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REVIEW

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Assessing adipokines as potential biomarkers of dementia, Alzheimer's disease, and mild cognitive impairment: A systematic review and meta-analysis

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Summary

Midlife obesity and late-life weight loss confer a greater risk for developing dementia and Alzheimer's disease (AD), but the exact mechanisms behind this phenomenon are currently unknown. The answer could lie on the involvement of gastrointestinal factors, such as adipokines (e.g., leptin, adiponectin, and resistin) and ghrelin. In this context, we conducted a pre-registered systematic review and meta-analysis of 42 cross-sectional and 13 longitudinal studies targeting the associations between leptin, adiponectin, resistin, and ghrelin and the prevalence of general dementia, AD, and mild cognitive impairment (MCI). We also examined the relationship between the four gastrointestinal factors and neurocognitive outcomes and AD-related cerebrospinal fluid biomarkers. Patients with AD had lower blood leptin and higher resistin levels than cognitively normal participants. Lower leptin and higher resistin were associated with higher degree of cognitive impairment. Additionally, lower late-life leptin levels might be associated with higher prospective risk of dementia and AD, although more studies are needed to corroborate this. Results in ghrelin and adiponectin were not conclusive, with age, sex distribution, obesity, and severity of dementia seemingly acting as moderators across several analyses. Our work might contribute to the identification of new preclinical blood markers of MCI and AD.

KEYWORDS
adipokines, gastrointestinal hormones, ghrelin, neurodegeneration

1 | INTRODUCTION

Alzheimer's disease (AD) represents around two thirds of all cases of dementia.[1] To date, no available treatments are able to reverse or pause the progression of the illness, which highlights the importance of designing preventive strategies aimed at maintaining a strong physical and mental health in older populations.

Alterations in body weight status, such as midlife obesity[2,3] and late-life weight loss,[4,5] confer a greater risk for the development of AD and other forms of dementia. Midlife obesity accounts for 1% of the total cases of dementia,[2] and it is associated with poorer indicators of brain health, such as higher brain atrophy and increased radiological signs of cerebral small-vessel disease such as white matter

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hyperintensities,[6,7] along with lower performance in executive functioning.[8] Part of these alterations might be reversible; for instance, bariatric surgery tends to ameliorate brain aging.[9] One of the mechanisms by which obesity might lead to poorer brain outcomes is by increases in low-grade inflammation.[10] While systemic inflammation is now considered a hallmark of aging,[11] neuroinflammation is a common characteristic of different neurodegenerative diseases.[12] In the central nervous system (CNS), microglia and astrocytes play a critical role in the neuroinflammatory process by releasing proinflammatory cytokines when they are stimulated by insoluble aggregates such as Aβ and tau. In turn, this response induces synaptic loss and neurodegeneration, and it further increases Aβ and tau levels, becoming a vicious cycle.[13]

In this field, the study of adipokines might provide further light into the mechanisms linking alterations in body weight, inflammation, and neurodegeneration (Figure 1). The term adipokines refers to hundreds of different molecules that are secreted by the peripheral white adipose tissue and that exert their actions via autocrine, paracrine, or endocrine mechanisms, most of them in both the central (CNS) and the peripheral nervous systems.[14] Three of the most well-studied adipokines in relation to AD and neurodegeneration are leptin, adiponectin, and resistin.[15,16] Additionally, in this review we will also focus on a gastrointestinal hormone whose homeostatic effects are largely regarded as complementary to leptin:ghrelin.

Leptin is primarily secreted in the adipose tissue, and it plays a significant role in satiety and reducing food intake.[14,17] Peripheral leptin can be transported through the blood–brain barrier (BBB) reaching the CNS, and robust expression of leptin receptors has been found in the hypothalamus (i.e., in its arcuate, paraventricular, dorsomedial, lateral, and ventromedial nuclei) and hippocampus,[14,15] where leptin has a role in homeostatic and memory functions, respectively.[15] With regard to memory, leptin has been considered as a cognitive enhancer, and it might avert neuronal loss and synaptic disruption in AD.[18] Results from a previous meta-analysis on cross-sectional case–control studies combining blood, CSF, and ex-vivo measurements showed that patients with AD have lower leptin concentrations than cognitively normal participants.[19] Of note, the hypothalamus seems to secrete some amount of leptin, meaning that the amount of leptin available in the CNS is probably the sum of blood leptin crossing the BBB and hypothalamic leptin.[15] Because of this, leptin levels measured in blood might not automatically translate to leptin levels available in the CNS.

