslipidemia (21.9%), higher psychological distress (12.5%), and use of supplements (21.3%) at baseline, whereas T1 participants exhibited a lower proportion of short (4.7%) and a higher proportion of long (14.8%) sleep durations. Regarding nutritional intake, T3 participants exhibited a higher carbohydrate (276.8 ± 80.5 g/d) and protein (108.2 ± 26.0 g/d) intake, alongside significantly lower saturated fat consumption (27.4 ± 9.8 g/d). Furthermore, T3 reflected the highest adherence to the MedDiet, characterized by peak intakes of fruits, vegetables, cereals, legumes, and fish, alongside a superior monounsaturated-to-saturated fat ratio. Conversely, this group presented the lowest consumption of meat and dairy (Table 1).

The distribution of the MDS followed a normal curve, with a mean of 4.12 (SD: 1.73) (Supplemental Figure 3). Pairwise correlations between dietary components were generally low to moderate ($r < 0.30$), with the highest correlation observed between fruit and vegetable intake ($r = 0.26$) and MUFA:SFA ratio and dairy ($r = 0.28$) with MDS, confirming no significant collinearity issues (Supplemental Figure 4).

Main findings

The longitudinal assessment revealed varying inverse associations between MedDiet adherence and the incidence of the evaluated conditions. A significant inverse association was observed for rheumatoid arthritis, where participants in the highest tertile (T3) had a 51% lower risk of developing the condition in the baseline multivariable-adjusted model compared with the lowest tertile (HR = 0.49; 95% CI: 0.30, 0.80; *P*-trend = 0.013). This inverse association was consistently maintained in the repeated-measures analysis updating diet over follow-up (HR = 0.53; 95% CI: 0.32, 0.89; *P*-trend = 0.020). For psoriasis, higher adherence (T3 compared with T1) showed a nonsignificant reduction in risk in both multivariable-adjusted baseline models (HR = 0.77; 95% CI: 0.50, 1.17; *P*-trend = 0.299) and repeated-measures analyses (HR = 0.86; 95% CI: 0.57, 1.32; *P*-trend = 0.491) (Figure 1).

These findings are further supported by the Nelson–Aalen cumulative hazard curves (Figure 2), which depict a separation of risk trajectories across adherence tertiles over the follow-up period, with the highest baseline adherence group (T3, green line) displaying lower cumulative hazards compared with the lowest adherence group (T1, red line). This risk curve separation was particularly pronounced for rheumatoid arthritis, reflecting a sustained long-term inverse association, whereas a more modest separation was observed for psoriasis. In restricted cubic splines based on repeated measures, modeled with 3 knots located at the 10th (2 points), 50th (4 points), and 90th (6 points) percentiles of the MDS, a statistically significant linear dose–response relationship was confirmed for rheumatoid arthritis (*P*-overall = 0.009; *P*-nonlinearity = 0.165), where higher MDS scores were monotonically associated with lower HRs. For psoriasis (*P*-overall = 0.924; *P*-nonlinearity = 0.926), repeated-measures dose–response curves demonstrated inverse linear trajectories without statistical significance (Figure 3).

Subgroup and sensitivity analysis

Repeated-measures subgroup analyses showed no significant interaction tests across strata (all *P*-interaction >0.05), indicating no evidence of statistical effect modification by sex, age, or smoking status. Sensitivity analyses confirmed the consistency of the primary findings (Figure 4). For rheumatoid arthritis, the repeated-measures inverse association with high MedDiet adherence (T3 compared with T1) remained stable across most sociodemographic and lifestyle strata. Repeated-measures sensitivity exclusions (such as excluding cases <5 y, baseline comorbidities, or adding adjustments) consistently showed statistically significant point estimates for rheumatoid arthritis (HRs range: 0.51–0.77), maintaining statistical significance across nearly all scenario analyses except when excluding pregnant women or participants with baseline depression. For psoriasis, repeated-measures subgroup and sensitivity analyses consistently reflected nonsignificant inverse associations across all evaluated strata and exclusion scenarios (Figure 4).

Accounting for all-cause mortality as a competing risk using Fine–Gray subdistribution hazard models yielded consistent results (Supplemental Table 1). In multivariable-adjusted competing risk analyses, high MedDiet adherence (T3 compared with T1) remained significantly inversely associated with rheumatoid arthritis risk [subdistribution HR (SHR) = 0.52; 95% CI: 0.32, 0.85; *P*-trend = 0.012]. Similarly, nonsignificant inverse trends persisted for psoriasis (SHR = 0.74; 95% CI: 0.49, 1.11; *P*-trend = 0.198), suggesting that potential informative censoring due to death did not materially alter the primary estimates.

