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RESEARCH PAPER

Adherence to a Mediterranean diet and leisure-time physical activity are associated with reduced initiation of antidepressant, anxiolytic, antipsychotic and antiseizure drug use in older adults: a cohort study

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Abstract

Background: We explored how adherence to the Mediterranean diet (MedDiet) and leisure-time physical activity (LTPA) impact psychoactive medication use in older adults.
Methods: We assessed the cumulative MedDiet adherence and LTPA's impact on mental health medication initiation in older individuals at high risk of chronic disease. Associations between the cumulative average of MedDiet adherence (per one-point increase in the adherence score) and LTPA (per increase in 20 metabolic equivalents of task-minute/day [METs-min/day]) with drug initiation were assessed by multivariable Cox regressions. We explored non-linear exposure-outcome associations using smoothed cubic splines and the multiplicative interaction between MedDiet and LTPA.
Results: A total of 5940–6896 participants (mean age 67, 58% women) over 4.2–4.7 years, each point increase in MedDiet adherence decreased the initiation of antidepressants by 23–28% (HR 0.72, 95% CI 0.67–0.77), anxiolytics (HR 0.75, 0.70–0.81), antipsychotics (HR 0.77, 0.65–0.91), and antiseizures (HR 0.77, 0.69–0.85). Associations for anxiolytics and antiseizures were strong at low MedDiet adherence levels. Relationships between LTPA and initiation of antidepressants and anxiolytics were linear in the lowest LTPA values (0–150 METs-min/day); every 20 METs-min/day increases were associated with 20% lower risk of initiating antidepressants (HR 0.80, 0.75–0.86) and 15% less risk in anxiolytics (HR 0.85, 0.79–0.90). Association with antiseizures was linear (+20 METs-min/day: HR 0.96, 0.94–0.99), and no associations were found for antipsychotics. High MedDiet adherence (≥10) and LTPA (≥150 METs-min/day) reduced psychoactive drug initiation by 42%–59%. Combination was additive for antidepressants, antipsychotics and antiseizures and synergistic for anxiolytics.
Conclusions: MedDiet and LTPA adherence reduced psychoactive drugs initiation in older adults.

Keywords: Mediterranean diet; leisure-time physical activity; antidepressants; anxiolytics; antipsychotics; antiseizure drugs; older people

Key Points

- Higher Mediterranean Diet (MedDiet) adherence reduced the initiation of psychoactive drugs in older adults.
- Increased leisure-time physical activity (LTPA) lowered the risk of starting antidepressants and anxiolytics.
- Combined high Mediterranean Diet (MedDiet) adherence and leisure-time physical activity (LTPA) reduced psychoactive drug initiation by 42%–59%.

Background

Mental health disorders represent a major burden for patients and society as they are linked to disability [1] and increased mortality [2, 3]. They are increasing across all age, sex and socioeconomic levels [1, 4]. The primary pharmacological treatments for these conditions are antidepressants, anxiolytics, and, to a lesser extent, antipsychotic and antiseizure medications. Older adults (≥65 years old) in European countries show a high prevalence of psychoactive drug use [5, 6]. However, conventional treatments exhibit limited effectiveness and adverse effects [7–9]. Older adults are particularly vulnerable to these effects due to age-related changes in pharmacokinetics, polypharmacy, cognitive impairment and frailty [10]. Nevertheless, these medications remain essential for managing mental health conditions when prescribed appropriately. As a result, there is a growing interest in exploring complementary approaches, such as adopting healthy dietary patterns or engaging in physical activity, to reduce the burden of mental disorders in older adults or, at least, delay and limit the initiation of psychoactive medication use [11, 12].

Lifestyle psychiatry is a complex field, largely due to the potential for reverse causation: an unhealthy lifestyle may increase the risk of mental and neurological disorders, which in turn may lead to a decline in dietary quality and reduced physical activity [13]. In addition, there is a complex interplay between mental health conditions and physical conditions like frailty [14]. However, recent observational prospective studies support the association between a healthy diet such as the Mediterranean diet (MedDiet) and a reduced incidence of depression [15–20]. Regarding anxiety, healthy dietary patterns, including MedDiet, have been associated with a reduced risk of anxiety and distress [18, 21–23]. In parallel, leisure-time physical activity (LTPA) has also been linked to a lower risk of mental disorders in some observational studies [13]. Nonetheless, there is a scarcity of research investigating the association of MedDiet and LTPA with the initiation of psychoactive medication in prospective studies.

The paucity of results is particularly notable for clinical diagnoses of anxiety, psychosis, and epilepsy. In addition, previous evidence has only focussed on linear associations or comparisons between extreme groups of dietary adherence or LTPA and has not explored whether these associations could be non-linear, as is the case for cardiometabolic drugs [24]. An association between MedDiet, LTPA and less initiation of psychoactive drugs would be plausible because both improve several risk factors for psychiatric and mental disorders including oxidative stress, low-grade inflammation, gut microbiome, blood pressure, and metabolic indicators [25–31]. Our study addresses this gap by investigating associations between cumulative adherence to MedDiet and LTPA, both individually and in combination, and the initiation of psychoactive medications in older adults at high risk of chronic disease.