Adiponectin is an adipokine that is exclusively produced in the adipose tissue, and it has important metabolic effects, such as enhancing insulin sensitivity.[14] Adiponectin levels are reduced in health conditions characterized by a compromised cardiometabolic health, such as obesity, type 2 diabetes mellitus, or metabolic syndrome.[14] Adiponectin has strong anti-inflammatory effects, because it interferes with the actions of inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α).[20,21] For this reason, low levels of adiponectin have been associated with chronic inflammation and might increase the risk for AD and neurodegeneration.[15] Animal (rodent) models have suggested that AD is characterized by a deficit in adiponectin.[15] Despite that, the mechanisms enabling blood adiponectin to cross the BBB are still largely unknown, so it is unclear whether blood levels of adiponectin are equivalent to adiponectin concentrations in the CSF.[14]

In humans, resistin is mostly secreted by macrophages in the adipose tissue.[22,23] Augmented levels of resistin are found in obesity and type 2 diabetes mellitus,[24] and are associated with an increased risk of cardiovascular death.[25] More specifically, in obesity, the adipose tissue undergoes several changes in response to a sustained excess of

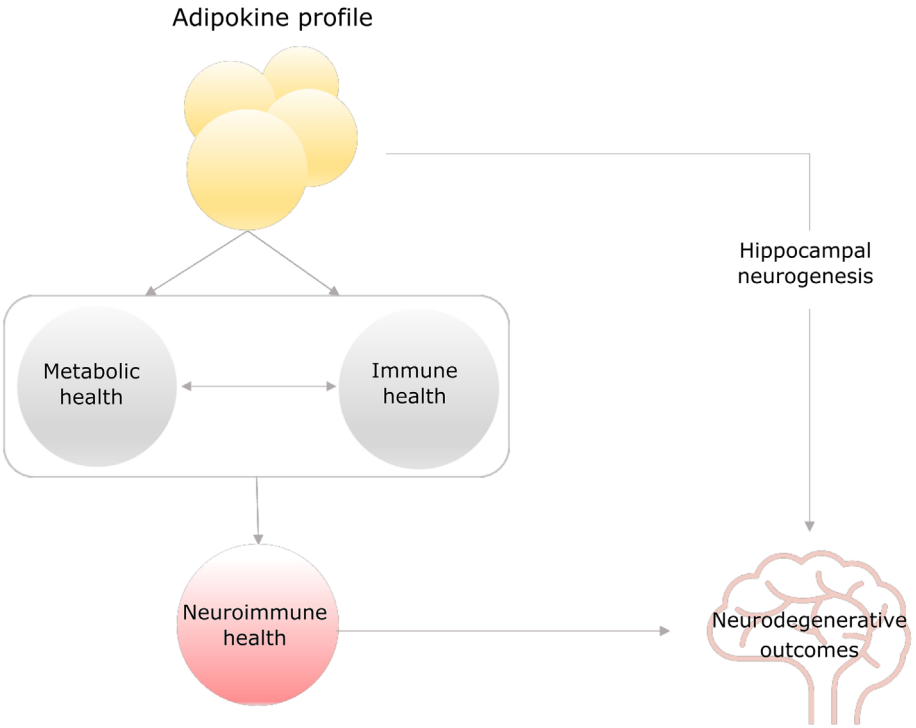

FIGURE 1 Different mechanisms may link the adipokine profile with brain outcomes such as brain senescence and neurodegeneration. Adiponectin and resistin act as modulators of the immune response, with adiponectin being an anti-inflammatory agent and resistin being proinflammatory. By increasing the permeability of the blood–brain barrier, chronic increases in systemic inflammation might lead to neuroinflammation, a hallmark of neurodegenerative disorders. At the same time, leptin and ghrelin seem to promote hippocampal integrity, which may confer some protection against neurodegeneration.

caloric intake,[26] including the enlargement of adipocyte cells and the increases in number of immune cells, such as macrophages, residing in the adipose tissue.[27] These processes lead to an inflammatory cascade that creates a chronic state of low-grade inflammation and promotes further metabolic dysfunctions, such as insulin resistance.[26–28] Resistin increases the inflammatory response by upregulating other proinflammatory cytokines, such as TNF-α or interleukin 6 (IL6),[24] and it is known to act on adipocyte cells promoting insulin resistance.[23] Moreover, inflammatory cytokines might, in turn, trigger inflammatory processes in the CNS, affecting the hypothalamus and other structures such as the hippocampus and the brainstem.[29] This creates a possible route explaining how the malfunction of the adipose tissue and the subsequent alterations in the secretion of resistin can increment the risk of neurodegeneration.