To evaluate individual dietary components under repeated-measures assessment, exploratory item-by-item analyses of the MDS were conducted (Figure 5). Lower meat consumption was the individual component most strongly associated with lower rheumatoid arthritis risk (HR = 0.41; 95% CI: 0.27, 0.61; *P*-adj < 0.001), followed by higher intake of fruits and nuts (HR = 0.64; 95% CI: 0.43, 0.95), which, however, did not retain statistical significance after correction for multiple testing (*P*-adj = 0.115). In minus-one analysis, omitting meat products produced a 15.7% attenuation of the inverse estimate (HR = 0.81; 95% CI: 0.66, 0.99; *P*-adj = 0.041). In sequential analysis, removing meat products (HR = 0.81; 95% CI: 0.66, 0.99; *P*-adj = 0.235) and cumulatively removing meat products and fruits/nuts (HR = 0.87; 95% CI: 0.71, 1.06; *P*-adj = 0.304) led to nonsignificant inverse estimates after multiple testing adjustment. For psoriasis, individual component analysis showed a nominal inverse association for high vegetable intake (HR = 0.72; 95% CI: 0.52, 0.99); however, after applying Simes' procedure for multiple testing correction, this association was not statistically significant (*P*-adj = 0.418), consistent with the nonsignificant findings for the overall dietary score (Figure 5).

Discussion

In this large prospective cohort of Spanish university graduates, we observed an inverse association between MedDiet adherence and the incidence of rheumatoid arthritis, whereas the association for psoriasis remained nonsignificant. High MedDiet adherence was significantly associated with a lower risk of incident rheumatoid arthritis, maintaining consistency across baseline and repeated-measures models. Overall, these findings highlight adherence to the MedDiet as a relevant, modifiable lifestyle pattern associated with a lower incidence of rheumatoid arthritis.

Our findings align with and extend the growing body of evidence supporting the potential immunomodulatory role of the MedDiet pattern. A recent meta-analysis by Hu et al. [9], pooling 6 studies including data from the UK Biobank, demonstrated a significant inverse association between highest compared with lowest MedDiet adherence and rheumatoid arthritis risk, with a pooled odds ratio (OR) of 0.838 (95% CI: 0.758, 0.926). Similarly, Song et al. [25], also using UK Biobank data from 109,565 participants, reported an HR of 0.73

