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ORIGINAL ARTICLE

# Adipokines and satiety hormones and incidence of Alzheimer's disease and dementia in older adults: a nested case-control study

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**Abstract** Obesity is known to have an intricate relationship with the development of Alzheimer's disease and dementia (mid-life obesity increases risk, whereas late-life adiposity may also have an effect). In this context, adipokines and satiety signals are suggested to play a role in late life, but their association with the incidence of these outcomes remains unclear. Our study aimed to assess whether five selected plasma adipokines and satiety hormones (leptin, ghrelin, resistin, adipsin, and fibroblast growth factor-21) were associated with incident Alzheimer's disease and dementia in older adults at high cardiovascular risk in a nested case-control study within the PREDIMED trial (90 dementia cases [73 of which were Alzheimer's disease], 156 controls). Participants were at high cardiovascular disease risk but free from dementia at baseline. Associations with biomarkers were assessed using multivariable conditional logistic regression. Higher resistin levels were associated with

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higher incidence of Alzheimer's disease in the multivariable-adjusted model (per one SD increase: OR 1.56, 95% CI 1.02 to 2.38); additional adjustment for body mass index slightly attenuated the association (OR 1.52, 95% CI 0.99 to 2.34). Our findings should be replicated in larger prospective studies but suggest that, despite the complex association between anthropometric measures and the incidence of dementia, high levels of resistin were tentatively associated with greater odds of incident Alzheimer's disease in older adults at high cardiovascular risk.

**Keywords** Resistin · Complement factor D · Fibroblast growth factor-21 · Dementia, Alzheimer's disease

## Introduction

Rates of dementia, particularly Alzheimer's disease (AD), are rising worldwide, largely in parallel with longer life expectancy [1]. Vascular health matters in dementia prevention, since patients with cardiovascular disease or its risk factors have a higher risk of dementia [2, 3]. Adiposity is one such risk factor [4, 5], yet its impact on the central nervous system is controversial and age-dependent. Mid-life obesity is associated with elevated dementia and AD risk, whereas later-life excess weight is apparently neutral or even inversely associated; nonetheless, central (visceral) adiposity measured as waist circumference (WC) remains associated with greater dementia risk at any age [6–9]. This apparently paradoxical relationship in later life may partly reflect reverse causation, because declining body weight can precede dementia diagnosis, together with age-related changes in body composition that are not adequately captured by body mass index (BMI) [10]. From a geroscience perspective, aging is also accompanied by adipose tissue dysfunction, chronic low-grade inflammation, and impaired metabolic and vascular homeostasis, which may reduce physiological resilience and increase vulnerability to cardiometabolic and neurodegenerative disease [11]. Anthropometric measures alone may therefore provide an incomplete representation of metabolic health in older adults. Age, timing, and body compartment thus modulate risk, suggesting the

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need for prospective data that consider both anthropometry and metabolic signals together. Circulating adipokines and satiety hormones may provide complementary information on age-related adipose tissue function, inflammatory activity, and metabolic regulation that is not captured by BMI or WC alone. Low leptin and high resistin levels have been observed among individuals with dementia, and low leptin has also been linked to a higher prospective risk of the condition, whereas evidence for other adipokines and ghrelin is inconclusive [12–15]. Adipsin, another complement-derived adipokine, was recently reported to be elevated in women with established AD [16], yet its prospective relevance is unknown. Other adipokines/hepatokines such as fibroblast growth factor-21 (FGF-21) have also shown neuroprotective effects in preclinical AD models [17]. The Spanish Prevención con Dieta Mediterránea (PREDIMED) randomized trial provides an opportunity to gain further insight into this gap. Among older adults at high cardiovascular risk but dementia-free at baseline, we examined whether five pre-defined plasma adipokines/satiety hormones (leptin, ghrelin, resistin, adipsin, and FGF-21) were associated with incident all-cause dementia and AD. These five biomarkers were selected a priori and pre-specified before the biomarker-outcome analyses, based on their complementary representation of metabolic and adipose-tissue signaling pathways potentially relevant to neurodegeneration: leptin and ghrelin are major regulators of appetite, satiety, and energy balance; resistin has been linked to systemic inflammatory activity; adipsin is an adipose-derived component of the alternative complement pathway; and FGF-21 is a metabolic stress hormone and adipokine/hepatokine with proposed neuroprotective actions [18–21].