Ghrelin is a gut hormone considered an appetite stimulator because it is released as a signal of hunger and its levels decrease after a meal.[30] Ghrelin thus has an important role in the homeostatic control of energy balance, and it has additionally been associated with cardiovascular regulation.[24] We can distinguish two different forms of blood ghrelin: unacylated and acylated ghrelin. Results in rodents have shown that acylated ghrelin has the potential to cross the BBB, facilitating neuronal growth and development in the hippocampus and contributing to hippocampal-dependent memory processes.[31,32] Nevertheless, most human population studies use the total value as a measurement of blood ghrelin levels.

A number of studies have revolved around the associations between gastrointestinal factors, such as adipokines, and the prevalence and risk of dementia and AD. This research could open up the possibility of finding new biomarkers of dementia, which would have important implications for the prevention and/or management of patients with neurodegenerative disorders. In this context, here we aim to analyze whether alterations in four gastrointestinal factors (leptin, adiponectin, resistin, and ghrelin) are associated with the diagnostic and with the prospective risk of general dementia, AD, and MCI. To this aim, we performed a systematic review and meta-analysis of the available literature in human studies, examining cross-sectional and longitudinal results separately. We also evaluated the associations between adipokines and cognitive performance, neuroimaging outcomes, and AD-related CSF biomarkers. To account for the heterogeneity of results, we included an examination of four potential moderating factors: age, sex, body weight status (i.e., body mass index [BMI]), and dementia severity.

2 | MATERIALS AND METHODS

2.1 | Eligibility criteria

We performed a systematic review of studies examining the association between leptin, adiponectin, resistin, and ghrelin and the presence of general dementia, AD, and MCI. We pre-registered the method of this systematic review in Open Science Framework (https://osf.io/h8k9y), and it follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[33]

We included case–control studies examining differences in adipokine levels between groups of patients with either general dementia, AD, or MCI, and controls (i.e., cognitively normal participants), as well as cohort studies reporting cross-sectional or longitudinal associations between dementia, AD, or MCI and adipokine levels.

We excluded meta-analyses, review articles, single-case studies, and studies using animal models (i.e., rodents). Studies without cognitively normal participants were excluded from the cross-sectional results. However, we included them in the longitudinal section if they examined the evolution of dementia, MCI, or AD. Studies lacking participants with general dementia, AD, or MCI were also excluded, as well as cohort studies omitting information about their prevalence of these diagnoses. Other exclusion criteria were small sample sizes (n < 40 participants), pharmacological intervention studies, and studies focusing specifically on Parkinson's disease, Lewy body disease, or vascular dementia.

For the synthesis, we grouped the results of the studies according to the nature of their analyses (i.e., cross-sectional or longitudinal) and according to the adipokine or gut hormone examined (i.e., leptin, adiponectin, ghrelin, or resistin). We also distinguished whether the measurement of the adipokine/hormone was taken peripherally (plasma or serum) or in the cerebrospinal fluid (CSF).

2.2 | Search strategy and data collection

The key terms and search strategy used in PubMed were the following: (dementia or Alzheimer's disease or Mild Cognitive Impairment) and (leptin or ghrelin or adiponectin or resistin). We additionally retrieved some papers of interest from a previous meta-analysis on leptin and AD.[19] The search was finalized during the month of March 2023. Three authors (I. G.-G., N. G.-C., and M. F.-A.) performed the search independently. The suitability of each paper included was evaluated by a second author, and disagreements were solved by consensus.