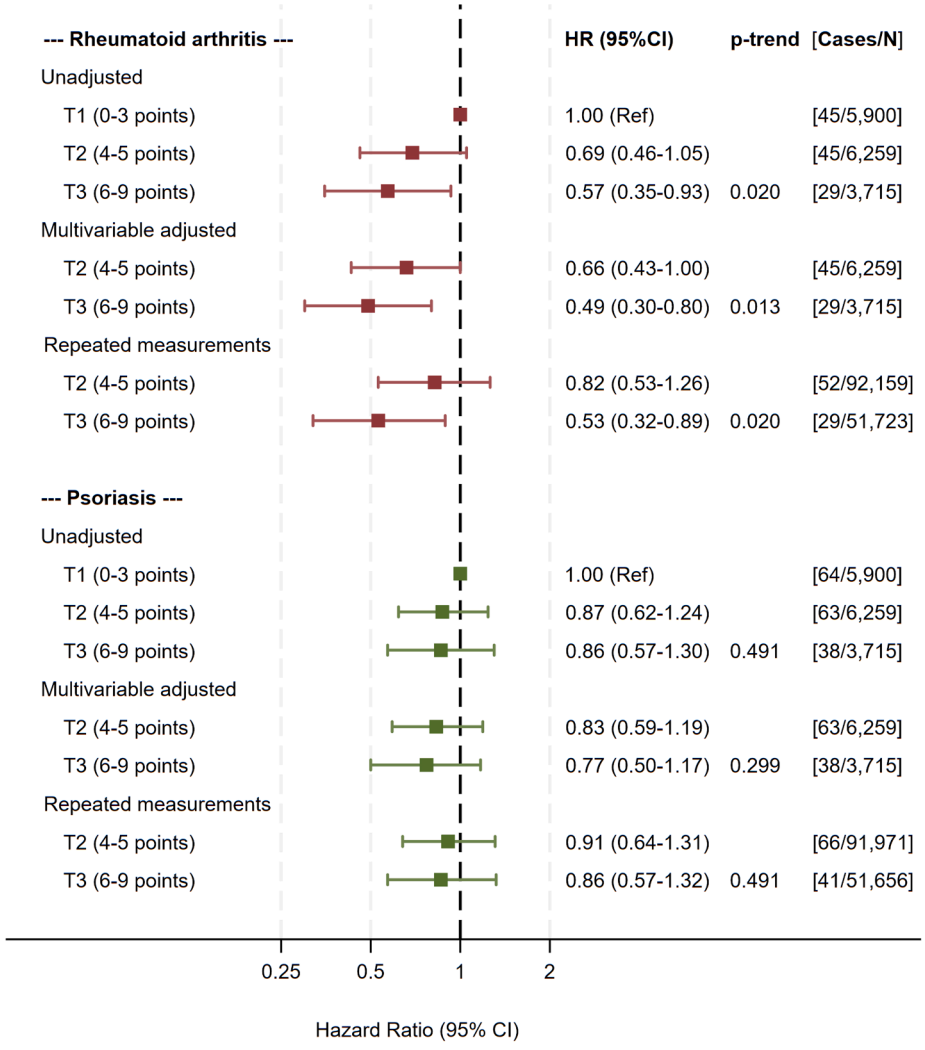


FIGURE 1. Association between adherence to the MedDiet and the incidence of rheumatoid arthritis and psoriasis. Baseline and repeated-measures analyses in the SUN Project. HR and 95% CI compare upper tertiles (T2: 4–5 points; T3: 6–9 points) against the lowest tertile (T1: 0–3 points; reference category, HR = 1.00) of adherence to the MedDiet, estimated using Cox proportional hazards regression models. Results are color-coded by outcome, where maroon represents rheumatoid arthritis and green represents psoriasis. In the plot, squares represent point estimates (HR), horizontal error bars denote 95% CIs, and the vertical dashed line at HR = 1.00 indicates the null effect. Baseline dietary adherence was evaluated using energy-adjusted MDS tertiles calculated via the residual method, whereas repeated-measures analyses evaluated exposure using the cumulative mean intake calculated from baseline, 10-y, and 20-y follow-up dietary assessments using multivariable Cox models to better represent long-term dietary habits and reduce measurement error. Consequently, case distributions across tertiles differ between baseline and repeated-measures analyses because exposure in repeated assessments was defined by calculating the cumulative mean of the continuous MDS across $\leq$3 evaluations before tertile reclassification, allowing participants' adherence classifications to shift over follow-up as updated dietary data were incorporated. All multivariable-adjusted and repeated-measures models were stratified by age (10-y categories) and follow-up period and adjusted for sex, university education, smoking status (pack-years), BMI, special diet adherence, snacking between meals, physical activity (METs-h/wk), television viewing time, and sleep duration. Reported *P* values (*P-trend* adj.) were corrected for multiple testing using the Benjamini–Hochberg FDR procedure (Simes method); because of rank-based adjustment and monotonicity correction, different raw *P* values may yield identical adjusted *P* values. Sample sizes are presented as cases/participants n for baseline analysis and cases/total person-years for repeated-measures analysis. Post hoc statistical power was evaluated for Cox regression models using Stata's power cox procedure ($\alpha = 0.05$, 2-sided), yielding 97.3% for rheumatoid arthritis and 38.9% for psoriasis. CI, confidence interval; FDR, false discovery rate; HR, hazard ratio; MDS, Mediterranean diet score; MedDiet, Mediterranean diet; MET, metabolic equivalent of task; Ref, reference category; SUN, Seguimiento Universidad de Navarra.

(95% CI: 0.63, 0.84) for rheumatoid arthritis when comparing the 90th with the 10th percentile of MedDiet adherence, identifying a 66-metabolite score that reflects the biological response to the MedDiet. This signature was found to mediate 22.4% of the association between diet and rheumatoid arthritis risk. The findings for psoriasis differed, showing only a nonsignificant inverse association. Recent clinical evidence from the MEDIPSO (Mediterranean Diet and Patients With Psoriasis) randomized trial (2025) underscores the therapeutic potency of this pattern. In that intervention, patients with mild-to-moderate psoriasis followed a 16-wk dietitian-guided