Materials and methods

Study population

This study is an observational, prospective analysis utilising data from participants enrolled in the PREvención con DIeta MEDiterránea (PREDIMED) trial [32]. It was a multicenter, randomised controlled trial conducted in Spain from 2003 to 2010 (www.predimed.es). Its primary aim was to assess the effects of a dietary intervention based on a MedDiet supplemented with extra-virgin olive oil and mixed nuts, compared to a low-fat control diet, on the primary prevention of major cardiovascular events [33]. Eligible participants were women (aged 60–80 years) and men (aged 55–80 years) without cardiovascular disease at enrolment who had type 2 diabetes or at least three of the following: hypertension, high concentrations of low-density lipoprotein cholesterol, low levels of high-density lipoprotein cholesterol, excess weight, smoking and family history of premature coronary disease [32].

We here used the PREDIMED data as an observational prospective cohort. We therefore adjusted all analyses for intervention groups. As described in Figure 1, of the 7447 PREDIMED participants, we first excluded participants with no baseline data on MedDiet adherence ($n = 22$), no data from food frequency questionnaire ($n = 39$), outliers of the MedDiet adherence longitudinal average (<5 points, $n = 14$), outliers of the LTPA longitudinal average (>1000 metabolic equivalents of task-minute per day [METs-min/day], $n = 39$), and no medication use data ($n = 328$). Analyses of initiation of psychoactive drugs were performed in non-users at baseline (we excluded users at baseline in the respective analyses). Our study is presented according the STrengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.

Exposures: Adherence to a Mediterranean diet and leisure-time physical activity

At each visit, adherence to a MedDiet was assessed using the MedDiet adherence score. It was based on 14 dietary traits of the MedDiet, validated for Spanish adults [34]. The consumption of the following items contributed positively: (i) use of olive oil as main fat for cooking/seasoning; (ii) ≥4 tablespoons/day of olive oil, (iii) ≥3 servings/week of mixed nuts (30 g), (iv) ≥2 servings/day of vegetables, (v) ≥3 servings/day of fruit, (vi) ≥3 servings/week of legumes (150 g, boiled), (vii) ≥3 servings/week of fish or seafood, (viii) ≥2 servings/week of 'sofrito'-based dishes (recipes with a base of stir-fried onion, garlic, tomato/pepper, and herbs cooked in olive oil), (ix) wine in moderation (100 ml/day on average, within meals), (x) <1 serving/day of red and processed meat, (xi) preference of poultry and rabbit over red and processed meat, (xii) <1 serving/day of butter, margarine, or cream, (xiii) <1 carbonated or sugar-sweetened beverage/day and (xiv) <2 servings/week of non-homemade pastries or sweets [34].

The estimation of LTPA was conducted using the Minnesota Leisure-Time Physical Activity Questionnaire, validated in both Spanish men and women [35, 36], also at each visit. This questionnaire captured information on the frequency and duration of 67 activities performed by participants over the course of the previous year. LTPA was quantified in METs-min/day by multiplying the METs associated with each activity by its average duration in minutes per day.

Outcomes: Initiation of use of psychoactive drugs

Information on medication use was collected at baseline and annual follow-up (up to seven years of follow-up). Using the list of psychoactive drugs available in Spain (2003–2010) and their Anatomical Therapeutic Chemical codes (Supplementary Data "Appendix 1"), we created binary variables (yes/no) for antidepressant, anxiolytic, antipsychotic, and antiseizure drug use. We defined the incidence of the initiation of use of any antidepressant, anxiolytic, antipsychotic, and antiseizure drug among those who were non-users at baseline. Initiation of use referred to the start of medication that persisted at least three subsequent follow-up visits and drug use was unreported in only one visit between these three [24].

Other variables

Trained professionals gathered baseline data on age (continuous), sex, educational attainment (primary/secondary/higher/unavailable), baseline body mass index (continuous) and baseline smoking status (never/former/current smoker) [32, 33]. A validated 137-item semiquantitative food frequency questionnaire was used to assess alcohol consumption (in grams/day) and energy intake (in kilocalories/day) at baseline [32].

Statistical analyses

The characteristics of the participants were described using means and standard deviations for normally distributed continuous variables, medians and interquartile ranges for non-normally distributed continuous variables, and proportions