## Methods

### Study design and participants

This research was conducted within the PREDIMED dietary randomized trial, which enrolled men aged 55–80 years and women aged 60–80 years who were free of cardiovascular disease and dementia at baseline but had type 2 diabetes or at least three additional risk factors: smoking, excess adiposity, hypertension, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, or family history of premature cardiovascular disease [22]. For the present work, we performed a nested case-control study with 95 incident dementia cases (73 AD) with stored plasma samples and 158 matched controls (same sex, ± 3 years of age, with equal or longer follow-up; further details in Fig. 1). Our study is presented following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies (checklist available in Supporting Information).

### Quantification of adipokines and satiety hormones

Fasting EDTA-K3 plasma had been collected at baseline and stored at −80 °C until analysis (under continuous temperature monitoring to prevent temperature drops). Leptin, ghrelin, resistin, and adipsin were quantified using the Bio-Plex Pro Human Diabetes

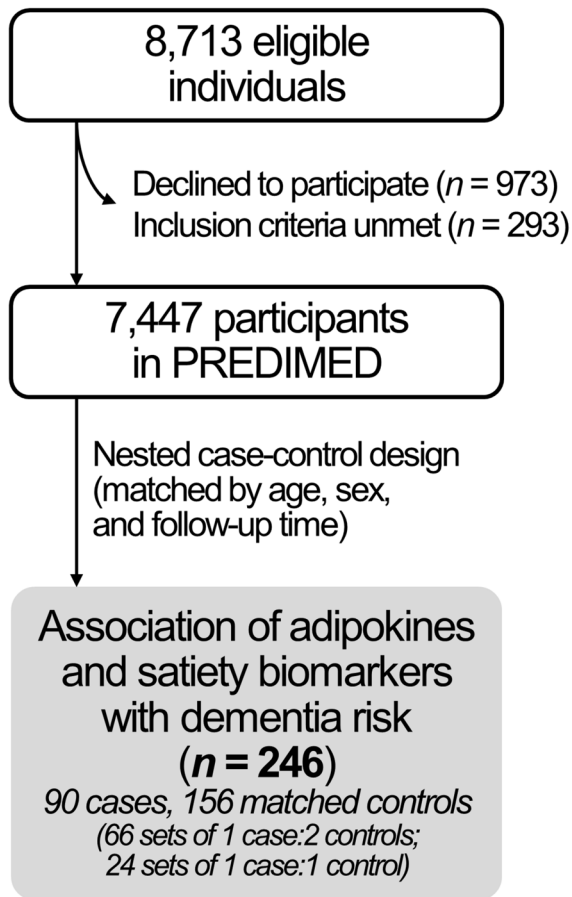



**Fig. 1** Flow chart

10-Plex Assay in a Bio-Plex® 200 system (Bio-Rad, CA, USA), and FGF-21 with a commercial enzyme-linked immunosorbent assay (Quantikine® Human FGF-21 Immunoassay; R&D, MN, USA). Samples had never been thawed before the present assays. All samples from each matched set were analyzed in the same run by technicians blinded to case-control status (to minimize the influence of between-run variability on within-set comparisons). Each run included an in-house reference plasma to monitor analytical variability. The inter-assay coefficients of variation for the biomarkers were as follows: 5.2% for leptin, 11.5% for ghrelin, 17.4% for resistin, 10.6% for adipsin, and 6.4% for FGF-21.

### Outcome

The composite dementia endpoint comprised AD [23], dementia with Lewy bodies [24], frontotemporal lobar degeneration [25], vascular dementia [26], and normal-pressure hydrocephalus [27]. Potential cases were detected through study visits, contacts with primary care physicians, medical records, and linkage to the National Death Index. Diagnoses between October 1, 2003, and June 30, 2012, that were blindly adjudicated by an independent Clinical Committee were considered for our analyses (median follow-up 6.2 years). Three of 11 participating study centers were excluded because systematic dementia surveillance had not been performed.