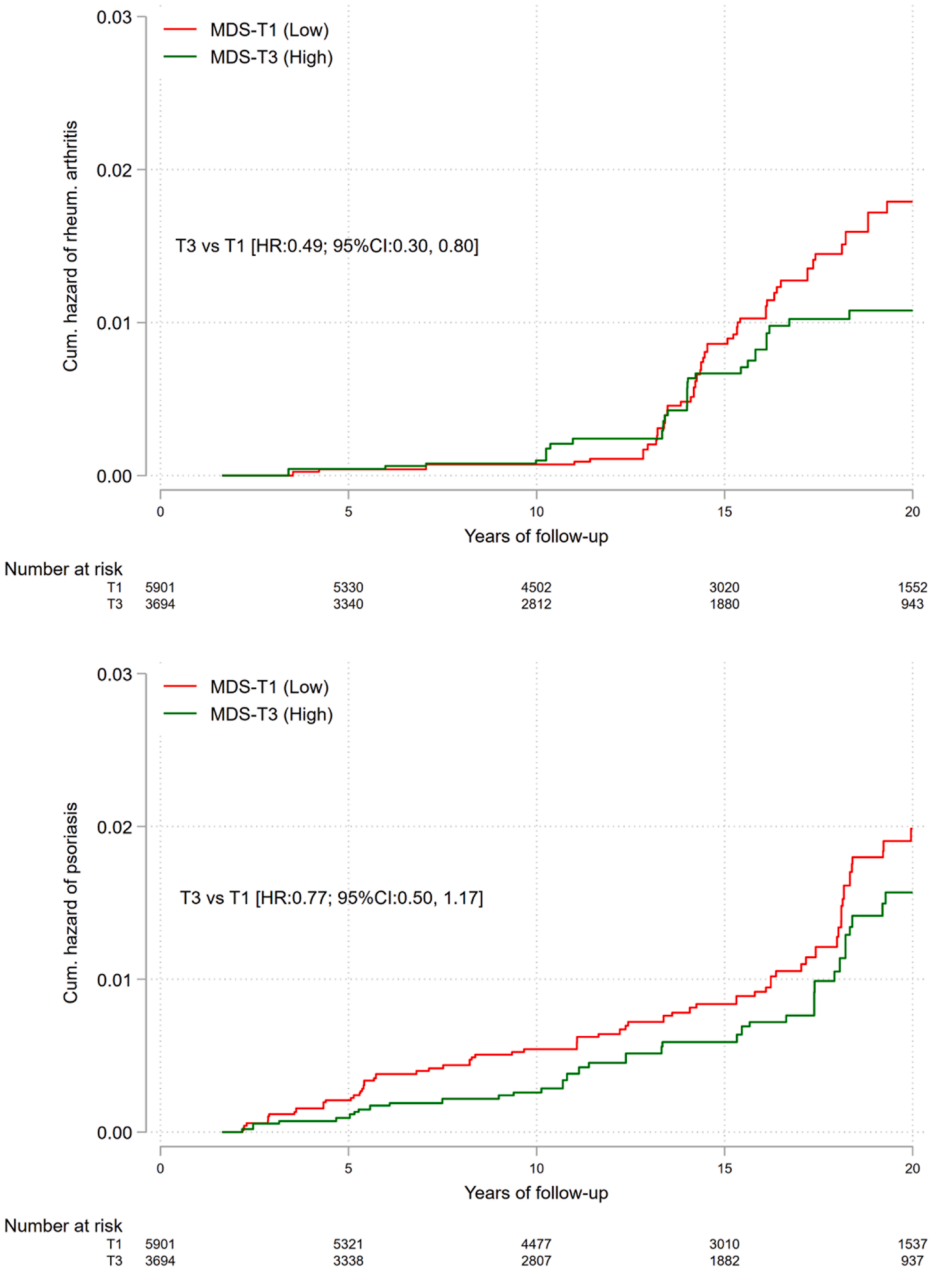


FIGURE 2. Nelson–Aalen curves of cumulative risk of rheumatoid arthritis and psoriasis according to baseline adherence to theMedDiet over the follow-up period. The SUN Project. Nelson–Aalen cumulative hazard curves display risk for rheumatoid arthritis (top panel) and psoriasis (lower panel), categorized by extreme tertiles of baseline adherence to the MedDiet [T1: lowest (0–3 points), T3: highest (6–9 points)]. Baseline exposure was analyzed for these curves because standard nonparametric Nelson–Aalen estimators cannot directly accommodate time-varying exposures or repeated-measures updates. Dietary adherence was assessed using energy-adjusted MDS tertiles, calculated via the residual method. The number at risk at baseline and at 5-y intervals are shown below each graph and reflect the IPW-weighted size of the pseudo-population at each time point. All models were adjusted using IPW for age, follow-up period, sex, university education, smoking status (pack-years), BMI, special diet adherence, snacking between meals, physical activity (METs-h/wk), television viewing time, and sleep duration. CI, confidence interval; HR, hazard ratio; MDS, Mediterranean diet score; MedDiet, Mediterranean diet; MET, metabolic equivalent of task; SUN, Seguimiento Universidad de Navarra.

MedDiet program, which achieved a significant reduction in the Psoriasis Area and Severity Index [10]. The lack of a significant preventive association in our prospective analysis, however, likely stems from differences in disease phenotyping. In the NutriNet-Santé cohort [26], the MedDiet was inversely associated only with severe psoriasis. Notably, for participants with nonsevere psoriasis, their findings (OR: 1.08; 95% CI: 0.93, 1.26) were nonsignificant and closely aligned with our results. In our study, the reliance on all