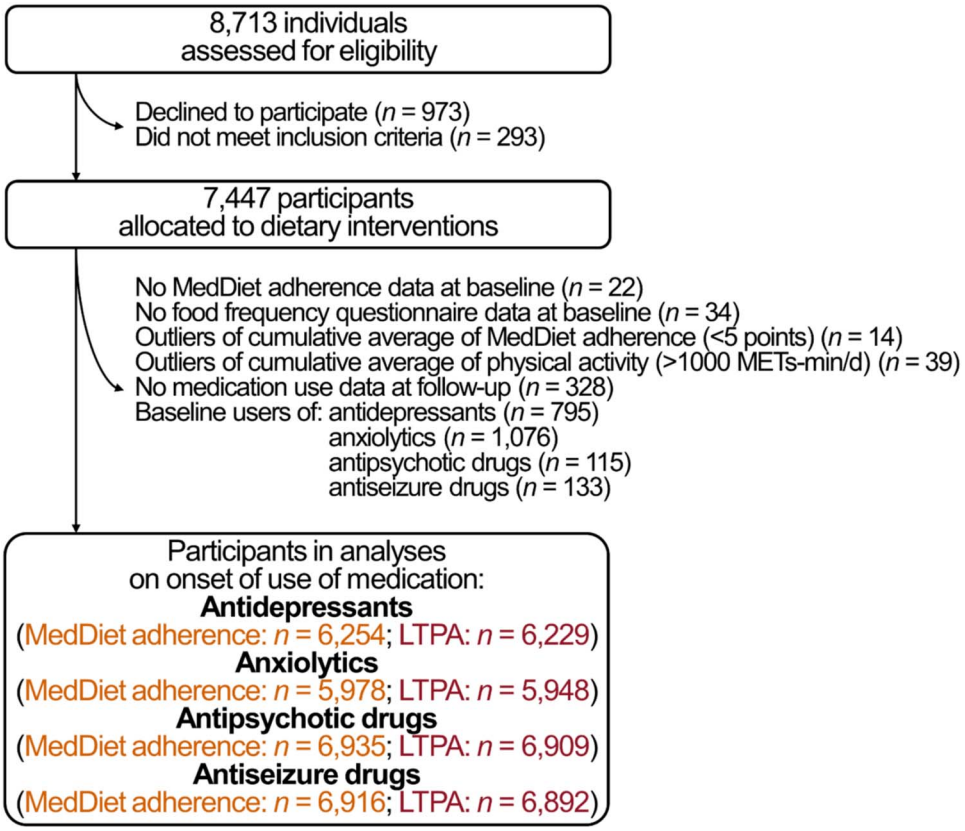

Figure 1. Flow chart.

for categorical variables, overall and across groups defined by MedDiet adherence (low [<10 points] and high [≥10 points]) and by LTPA levels (an arbitrary threshold for low [<100 METs-min/day] and high levels [≥100 METs-min/day]).

We examined the relationships between the cumulative mean of MedDiet adherence or LTPA levels and the risk of initiating psychoactive medication use (as hazard ratios, HR) using Cox proportional hazards regression models. The cumulative mean of MedDiet adherence or LTPA was calculated as the average of all MedDiet adherence scores or LTPA values up until the occurrence of the outcome (incident cases) or the last available study visit (non-cases). The reference cut-point was set at the minimum value for each exposure variable (5 points for MedDiet adherence score and 0 METs-min/day for LTPA). The follow-up time for each event was the time elapsed between the date of entry into the study and the date of the event or end of follow-up (1 December 2010), whichever came first. We assumed that the occurrence of the event is dated at the midpoint between the last visit at which the volunteer was not treated with the medication and the first visit at which the treatment was registered [24, 37, 38]. Analyses were adjusted for sex, recruitment site, educational level (as strata variables), age, smoking habit, body mass index, alcohol consumption, energy intake and intervention group. MedDiet adherence analyses were further adjusted for LTPA at baseline, while the LTPA analyses were further adjusted for MedDiet adherence score at baseline. To address intra-cluster correlations, robust variance estimators were used in all survival analyses considering as clusters the members of the same household [33]. Results were reported as HRs per each 1-point increase in MedDiet score and per each increase in 20 METs-min/day for LTPA. We corrected our findings in linear analyses for multiple comparisons (two exposures × four outcomes = eight comparisons) by the Bonferroni method (P-value threshold <0.00625).

We also examined the potential non-linear relationships between the cumulative mean of MedDiet adherence or LTPA levels and the risk of initiating psychoactive medication use. Initially, we explored whether a model using smoothed cubic splines (with $K + 4$ degrees of freedom) to model the relationship between the exposure and the outcome. We used a likelihood ratio test to assess if this fitted the data better than a simple linear term. When the test was significant, we presented the predicted HRs and their confidence intervals for each value of the exposures graphically [39]. We further reported associations between MedDiet adherence or LTPA and the risk of drug initiation at the lowest part of the curves (after graphic inspection, for participants with MedDiet adherence scores ranging from 5 to 8 points and LTPA levels ranging from 0 to 150 METs-min/day).

Finally, we investigated whether the combination of high MedDiet adherence (≥10 points [40]) and high LTPA levels (≥150 MET-min/day, based on our findings, see below) was associated with a lower risk of drug use initiation, either additively or synergistically. Participants were classified into four groups: (i) low MedDiet adherence + low LTPA levels (reference group); (ii) low MedDiet adherence + high LTPA levels; (iii) high MedDiet adherence + low LTPA levels and (iv) high MedDiet adherence + high LTPA levels. We examined the difference in the risk of drug use initiation for groups 2, 3 and 4 compared to the reference group using Cox proportional hazards regression models. To assess potential synergy, we applied a likelihood ratio test comparing models with and without the interaction term for 'MedDiet adherence × LTPA levels.' A significant interaction would suggest that the combination of the two exposures is associated with a stronger relationship than expected from their independent associations.