From each individual study, we extracted the following variables: (i) design-related which were the total sample size, cross-sectional versus longitudinal, and follow-up period (if applicable); (ii) adipokines/ghrelin and their origin (i.e., serum, plasma, or CSF); (iii) characteristics of the participants which were the age, sex distribution, name of the study cohort (if applicable), number of participants with general dementia, AD, MCI, or cognitively normal, BMI distribution; (iv) characterization of AD which were the criteria followed to determine the presence of AD or MCI, neuropsychological tests performed to characterize the cognitive impairment, whether the study presents additional brain MRI variables or CSF biomarkers of AD, severity of cognitive impairment of the groups with dementia or MCI, as reflected with the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment test (MoCA) tests; (vi) main results which were group differences in adipokine levels between dementia, AD, or MCI, and cognitively normal participants, associations with prospective risk of dementia or MCI, and associations between adipokines and cognitive performance, neuroimaging outcomes, and CSF biomarkers of AD. The data extraction was performed by three authors working independently (I. G.-G., N. G.-C., and M. F.-A.),

and the data retrieved were cross-validated by a second author. Disagreements were solved by consensus.

Some studies analyzed the same cohort of participants (such as participants from the Alzheimer's Disease Neuroimaging Initiative). We avoided sample overlaps in the systematic review and meta-analyses by discussing or including only the most comprehensive paper among them.

2.3 | Qualitative assessment and risk of bias of the studies

We performed a qualitative assessment of the studies by administering a modified version of the Newcastle–Ottawa Scale (NOS) for case–control and cohort studies.[34] The main modifications of the NOS scale were the following. First was whether or not the diagnostic of the participants (i.e., general dementia, AD, or MCI) or their absence of cognitive impairment was adequately evaluated (i.e., based on a clinical diagnosis from a physician and validated using cognitive tests, as opposed to self-reported or based entirely on hospital records). Second was whether the analyses accounted for possible differences between participants with cognitive decline (dementia, AD, or MCI) and cognitively normal participants in terms of (a) age, sex, and BMI (or another obesity-related variable)[14,35,36] and in terms of (b) years of education and presence of other vascular risk factors.[37] Finally, in the case of longitudinal cohorts, we distinguished whether or not the mean follow-up period could capture neurodegenerative progression. We considered as appropriate those follow-ups that were equal or longer than 40 months because previous research has shown that after 40 months, 25% of patients with late-onset MCI tend to convert to AD.[38] After deleting some items that were not applicable, the scores for cross-sectional case–control studies ranged from 0 to 6, and scores for cohort studies were from 0 to 7. Two authors (I. G.-G. and M. F.-A.) scored each of the articles independently, and discrepancies were solved by consensus.

2.4 | Effect measures and synthesis methods: meta-analyses

When feasible, we conducted meta-analyses from the results of the systematic review. From the studies retrieved, we were able to perform two types of analyses: (a) cross-sectional comparisons between groups of patients with AD or with MCI and cognitively normal participants on adipokine levels, and (b) cross-sectional associations between adipokine levels and scores on two screening tests for dementia, MMSE and MoCA.

For the first type of analysis, we collected means and standard deviations (*SD*) in adipokine levels, as well as sample sizes. Some papers reported adipokine values as medians and interquartile ranges, which were transformed to means and *SD* using the automatic transformation method available in Wan et al.[39] Some studies segregated participants that belonged to the same cohort into subgroups (e.g., they divided participants with AD and control participants according to sex). Whenever possible, we grouped together the data available to obtain a single value for the group of interest and a single value for the control group so that the final effect of a single paper on the meta-analyses would not be inflated.

For the second type of analysis, we collected sample sizes and correlation values reflecting the association between adipokine levels and dementia screening scores (from MMSE and MoCA). Whenever a study presented correlations between adipokines and both dementia screening tests, we calculated the average of the *r* correlation value. When the study presented standardized beta weights, the conversion to *r* values was performed.[40]

The meta-analyses and their plots associated were performed using Meta-essentials-Workbook for meta-analysis (version 1.5)[41] implemented in Excel, and rmeta (version 3.0) package[42] implemented in R. We used a random effects model to calculate a pooled effect size from the individual effect sizes. A forest plot was then created to examine the individual and the pooled effect sizes and standard errors. We examined the heterogeneity across studies using the I^2 index, and tested for the possible presence of publication bias with visual inspection of the funnel plot and with the Egger test. Separate moderator analyses were run to test for the possible effect on the results of four potentially confounding variables: age, sex, BMI, and severity of cognitive impairment in patients with either dementia, AD, or MCI, as measured with the MMSE.