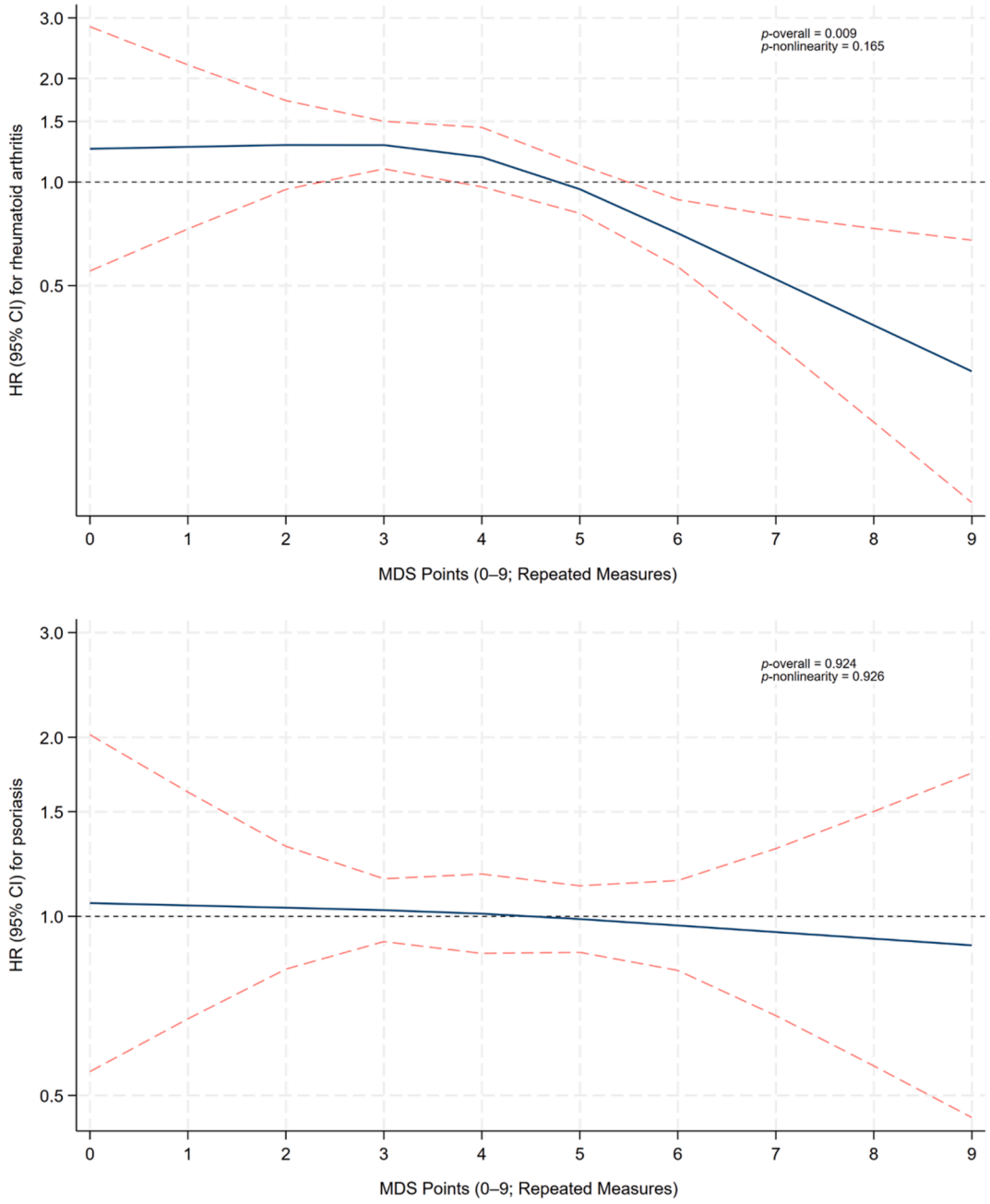


FIGURE 3. Dose–response association between cumulative mean adherence to the MDS and risk of rheumatoid arthritis and psoriasis. The SUN Project. The panels in grid layout illustrate the multivariable-adjusted HR and 95% CI (dashed lines) for the incidence of rheumatoid arthritis (top panel) and psoriasis (lower panel), according to long-term adherence to the MDS, ranging from 0 to 9 points. Associations were evaluated using Cox proportional hazards models based on the cumulative mean intake calculated from baseline, 10-y, and 20-y follow-up dietary assessments to better represent long-term dietary habits and reduce measurement error. The associations were modeled using restricted cubic splines, with 3 knots located at the 10th, 50th, and 90th percentiles of the MDS distribution. Dietary adherence was assessed using energy-adjusted MDS, calculated via the residual method. All models were stratified by age (10-y categories) and follow-up period and adjusted for sex, university education, smoking status (pack-years), BMI, special diet adherence, snacking between meals, physical activity (METs-h/wk), television viewing time, and sleep duration. CI, confidence interval; HR, hazard ratio; MDS, Mediterranean diet score; MET, metabolic equivalent of task; SUN, Seguimiento Universidad de Navarra.

incident cases without clinical data may have diluted the observable association. In subgroup analyses, formal tests for interaction were nonsignificant across all evaluated strata (all P-interaction > 0.05). Although point estimates appeared nominally lower in certain subgroups (such as females, participants with lower physical activity, or ever-smokers for rheumatoid arthritis), the absence of statistically significant interaction indicates no solid evidence of effect modification by sex, age, smoking status, or physical activity.