We performed the analyses using the 'survival' package in R Software (version 4.3.1).

Results

Study population

The characteristics of the participants at baseline were as follows: average age of 67 years, 58% of them were women, 14% were current smokers, 45% were overweight, 47% were obese and showed moderate values of adherence to a MedDiet (9.6 score points on average) and LTPA (median: 194 METs-min/day) (Table 1). Participants with a high adherence to a MedDiet and high LTPA levels were more likely to be men, to have higher education, lower prevalence of obesity, and slightly higher intakes of energy and alcohol.

The analytical samples were as follows: for antidepressants, $n = 6215$, with a median follow-up of 4.2 years (25 897 person-years) and 7.9% became new users; for anxiolytics, $n = 5940$, with a 4.2-year follow-up (24,717 person-years) and 8.8% became new users; for antipsychotics, $n = 6896$, with a 4.7-year follow-up (28 610 person-years) and 1.1% became new users; for antiseizure medications, $n = 6878$, with a 4.7-year follow-up (28 639 person-years) and 2.8% became new users.

MedDiet adherence and risk of psychoactive drug initiation

A one-point increase in cumulative MedDiet adherence was linearly associated with a 28% lower risk of initiating antidepressant use (HR 0.72, 95% CI 0.67 to 0.78, Figure 2A). The risk of initiating anxiolytics, antipsychotics and antiseizure drugs was better explained by non-linear equations. There was a greater reduction in the risk of starting anxiolytics or antiseizure for each one-point MedDiet score increase in participants with low adherence scores (5–8 points) — a 55% lower risk for anxiolytics (Figure 2B) and a 43% lower risk for antiseizure drugs (Figure 2D). In the case of antipsychotics (Figure 2C), the association between greater MedDiet adherence and a lower risk of initiating such treatment was only observed among participants with greater adherence (8 points or more).

LTPA levels and risk of psychoactive drug initiation

A 20 METs-min/day increases in LTPA were linearly associated with a 4% less risk of initiating antiseizure drugs (HR 0.96, 95% CI 0.94 to 0.99, Figure 3D). The risk of initiating antidepressant and anxiolytic drug use was better explained by non-linear equations. Among participants with the lowest LTPA values (0–150 METs-min/day), 20 METs-min/day increments in LTPA were associated with a 20% reduced risk of initiating antidepressant use (Figure 3A) and a 15% less risk of initiating anxiolytic medication (Figure 3B). No clear associations were found for antipsychotic drugs (Figure 3C).

Combination of MedDiet adherence and LTPA levels and risk of initiation of psychoactive drug use

High levels of MedDiet adherence (≥10 score points) and LTPA (≥150 METs-min/day) combined were associated with lower initiation of psychoactive therapy (relative to participants with low MedDiet adherence and low LTPA levels combined): 59% less risk of initiating antidepressant use (HR 0.41, 95% CI 0.30 to 0.56), 46% less risk of initiating anxiolytics (HR 0.54, 95% CI 0.41 to 0.71), 55% less risk of initiating antipsychotics (HR 0.45, 95% CI 0.21 to 0.95) and 41% less risk of initiating antiseizure therapy (HR 0.58, 95% CI 0.37 to 0.90) (Figure 4). The magnitude of the association of high MedDiet and high LTPA combined was synergistic for anxiolytics (P-value for interaction = 0.076) and additive for antidepressants, antipsychotics, and antiseizure medications.

Discusion

Among older adults at high risk of chronic disease, higher adherence to the MedDiet was associated with a lower risk of initiating the use of antidepressants, anxiolytics, antipsychotics, and antiseizure drugs. Notably, the association for anxiolytics and antiseizure drugs was particularly pronounced among participants with poor adherence to a MedDiet. Our findings also indicate a strong association between slight increases in LTPA (equivalent to 40 minutes/week of brisk walking or Pilates, or 30 minutes/week of dancing or aerobic classes) and lower risk of initiating the use of antidepressants, anxiolytics and antiseizure medication. The magnitudes of the associations were stronger at lower levels of LTPA. Individuals with high levels of both exposures disclosed a particularly strong association with lower risk of initiation of psychoactive drugs, which was synergistic for anxiolytic medication.

Previous studies have highlighted the neuroprotective properties of a traditional MedDiet on mental health. These benefits could be due to its capacity to reduce oxidative stress and low-grade inflammation thanks to its array of bioactive compounds, including antioxidants, unsaturated