### Covariates

Trained staff collected baseline data on age, sex, educational level (primary, secondary or higher), smoking status (never, former, current), anthropometry (weight, height), and major cardiovascular risk factors (type 2 diabetes, hypercholesterolemia, hypertension) using standardized questionnaires. Baseline weight and height were measured with calibrated instruments, and body mass index (BMI) was calculated as kilograms per square meter. Diabetes was defined as fasting plasma glucose $\geq$ 126 mg/dL or current hypoglycemic medication (oral antidiabetics or insulin); hypercholesterolemia as total cholesterol $\geq$ 200 mg/dL or cholesterol-lowering therapy; and hypertension as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or antihypertensive treatment. DNA was isolated from buffy coats and the *APOE* genotyping was carried out using TaqMan probes (Applied Biosystems, Foster City, CA, USA). Carriers of the ε4 allele were grouped as APOE-ε4 carriers versus all other genotypes combined.

### Sample size

Assuming a two-sided α of 0.05 and 80% power, the available sample in the nested case-control study provides 80% power to detect an odds ratio (OR) $\leq$ 0.70 or $\geq$ 1.44 per one standard deviation (SD) increment in each biomarker.

### Statistical analyses

Conditional logistic regression estimated ORs of AD or dementia per one SD increase in each biomarker. Model 1 was adjusted for intervention group, educational level, smoking, diabetes, hypercholesterolemia, hypertension, and *APOE*-ε4 allele carrier status; model 2 additionally included BMI. Missing values for education (0.4%) were imputed with random forest algorithms, using the covariates in the conditional logistic regressions. We did not use a multiplicity-adjusted significance threshold in the primary analyses because the five biomarkers were selected a priori, the analyses were considered exploratory, and AD and all-cause dementia were overlapping rather than independent outcomes. We therefore interpreted results according to the magnitude and precision of the estimates and their consistency across models.

All analyses were performed with R, version 4.3.1. Our code is available at https://github.com/alvarohernaez/dementia_cohorts.

## Results

### Study population

The study population comprised 246 older adults; 61% were women; educational level was generally low, and, as per study design, cardiometabolic risk factors were common (Table 1). Even after matching, there was a higher prevalence of diabetes in dementia cases. Differences between the 246 individuals of the study and the other PREDIMED study participants are available in Supplemental Table 1.