Our componentwise analysis provided exploratory insights into the relative contributions of individual food groups. The minus-one analysis showed minimal attenuation after removal of individual components, supporting the notion that the overall dietary pattern, rather than isolated foods, drives the observed associations. This is biologically plausible, as plant-based foods are rich in polyphenols and antioxidants that have been shown in experimental models to modulate inflammatory pathways [27,28], whereas red and processed meats

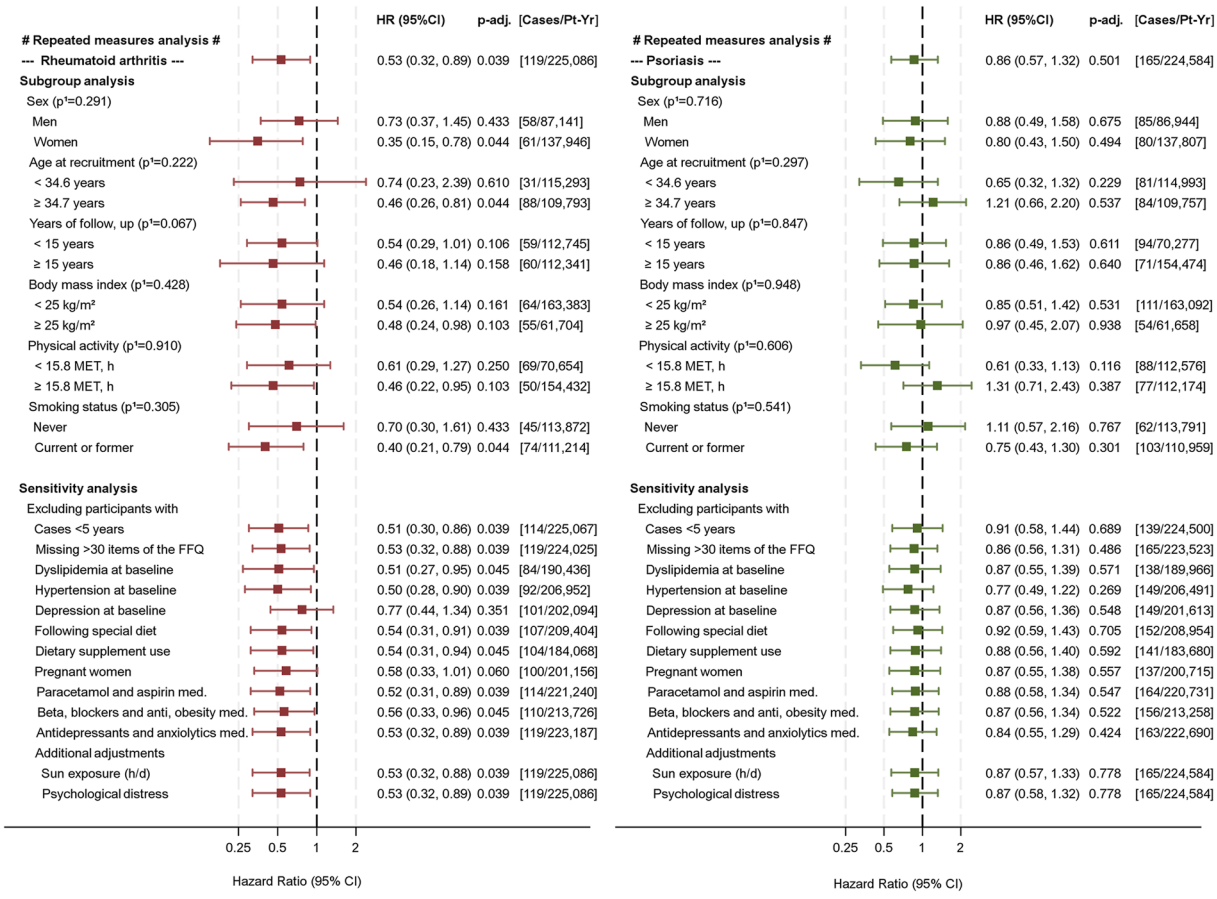


FIGURE 4. Forest plot of stratified subgroup and sensitivity analyses using cumulative mean intake for the association between MDS and the risk of rheumatoid arthritis and psoriasis. The SUN Project. HR and 95% CI evaluate the association between long-term higher adherence to MDS (the highest tertile, T3, vs. the lowest tertile, T1) and the risk of rheumatoid arthritis (maroon) and psoriasis (green), stratified by potential modifiers. Exposure was evaluated using cumulative mean intake from repeated dietary assessments (baseline, 10-y, and 20-y) using multivariable Cox proportional hazards models. For each subgroup, the square represents the point estimate (HR), horizontal lines denote 95% CIs, and sample sizes are presented in brackets as cases/total person-years. *P* values for interaction (P^1) were calculated by adding cross-product multiplicative interaction terms between cumulative MDS tertiles and each categorical subgroup modifier into the multivariable Cox models. Reported *P* values (*P*-adj) refer to T3 vs. T1 and were corrected for multiple testing using the Benjamini–Hochberg FDR procedure (Simes method); because of rank-based adjustment and monotonicity correction, different raw *P* values may yield identical adjusted *P* values. Dietary adherence was assessed using energy-adjusted MDS tertiles, calculated via the residual method. All models were stratified by age (10-y categories) and follow-up period and adjusted for sex, university education, smoking status (pack-years), BMI, special diet adherence, snacking between meals, physical activity (METs-h/wk), television viewing time, and sleep duration. The *x*-axis (HR) is plotted on a logarithmic scale. CI, confidence interval; FDR, false discovery rate; FFQ, food frequency questionnaire; HR, hazard ratio; MDS, Mediterranean diet score; MET, metabolic equivalent of task; SUN, Seguimiento Universidad de Navarra.