Table 1. Baseline characteristics of the study population

	All participants	MedDiet adherence score (cumulative average)			LTPA levels (cumulative average)		
		Low	High	*P*-value	Low	High	*P*-value
Age, years (mean ± SD)	67.0 ± 6.17	67.2 ± 6.25	66.7 ± 6.07)	0.001	67.6 ± 6.50)	66.8 ± 6.05)	<0.001
Females (*n*, %)	4080 (57.8%)	2277 (60.9%)	1803 (54.2%)	<0.001	1277 (75.3%)	2803 (52.2%)	<0.001
Education:				0.001			<0.001
Primary (*n*, %)	5367 (76.0%)	2895 (77.5%)	2472 (74.3%)		1344 (79.2%)	4023 (75.0%)	
Secondary (*n*, %)	1066 (15.1%)	539 (14.4%)	527 (15.8%)		240 (14.1%)	826 (15.4%)	
Higher (*n*, %)	503 (7.12%)	230 (6.16%)	273 (8.21%)		82 (4.83%)	421 (7.85%)	
Not available (*n*, %)	127 (1.80%)	72 (1.93%)	55 (1.65%)		31 (1.83%)	96 (1.79%)	
Tobacco use:				0.001			<0.001
Never smokers (*n*, %)	4345 (61.5%)	2356 (63.1%)	1989 (59.8%)		1194 (70.4%)	3151 (58.7%)	
Ex-smokers (*n*, %)	1733 (24.5%)	848 (22.7%)	885 (26.6%)		293 (17.3%)	1440 (26.8%)	
Current smokers (*n*, %)	985 (13.9%)	532 (14.2%)	453 (13.6%)		210 (12.4%)	775 (14.4%)	
BMI categories:				<0.001			<0.001
<25.0 kg/m^2 (*n*, %)	523 (7.40%)	237 (6.34%)	286 (8.60%)		90 (5.30%)	433 (8.07%)	
25.0–29.9 kg/m^2 (*n*, %)	3207 (45.4%)	1564 (41.9%)	1643 (49.4%)		583 (34.4%)	2624 (48.9%)	
≥30.0 kg/m^2 (*n*, %)	3333 (47.2%)	1935 (51.8%)	1398 (42.0%)		1024 (60.3%)	2309 (43.0%)	
MedDiet adherence, cumulative mean (mean ± SD)	9.63 ± 1.55	8.46 ± 1.07	10.9 ± 0.77	<0.001	9.11 ± 1.54	9.79 ± 1.52	<0.001
LTPA, cumulative mean, METs-min/day (median, 1st-3rd quartile)	194 [104; 324]	168 [83.0; 286]	228 [128; 363]	<0.001	49.7 [22.0; 75.3]	249 [168; 371]	<0.001
Alcohol, g/day (median, 1st-3rd quartile)	1.49 [0.00; 10.4]	1.09 [0.00; 8.84]	4.38 [0.00; 12.4]	<0.001	0.68 [0.00; 5.92]	2.17 [0.00; 11.7]	<0.001
Energy, kcal/day (mean ± SD)	2274 ± 604	2201 ± 609	2356 ± 587	<0.001	2239 ± 633	2285 ± 594	0.009

fatty acids, and prebiotic fibre [28, 41, 42]. Our findings indicate a significant an association between higher adherence to a MedDiet and a lower incidence of initiating antidepressant, anxiolytic, antipsychotic, and antiseizure medications in older adults, with a particularly pronounced association for anxiolytics and antiseizure drugs among those with sustained low MedDiet adherence. Our findings agree with previous evidence of the potentially protective role of MedDiet on depression and anxiety [18–20, 22, 23] and describe for the first time a relationship between MedDiet adherence and lower initiation of anxiolytics, antipsychotics and antiseizure drugs. These observations may be explained by several neuroprotective mechanisms, including reduced neuroinflammation and oxidative stress, enhanced neurotransmitter function, increased brain-derived neurotrophic factor expression, and beneficial epigenetic modifications [43, 44].

Our results have also shown a link between increases in LTPA and a reduced incidence of initiating antidepressant and anxiolytic medications among participants with very low LTPA levels, as well as a relationship with lower initiation of antiseizure medication. These results are consistent with previous evidence, as exercise interventions have been shown to effectively treat symptoms of depression [45], anxiety [46] and epilepsy [47]. In addition, our results suggested a trend towards a lower incidence of initiating antipsychotic medication. Although this trend was not entirely significant, likely due to the low incidence rate in our population (1.1%), it aligns with previous evidence indicating that physical activity is beneficial for improving symptoms of psychotic disorders [48]. However, it should be noted that our results extend beyond previous evidence by showing that modest increases in physical activity—equivalent to a weekly session of 30–50 minutes of mild to moderate intensity exercise—are linked to a lower risk of starting antidepressant or anxiolytic medication, especially in those significantly below the recommended LTPA levels.

Our findings also suggest a synergistic association between a high adherence to MedDiet diet combined with high levels of LTPA and the initiation of anxiolytic drugs,