**Table 1** Study population

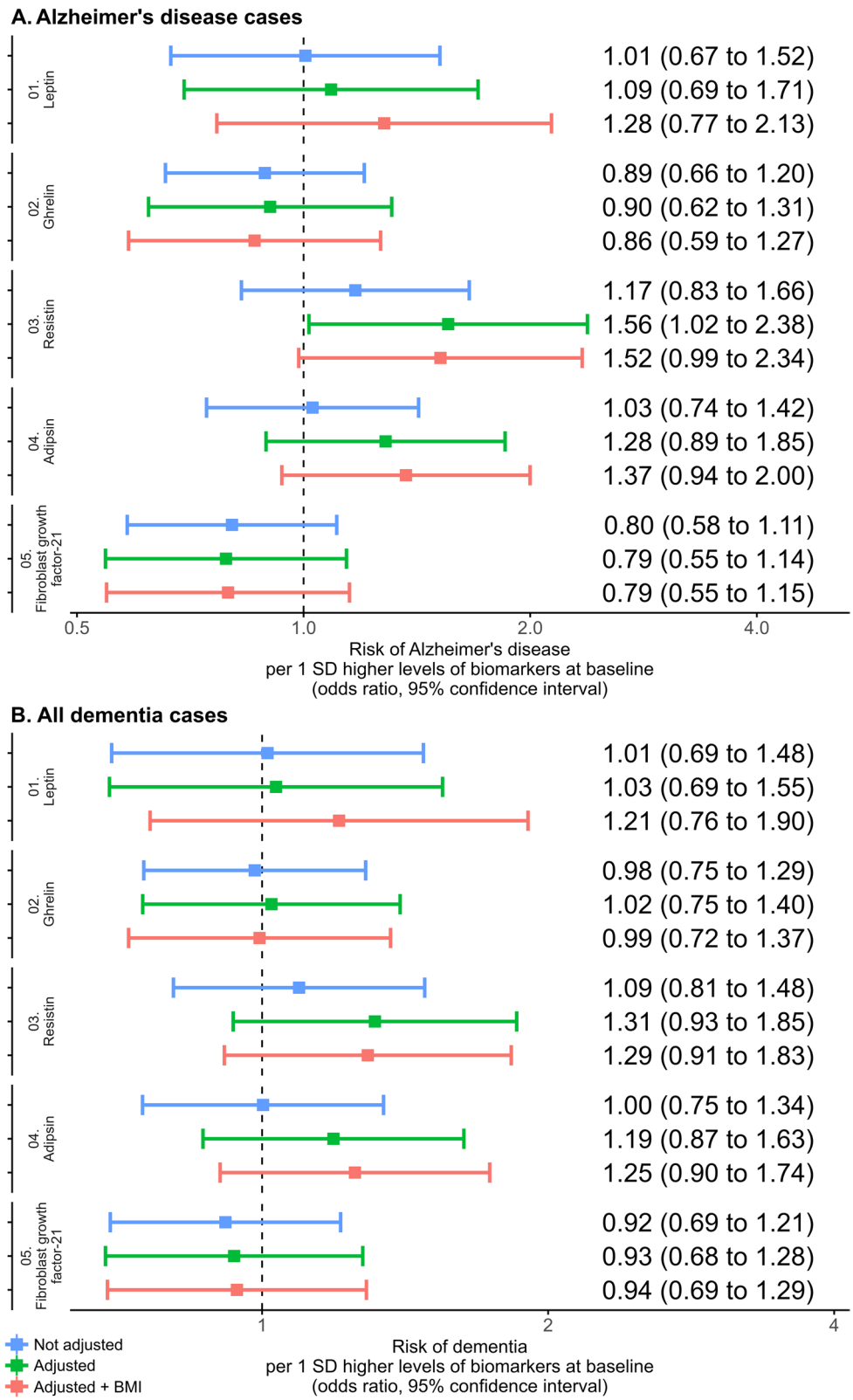
| | All participants ($n=246$) | Non-cases ($n=156$) | Cases ($n=90$) |
|---|---|---|---|
| Age, years (mean ± SD) | 71.8 ± 5.13 | 71.7 ± 5.16 | 72.0 ± 5.11 |
| Female sex ($n$, %) | 150 (61.0%) | 94 (60.3%) | 56 (62.2%) |
| Educational level: | | | |
| Primary education ($n$, %) | 94 (38.2%) | 63 (40.4%) | 31 (34.4%) |
| Secondary education ($n$, %) | 68 (27.6%) | 48 (30.8%) | 20 (22.2%) |
| Higher education ($n$, %) | 84 (34.1%) | 45 (28.8%) | 39 (43.3%) |
| Type-2 diabetes ($n$, %) | 126 (51.2%) | 68 (43.6%) | 58 (64.4%) |
| Hypercholesterolemia ($n$, %) | 172 (69.9%) | 115 (73.7%) | 57 (63.3%) |
| Hypertension ($n$, %) | 208 (84.6%) | 136 (87.2%) | 72 (80.0%) |
| Body mass index status | | | |
| $<25$ kg/m$^2$ ($n$, %) | 25 (10.2%) | 14 (8.97%) | 11 (12.2%) |
| $\geq 25$ and $<30$ kg/m$^2$ ($n$, %) | 113 (45.9%) | 71 (45.5%) | 42 (46.7%) |
| $\geq 30$ kg/m$^2$ ($n$, %) | 108 (43.9%) | 71 (45.5%) | 37 (41.1%) |
| Abdominal obesity by waist circumference ($\geq 89$ cm women, $\geq 103$ cm men) ($n$, %) | 184 (74.8%) | 120 (76.9%) | 64 (71.1%) |
| Smoking | | | |
| Never smokers ($n$, %) | 167 (67.9%) | 104 (66.7%) | 63 (70.0%) |
| Former smokers ($n$, %) | 22 (8.94%) | 17 (10.9%) | 5 (5.56%) |
| Current smokers ($n$, %) | 57 (23.2%) | 35 (22.4%) | 22 (24.4%) |
| Leptin, ng/mL (mean ± SD) | 3.60 ± 1.75 | 3.55 ± 1.62 | 3.70 ± 1.96 |
| Ghrelin, pg/mL (mean ± SD) | 264 ± 152 | 265 ± 153 | 263 ± 151 |
| Resistin, ng/mL (mean ± SD) | 6.93 ± 3.06 | 6.92 ± 3.02 | 6.96 ± 3.14 |
| Adipsin, ng/mL (mean ± SD) | 1,020 ± 323 | 1,023 ± 312 | 1,013 ± 341 |
| FGF-21, pg/mL (median, 1st–3rd quartile) | 330 (203–498) | 338 (206–548) | 288 (192–470) |