contain compounds, such as saturated fats and heme iron, that have been linked to systemic inflammatory responses [29]. Consistent with this, previous analyses from the SUN cohort linked higher red and processed meat consumption and higher Dietary Inflammatory Index scores to increased all-cause mortality, elevated inflammatory biomarkers, and greater cardiovascular disease risk [30,31]. Nevertheless, these component-level findings should be interpreted cautiously because MDS components are intercorrelated, observational data do not support mechanistic inference, and the attenuation observed in the sequential removal analysis may partly reflect reduced score variability and statistical power rather than causal contributions of individual components.

Despite the prospective design and long follow-up of this study, several limitations warrant consideration. First, for psoriasis ($n = 165$; post hoc statistical power = 38.9%), statistical power was limited to detect modest inverse associations. Second, other immune-mediated inflammatory conditions, such as alopecia areata or autoimmune bullous diseases, were not captured because of the structure of the baseline questionnaire. Furthermore, the lack of detailed clinical phenotyping precluded subgroup analyses according to disease subtype, severity, or serological status (e.g., positivity for anti-cyclic citrullinated peptide [anti-CCP] antibodies in rheumatoid arthritis). Incident cases were identified based on self-reported physician diagnoses without secondary medical record validation for these specific outcomes. Although these conditions typically prompt medical consultation because of their substantial impact on quality of life, mild cases may have remained undiagnosed, leading to potential underascertainment of disease incidence. In addition, because a small proportion of participants reported diagnoses of both psoriasis and rheumatoid arthritis, diagnostic misclassification with psoriatic arthritis cannot be entirely ruled out.

Healthy user bias is also possible, as participants with higher MedDiet adherence exhibited a higher baseline prevalence of hypertension and dyslipidemia and reported more frequent supplement