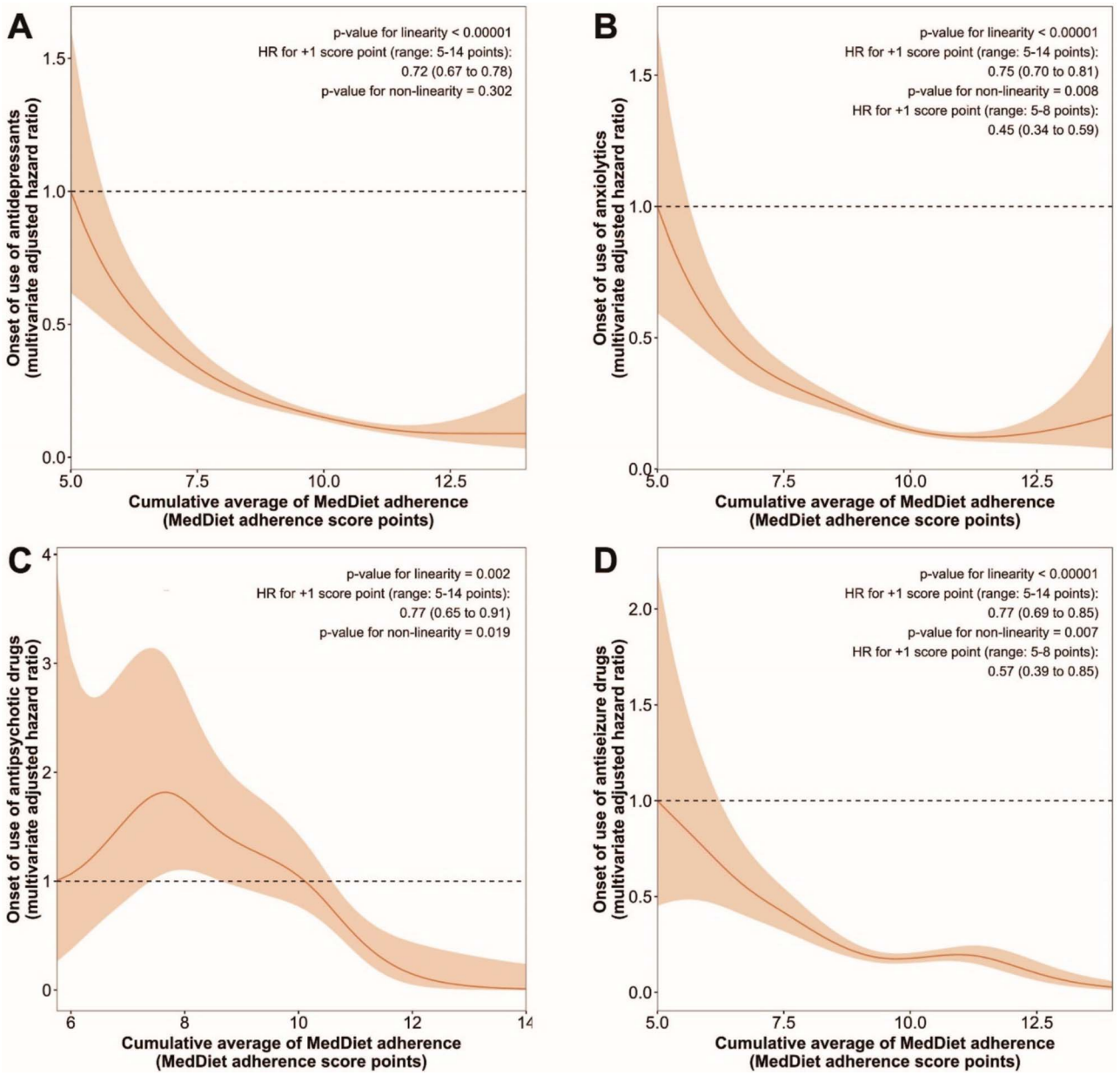

Figure 2. Hazards ratios and confidence intervals of the association between long-term adherence to a MedDiet and the risk of initiating the use of antidepressants (A), anxiolytics (B), antipsychotics (C) and antiseizure medication (D). Cox proportional hazards regression models with smoothed cubic splines were stratified by sex, recruitment site, and educational level, and adjusted for: age, smoking habit, body mass index, alcohol consumption, energy intake, leisure-time physical activity, and PREDIMED intervention group. Robust variance estimators were used to account for intra-cluster correlations.

as well as an additive relationship with the initiation of antidepressants, antipsychotics, and antiepileptic drugs. A healthy diet combined with physical activity has been linked to enhanced mental wellbeing [49], particularly in terms of depression [50] and improved symptoms of psychosis [51]. Regarding medication, their combination has been associated with reduced initiation of use of cardiovascular drugs in older adults [24]. However, to the best of our knowledge, this is the first study to report similar findings in relation to mental health medications and a potentially synergistic benefit regarding anxiety. The shared protective effects of the MedDiet and LTPA at the biochemical level—such as reducing oxidative stress, lowering low-grade inflammation, and other metabolic benefits—may explain the particularly strong association with a reduced likelihood of initiating psychoactive medication in people who adhere highly to both.