### Adipokines, satiety hormones, and dementia incidence

One SD increase in plasma resistin was directly associated with a higher risk of AD in the multivariable-adjusted model (OR 1.56, 95% CI 1.02 to 2.38). After additional adjustment for BMI, the point estimate remained similar, although the 95% CI became slightly more imprecise (OR 1.52, 95% CI 0.99 to 2.34; Fig. 2A). The estimates for the rest of the biomarkers were compatible with no association. Estimates were generally weaker and less precise when all-cause dementia was considered as the outcome (Fig. 2B).

## Discussion

In this nested case-control study of older adults at high cardiovascular risk, higher baseline resistin concentrations were associated, albeit imprecisely, with greater odds of incident AD. Among the five biomarkers examined, resistin showed the clearest positive estimate in relation to incident AD; nevertheless, the limited precision of this estimate and its statistical uncertainty after BMI adjustment warrant caution. From a geroscience perspective, circulating adipokines may capture age-related changes in adipose tissue function, inflammatory regulation, and metabolic homeostasis that are not fully reflected by BMI alone [11]. Previous clinical and experimental studies have linked resistin to systemic inflammatory activity [28], which may contribute to neuronal injury, and to alterations in blood-brain barrier permeability through impaired astrocyte differentiation [29]. Further studies should also examine other biomarkers in our study that showed suggestive but statistically inconclusive associations with AD, such as circulating adipsin (with an OR of 1.37, and a 95% CI of 0.94 to 2.00). Although these findings


A. Alzheimer's disease cases
01. Leptin
02. Ghrelin
03. Resistin
04. Adipsin
05. Fibroblast growth factor-21
1.01 (0.67 to 1.52)
1.09 (0.69 to 1.71)
1.28 (0.77 to 2.13)
0.89 (0.66 to 1.20)
0.90 (0.62 to 1.31)
0.86 (0.59 to 1.27)
1.17 (0.83 to 1.66)
1.56 (1.02 to 2.38)
1.52 (0.99 to 2.34)
1.03 (0.74 to 1.42)
1.28 (0.89 to 1.85)
1.37 (0.94 to 2.00)
0.80 (0.58 to 1.11)
0.79 (0.55 to 1.14)
0.79 (0.55 to 1.15)
0.5
1.0
2.0
4.0
Risk of Alzheimer's disease
per 1 SD higher levels of biomarkers at baseline
(odds ratio, 95% confidence interval)
B. All dementia cases
01. Leptin
02. Ghrelin
03. Resistin
04. Adipsin
05. Fibroblast growth factor-21
1.01 (0.69 to 1.48)
1.03 (0.69 to 1.55)
1.21 (0.76 to 1.90)
0.98 (0.75 to 1.29)
1.02 (0.75 to 1.40)
0.99 (0.72 to 1.37)
1.09 (0.81 to 1.48)
1.31 (0.93 to 1.85)
1.29 (0.91 to 1.83)
1.00 (0.75 to 1.34)
1.19 (0.87 to 1.63)
1.25 (0.90 to 1.74)
0.92 (0.69 to 1.21)
0.93 (0.68 to 1.28)
0.94 (0.69 to 1.29)
1
2
4
Not adjusted
Adjusted
Adjusted + BMI
Risk of dementia
per 1 SD higher levels of biomarkers at baseline
(odds ratio, 95% confidence interval)

◂**Fig. 2** Association of adipokine and satiety hormone levels with incidence of Alzheimer's disease (**A**) and all-cause dementia (**B**) by conditional logistic regression models (for a nested case-control design matched for age, ± 3 years, and follow-up time): non-adjusted (blue); adjusted for intervention group, educational level, smoking, diabetes, hypercholesterolemia, hypertension and *APOE-ε4* genotype (green); and additionally adjusted for BMI (red)

may reflect limited precision, insufficient statistical power, or a true absence of association, adipsin remains of biological interest because it participates in activation of the alternative complement pathway, the dysregulation of which has been implicated in neuroinflammation and synaptic elimination in AD [16]. Accordingly, this work should be interpreted as an observational study of circulating biomarkers and incident clinical outcomes, not as a direct investigation of the cellular or molecular mechanisms underlying neurodegeneration.