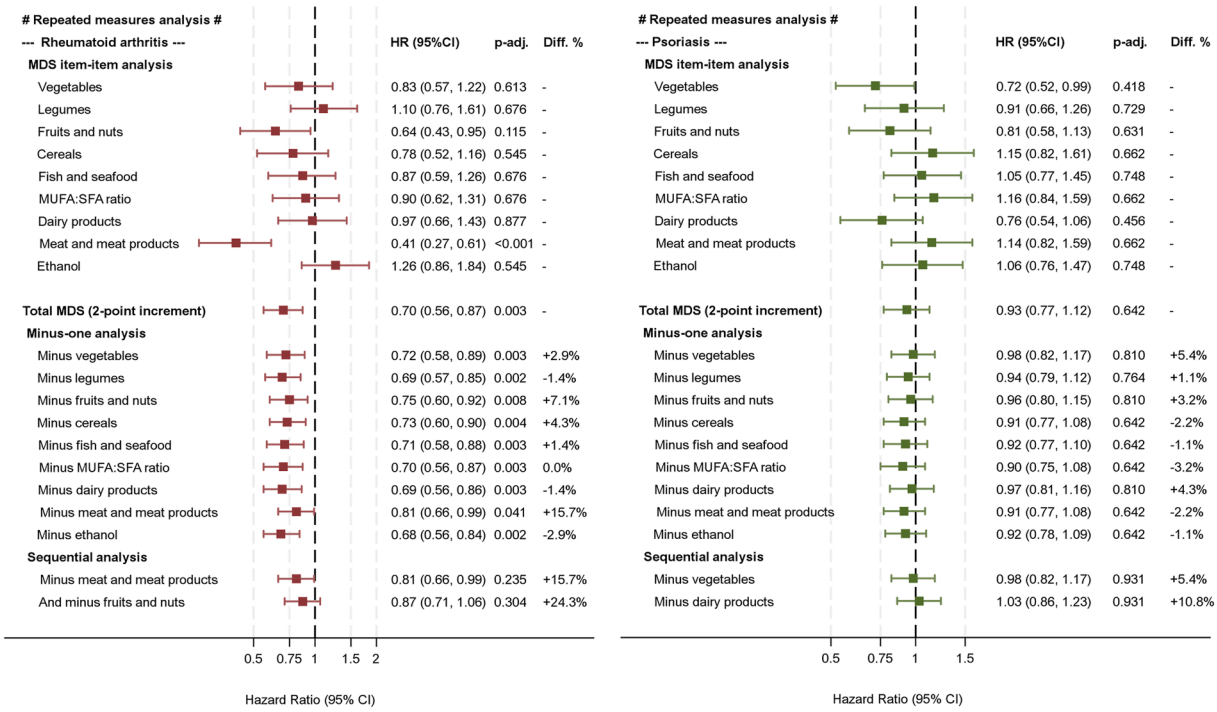


FIGURE 5. Risk of rheumatoid arthritis and psoriasis associated with item-item MDS analysis and alternate component subtraction using cumulative mean dietary intake. The SUN Project. Dietary adherence was assessed using cumulative mean intake of energy-adjusted MDS (calculated via the residual method) from repeated dietary assessments (baseline, 10 y, and 20 y). HRs and 95% CIs were estimated using multivariable Cox proportional hazards models stratified by age (10-y categories) and follow-up period and adjusted for sex, university education, smoking status (pack-years), BMI, special diet adherence, snacking between meals, physical activity (METs-h/wk), television viewing time, and sleep duration. The item-item analysis shows the independent risk associated with rheumatoid arthritis (maroon) and psoriasis (green), with each component (0 vs. 1 point), adjusted for the remaining items of the score and other covariates. The total MDS row represents the risk associated with a 2-point increment in the full 9-point score. The minus-one analysis displays the HR for a 2-point increment in the total score after alternately removing each specific component, with coefficients rescaled to ensure comparability with the original 9-point scale. The Diff. % represents the percentage change in the HR upon the exclusion of specific component(s) from the total MDS score. Positive values indicate an attenuation of the inverse association (i.e., the estimate moves toward the null), whereas negative values suggest an enhancement of the inverse association. The sequential analysis shows the cumulative impact of removing components in descending order of statistical importance (*Z*-scores/largest attenuations), stopping at nullity (HR = 1.00) or when attenuation plateaus. Reported *P* values (*P*-adj.) were corrected for multiple testing using the Benjamini–Hochberg FDR procedure (Simes method); due to rank-based adjustment and monotonicity correction, different raw *P* values may yield identical adjusted *P* values. CI, confidence interval; FDR, false discovery rate; HR, hazard ratio; MDS, Mediterranean diet score; MET, metabolic equivalent of task; SUN, Seguimiento Universidad de Navarra.

use, raising the possibility of dietary modification secondary to baseline health awareness. However, sensitivity analyses excluding participants with major baseline comorbidities yielded consistent results. Detection bias also remains a consideration, as health-conscious individuals with high MedDiet adherence may seek healthcare more frequently, potentially increasing disease detection rates in the exposed group; however, such bias would typically operate toward the null, suggesting our inverse estimates for rheumatoid arthritis are unlikely to be artifactual. Regarding reverse causality, participants with subclinical inflammatory symptoms before diagnosis might have altered their diet toward healthier patterns, which would attenuate HRs toward the null. Reassuringly, sensitivity analyses excluding cases diagnosed within the first 2 and 5 y of follow-up confirmed stable point estimates. Finally, despite extensive adjustment for sociodemographic, dietary, and lifestyle factors, residual confounding cannot be completely excluded in an observational design. However, *E* value calculations indicated that an unmeasured confounder would require a risk ratio of $\geq$3.50 (lower CI limit: 1.81) with both exposure and outcome to fully explain the observed association for rheumatoid arthritis.

The homogeneous educational profile of the SUN cohort has both strengths and limitations. All participants are university graduates, and more than half are healthcare professionals, a profile associated with high-quality questionnaire data, reliable self-reported physician diagnoses, previously validated for other chronic diseases within the cohort [32–35], and low loss to follow-up. This homogeneity likely reduced confounding related to education and socioeconomic status [15]. However, it may limit the generalizability of our findings to populations with different educational or socioeconomic backgrounds. Nevertheless, the consistency of the associations across multiple sensitivity analyses and repeated-measures models supports the robustness of the findings, whereas the component analyses should be interpreted as exploratory.

In conclusion, our findings demonstrate that long-term adherence to the MedDiet is inversely associated with risk of incident rheumatoid arthritis, whereas the association for psoriasis remained inconclusive. These results support dietary recommendations promoting MedDiet patterns as a potential lifestyle component associated with a lower incidence of rheumatoid arthritis. Future prospective cohorts incorporating molecular immunophenotyping and clinical biobanks will be

valuable to further clarify potential underlying mechanisms across distinct autoimmune disease phenotypes.

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Author contributions

The authors' responsibilities were as follows – LM-J, MAM-G, MB-R: designed research, analyzed data, and performed statistical analysis; MAM-G, MB-R: provided essential materials; LM-J: wrote the paper; MAM-G, MB-R, VB-V, ÁG-C, AM-G: reviewed and edited the manuscript; MB-R: took primary responsibility for final content; and all authors: read and approved the final manuscript.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The complete disclosure statements for all authors will be submitted through the Elsevier Declaration of Interests tool during the submission process.

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Data availability

Data described in the manuscript, codebook, and analytic code will be made available upon request pending a reasonable research application and institutional approval. Interested researchers may contact the Department of Preventive Medicine and Public Health at the University of Navarra (Pamplona, Spain) by emailing sun@unav.es for information regarding data access.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Gemini (version 1.5 Pro, Google) in order to support the review, styling, and formatting of technical text and references according to standard journal guidelines. After using this service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2026.101511.

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