We acknowledge some limitations in our study. Firstly, our analyses were based on data from the PREDIMED trial, which primarily focussed on dietary intervention and did

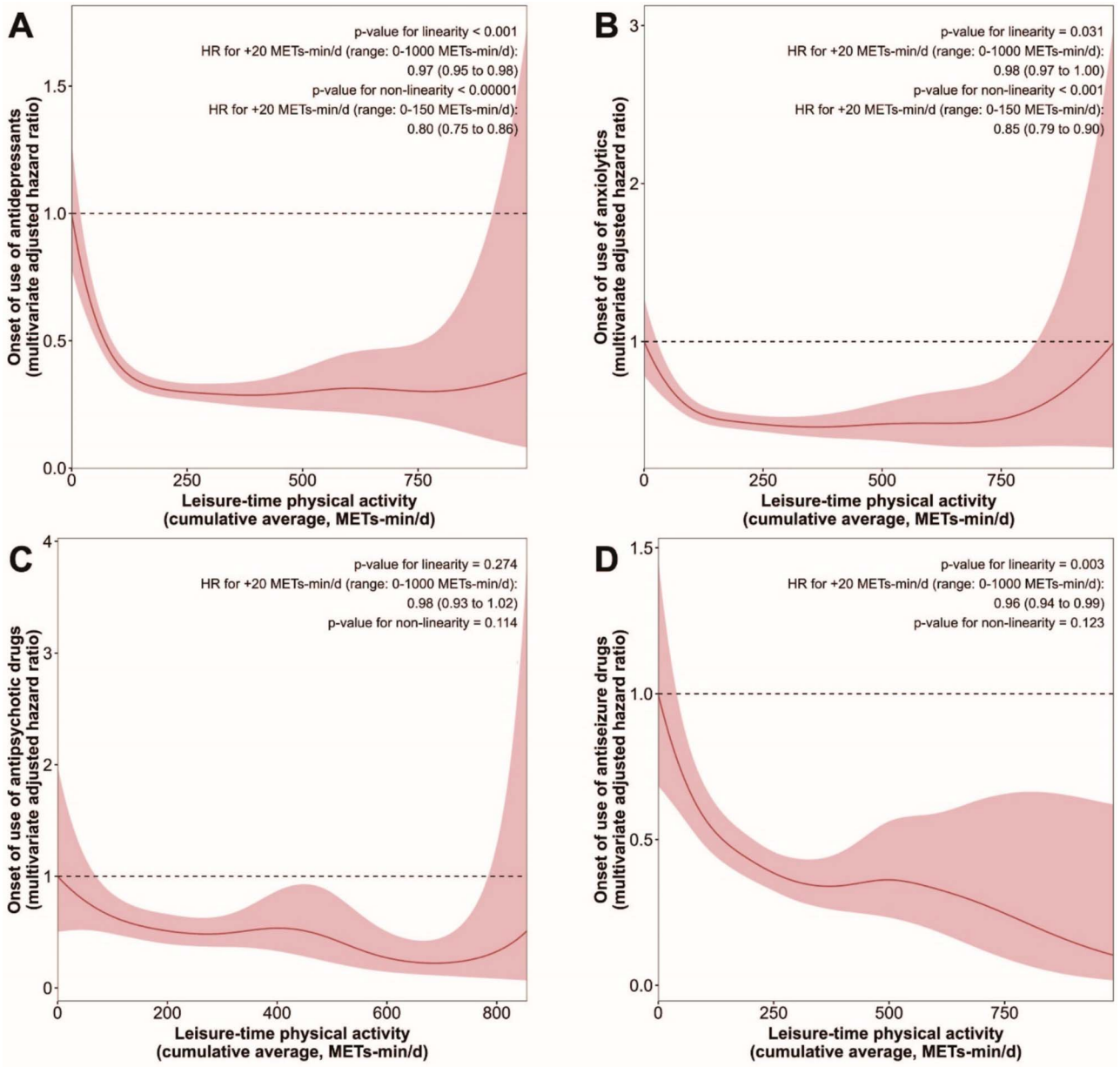

Figure 3. Association between long-term levels of leisure-time physical activity and the risk of initiating the use of antidepressants (A), anxiolytics (B), antipsychotics (C) and antiseizure drugs (D). Cox proportional hazards regression models with smoothed cubic splines were stratified by sex, recruitment site, and educational level, and adjusted for: age, smoking habit, body mass index, alcohol consumption, energy intake, adherence to a MedDiet, and PREDIMED intervention group. Robust variance estimators were used to account for intra-cluster correlations.

not include specific advice on LTPA. As a result, we treated the data as a cohort study, adjusting all our analyses for the intervention group. This design prevents the establishment of causal relationships between adherence to the MedDiet, LTPA and the initiation of psychoactive medication; therefore, we have only described associations in our study. The use of cumulative averages of MedDiet adherence and LTPA levels as exposure variables, rather than a single baseline measurement, helped reduce measurement error, better reflect long-term exposure, and is a strength of the study. Secondly, due to the available data, we could only collect categorical information regarding drug use, preventing us from studying dose changes or other aspects of medication use. Thirdly, the initiation of psychoactive-related therapy was not a predetermined endpoint in the PREDIMED study and there was no standardisation of treatments. Variability in follow-up intervals could affect the detection and timing of initiation. Fourthly, main exposures and certain covariates, such as alcohol and energy intake, relied on self-reported data, which introduces the possibility of misclassification. Fifth, despite adjusting for a wide range of confounders, residual confounding from unmeasured measured factors