Statistical inference criteria were set at $p < 0.05$. Because there are partial overlaps between the datasets across the different molecules (i.e., some studies examine both leptin and adipokine whereas others focus on a single molecule), we also report if the significant results withstand a stringent Bonferroni correction, accounting for the six main meta-analyses performed.

Finally, we performed sensitivity analyses to test whether significant results were maintained after the removal of those articles with the lowest qualitative scores according to the ratings of the NOS scale (i.e., studies scoring 0 or 1).

2.5 | Modifications regarding the original pre-registered protocol

There are three main modifications with regard to the original pre-registered protocol.

First, the pre-registered meta-analyses method required a minimum of 10 articles in order to be performed. However, the current paper includes the results of several meta-analyses performed with fewer studies (i.e., 7 to 9 datasets). These analyses will be identified through the text as "unregistered and preliminary."

Second, we included an examination of the relationship between adipokine levels and general dementia scores (i.e., MMSE and MoCA scores). This point was not pre-registered and was decided a posteriori after noticing that a substantial number of the studies report such correlations in their results. These analyses will be identified through the text as "unregistered and preliminary".

Third, in the pre-registered protocol, we stated that we would run a moderator analysis to test for possible effects of age in the meta-analytic results. This paper extends this analysis to include the examination of three other potentially confounding factors and sources of heterogeneity: sex distribution (i.e., percentage of females), BMI, and severity of cognitive impairment (MMSE scores).

3 | RESULTS

Our literature search retrieved 624 records, and from these, we filtered out 197 duplicates, reviews, systematic reviews, and meta-analyses. From the remaining 427 studies, we excluded 347 records on animal species other than humans. These steps were performed by applying automatic filters available in PubMed. The remaining 80 records were thoroughly assessed for eligibility criteria, and a list of the excluded articles in this stage and the reason for exclusion is provided in Table S1. Forty-two studies presenting cross-sectional results and 13 studies reporting longitudinal data were included in the systematic review. Figure 2 presents the steps of the search and identification of studies, conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

3.1 | Results of the cross-sectional studies

3.1.1 | Leptin: systematic review

We included 24 cross-sectional studies published between 2009 and 2023.[43–66] All of them measured leptin values in blood (serum or plasma), and one of them provided an additional measure of leptin in the CSF. They included 4892 participants, 2771 of which were