Our work has some limitations. First, AD and other dementias develop through prolonged preclinical phases, with neuropathological and biomarker changes beginning many years before the onset of clinically evident cognitive impairment. Therefore, a baseline biomarker measurement obtained several years before clinical diagnosis may already capture the metabolic consequences of an evolving neurodegenerative process [30]. Prodromal disease may be accompanied by unintentional weight loss and increasing frailty [10], potentially reflecting changes in appetite, energy regulation, body composition, and general health that could influence circulating adipokine or satiety-hormone concentrations. Therefore, our findings could be affected by reverse causation. In addition, residual confounding remains possible. Type 2 diabetes was substantially more frequent among dementia cases than controls and was included in the multivariable models. Adjustment may therefore have reduced, but not eliminated, confounding by the underlying metabolic status of the participants. Other sources of residual confounding beyond age, sex, educational level, smoking, APOE-ε4 genotype, and cardiovascular risk factors also cannot be completely ruled out. Second, the modest number of incident AD and dementia cases limited statistical power and resulted in imprecise estimates, particularly for modest biomarker-outcome associations. Most confidence intervals were wide, the statistical evidence for resistin weakened after additional adjustment for BMI, and the estimates for the rest of biomarkers were compatible with no association. The results should therefore be regarded as exploratory and hypothesis-generating. Third, no formal correction for multiple comparisons was applied in the primary analyses. Consequently, chance cannot be excluded as an explanation for the nominal resistin finding, particularly given the modest number of events and the statistical uncertainty of the fully adjusted estimate. Fourth, the inter-assay coefficient of variation for resistin was relatively higher than those observed for the other biomarkers (17.4%). Although samples from each matched set were analyzed in the same run and laboratory personnel were blinded to case-control status, this analytical imprecision may have attenuated or destabilized the estimated association and may limit its reproducibility. Replication using assays with greater analytical precision is therefore required. Fifth, some dementia cases may have been missed due to incomplete records. Finally, because our participants were older adults at increased cardiovascular risk, generalizability of our findings to other populations remains uncertain.

## Conclusions

Within this Mediterranean cohort of older adults at high risk of cardiovascular disease, higher resistin concentrations were associated with greater odds of incident AD. The results should be considered exploratory and should not be interpreted as evidence that this adipokine contributes causally to AD or has established predictive utility, as the observed estimates could reflect antecedent metabolic vulnerability, consequences of prodromal disease, or other sources of bias. Studies with longer follow-up periods, larger sample sizes, repeated biomarker measurements, and detailed trajectories of adiposity and cardiometabolic indicators are necessary. Nevertheless, the potential predictive or prognostic utility of adipokines for AD and dementia warrants further investigation.

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**Author contribution** Conceptualization: Á.H., O.C. methodology: Á.H., O.C. project administration: O.C., R.E., M.A.M.-G. formal analysis and investigation: Á.H. writing—original draft preparation: Á.H. writing—review and editing: J.H.-R., J.J.C., M.H.H., E.R., M.Á.M.-G., D.C., J.S.-S., R.E., A.S.-V., J.T., R.C.-G., M.F., J.L., L.S.-M., X.P., K.A.P.-V., E.T., E.M.A., I.P.-G, and O.C. A.H. and O.C. had full access to all the data in the study and take responsibility for its integrity and the data analysis. All authors read and approved the final manuscript.

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**Data availability** Code for statistical analyses is publicly available at GitHub (https://github.com/alvarohernaez/dementia_cohorts). Individual-level participant data cannot be shared publicly due to Spanish data protection law and ethics approvals; de-identified data may be made available to bona-fide researchers upon reasonable request to the PREDIMED Steering Committee (predimed-steering-committee@googlegroups.com ).

**Declarations**

**Ethics approval and consent to participate** The study was conducted following the Declaration of Helsinki and was approved by the Hospital del Mar Clinical Research Ethics Committee (ref. 2017/7482/I). All participants provided written informed consent before joining the study. The PREDIMED protocol is registered at https://www.isrctn.com/ISRCTN35739639.

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