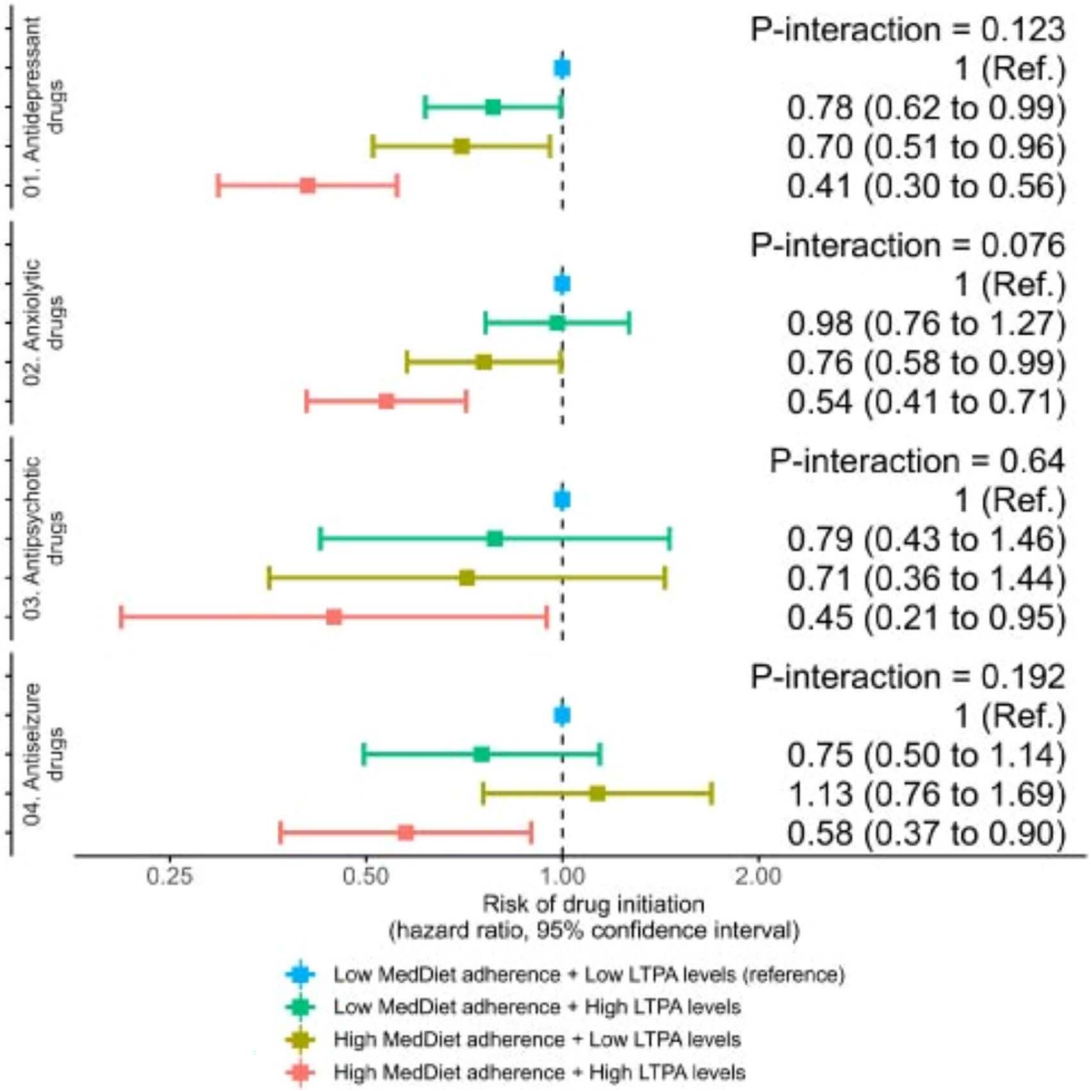

Figure 4. Levels of MedDiet adherence and leisure-time physical activity and risk of initiating psychoactive drugs.

such as economic status, stress levels, social support, connectedness, environmental factors and genetic predisposition may have influenced our findings. Lastly, our conclusions are specifically applicable to older adults at high risk of chronic disease and may not be generalizable to other populations, as this group typically undergoes more intensive medical monitoring and has a greater burden of comorbidities and polypharmacy.

Conclusions

In a cohort of older adults at high risk of chronic disease, our results showed that both higher adherence to the MedDiet and higher LTPA levels were associated with a lower incidence of initiating common psychoactive medication, both isolated and combined. These findings highlight the potential of a healthy diet and regular physical activity to enhance mental health and neurological outcomes among older individuals. Our work sets the stage for future randomised controlled trials to assess the effectiveness of MedDiet and physical activity interventions in preventing the onset of depression, anxiety, psychotic disorders, and seizures, particularly given the high prevalence and disabling nature of these conditions in older adults, along with their associated economic burden.

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Supplementary Data: Supplementary data is available at *Age and Ageing* online.

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Data Availability: The dataset analysed during the current study cannot be made publicly available due to national data regulations and ethical considerations, including the absence of explicit written consent from study participants to make their deidentified data available upon study completion. However, data described in the manuscript will be provided to bona fide investigators for collaboration upon request and approval. Requests can be made by sending a letter to the PREDIMED Steering Committee (predimed-steering-committee@googlegroups.com).

Code for data management and analysis is available in https://github.com/alvarohernaez/MedDiet_LTPA_psychoactive_drugs.

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