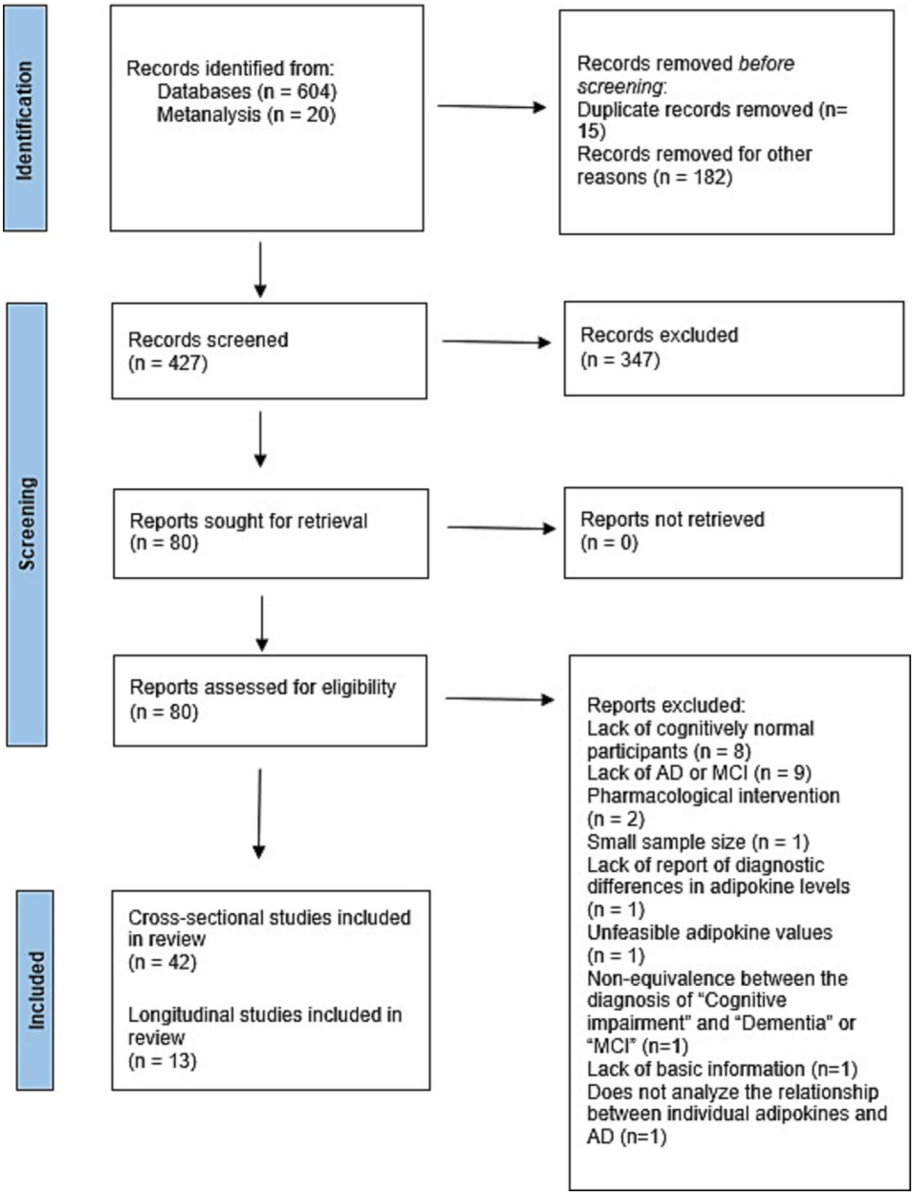

FIGURE 2 PRISMA diagram of study identification and selection.

women. Of note, two studies analyzed the same dataset of participants, and consequently, this systematic review includes only the results of the most comprehensive study of the two. One paper presented results grouping patients in a broad category of general dementia and differentiated between a subgroup of patients with AD. For comparability with the other studies, here we only refer to its results in patients with AD. With regard to the overall quality of the studies included, four studies obtained very low scores (0–1) in the NOS scale, indicating that 17% of the studies had a very high risk of bias (Table S2).

Eighteen studies examined differences in blood leptin density between patients with AD (pooled $n = 1172$) and cognitively normal participants (pooled $n = 1995$). Among them, 12 studies did not find differences in leptin between groups, and 6 studies found that patients with AD had lower leptin levels than cognitively normal participants. Additionally, one study examined leptin levels in the CSF and reported that patients with AD had lower central leptin than cognitively normal participants.

Eight studies compared blood leptin density between patients with MCI (pooled $n = 833$) and cognitively normal participants (pooled $n = 829$). Among them, four studies reported that patients with MCI had lower leptin levels than cognitively normal participants, three studies did not find differences in leptin levels between groups, and one study found that patients with MCI had higher leptin levels relative to cognitively normal participants. One study provided an additional examination of leptin levels in the CSF and reported that patients with MCI had lower central leptin than cognitively normal participants.

With regard to cognitive function, 12 studies (pooled $n = 2220$) examined the association between blood leptin density and dementia scores (i.e., MMSE or MoCA scores). Among them, nine studies reported no significant associations between leptin and dementia scores while three studies found that higher leptin levels were associated with better MMSE or MoCA scores. Six studies (pooled $n = 1352$) examined the relationship between blood leptin levels and specific cognitive functions. Three of them reported no significant correlations between leptin levels and memory performance, two of them reported that higher leptin levels were associated with better performance in executive function, and one found an inverse relationship between leptin and performance in executive function.

Finally, one study ($n = 80$) included neuroimaging markers in its statistical analysis and reported that higher blood leptin levels were associated with better hippocampal integrity.

3.1.2 | Leptin: Meta-analysis

Out of 18 studies, 14 papers comparing patients with AD (pooled $n = 928$) and cognitively normal participants (pooled $n = 705$) in blood leptin density presented sufficient data to be included in the meta-analysis. Patients with AD had lower leptin than cognitively normal participants (combined Cohen's $d = 0.56$; combined standard error = 0.20; 95% confidence interval [CI] [0.13. 1.13]; uncorrected $p = 0.005$; Bonferroni corrected $p = 0.03$) (Figure 3A). A sensitivity analysis showed that the removal of four studies with very low scores in the NOS scale did not substantially change the results (combined Cohen's $d = 0.63$; combined standard error = 0.27; 95% CI [0.01, 1.24], $p = 0.021$). Visual inspection of the funnel plot showed no asymmetry (Figure S1A) and the Egger test was not significant ($t = 0.30$, $p = 0.766$), indicating low risk of publication bias. The heterogeneity across the studies was high ($I^2 = 93.9\%$). Moderator analyses showed that higher mean BMIs (beta = −0.65; 95% CI [−0.42, −0.06], $p = 0.003$), and better MMSE scores in the AD group (beta = −0.90; 95% CI [−0.19, −0.08], $p < 0.001$) were associated with lower effect sizes. Age and sex did not have an impact on the effect sizes (Figure S1B–E).

Out of eight datasets, seven studies comparing patients with MCI (pooled $n = 815$) and cognitively normal participants (pooled $n = 816$) presented adequate data for an additional unregistered and preliminary meta-analysis on blood leptin density. The results showed that patients with MCI did not differ from cognitively normal participants in leptin levels (combined Cohen's $d = 0.38$; combined standard error = 0.25; 95% CI [−0.25, 1], uncorrected $p = 0.139$) (Figure 3B). The funnel plot presented some asymmetry, suggesting the presence of publication bias (Figure S2A); however, the Egger test was not significant ($t = 1.11$, $p = 0.31$). The heterogeneity across studies was high ($I^2 = 92\%$), but despite this, none of the factors examined were significant in the moderator analyses: age (beta = −0.5; 95% CI [−0.16, 0.04], $p = 0.125$), sex (beta = 0.51; 95% CI [−0.01, 0.05], $p = 0.147$), BMI (beta = −0.60; 95% CI [-0.45, 0.06], $p = 0.066$), and MMSE scores in patients with MCI (beta = −0.60; 95% CI [−0.45, 0.06], $p = 0.066$) (Figure S2B–E).

Out of 12 papers testing the association between blood leptin levels and dementia scores (i.e., MMSE or MoCA scores), eight studies (pooled $n = 1701$) presented enough data for an additional unregistered and preliminary meta-analysis. The results showed that higher leptin levels were associated with better scores in the MMSE and/or MoCA (combined r coefficient = 0.18; 95% CI [0.03, 0.32]; uncorrected $p = 0.004$; Bonferroni corrected $p = 0.024$) (Figure 3C). The results remained significant after excluding one study with low scores in the NOS scale (combined r coefficient = 0.20; 95% CI [0.04, 0.35]; uncorrected $p = 0.002$). The funnel plot was symmetric (Figure S3A), and the Egger test was not significant ($t = 0.45$, $p = 0.67$), indicating that the risk of publication bias was low. Heterogeneity across the studies was high ($I^2 = 72.8\%$), and the moderator analyses showed that both age (beta = −0.91; 95% CI [−0.05, −0.02], $p < 0.001$) and BMI (beta = −0.47; 95% CI [−0.10, 0.00], $p = 0.022$) had an effect on this correlation. The moderator analyses were not significant for neither sex nor mean MMSE scores (Figure S3B–E).

3.1.3 | Adiponectin: A systematic review

We included 24 studies published between 2009 and 2023. All of them presented results on blood (serum or plasma) adiponectin.[45,47–50,52,53,59–61,65,67–79] Additionally, two of them included CSF measurements of adiponectin. They included 6757

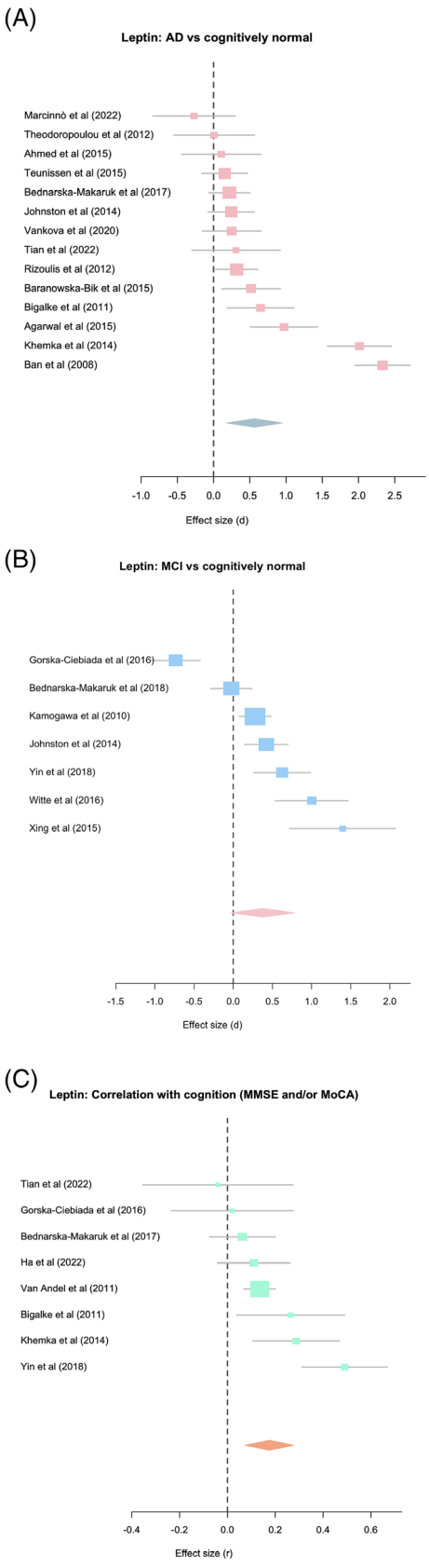

FIGURE 3 Forest plots of individual effect sizes of studies focusing on blood (serum or plasma) leptin. (A) Differences between patients with Alzheimer's disease (AD) and cognitively normal participants in leptin. (B) Differences between patients with mild cognitive impairment (MCI) and cognitively normal participants in leptin. (C) Associations between leptin and dementia screening scores (Mini-Mental State Examination [MMSE] and/or Montreal Cognitive Assessment test [MoCA] tests).

participants, and 3778 of them were women. Two studies obtained very low scores in the NOS scale (0 or 1), indicating that 8.3% of studies were at a very high risk of bias (Table S2).

Eighteen studies compared patients with AD (pooled $n = 1406$) and cognitively normal participants (pooled $n = 1324$) in blood adiponectin levels. Ten studies reported that patients with AD had higher adiponectin than cognitively normal participants, seven papers showed no statistically significant differences in adiponectin between patients with AD and controls, while one study detected lower adiponectin in patients with AD relative to cognitively normal participants. Two studies included an examination of CSF measurements of adiponectin in patients with AD (pooled $n = 90$) and cognitively normal participants (pooled $n = 90$). One of them reported that patients with AD had lower central adiponectin than cognitively normal participants while the other found no statistically significant differences between groups.

Eleven studies compared patients with MCI (pooled $n = 1267$) and cognitively normal participants (pooled $n = 2120$) in blood adiponectin concentrations. Five of them did not find statistically significant differences between groups, three studies reported lower adiponectin levels in patients with MCI compared with cognitively normal participants, and two studies found that patients with MCI had higher adiponectin levels compared with controls. One study separated participants by sex. This study found that women with MCI had higher blood adiponectin density relative to controls while in men, no group differences were found. Additionally, two studies included CSF measurements of adiponectin in patients with MCI (pooled $n = 82$) and cognitively normal participants (pooled $n = 90$). One of them found higher density of this molecule in patients with MCI relative to cognitively normal participants whereas the other reported no differences across groups.

With regard to cognitive function, fourteen studies (pooled $n = 3042$) examined the association between blood adiponectin concentration and severity of dementia (MMSE or MoCA scores). Among them, seven studies reported no correlations between adiponectin levels and dementia severity. Five studies found that higher adiponectin levels were associated with poorer scores in the MMSE or MoCA tests. Two studies reported that higher adiponectin levels were associated with better MMSE or MoCA scores. One additional study ($n = 189$) examining CSF adiponectin density reported that higher

central adiponectin levels were associated with better scores in the MMSE test. Six studies (pooled $n = 2274$) included an examination of blood adiponectin levels and specific cognitive domains. Among them, three studies found no correlations between adiponectin and executive functions, one study reported that higher adiponectin was associated with higher memory, executive function, and attention performance while another study reported that higher adiponectin was associated with lower performance in memory and executive function. An additional study that segregated participants according to their sex reported that, only in women, higher adiponectin was associated with lower performance in language.

Three studies (pooled $n = 1220$) analyzed the associations between blood adiponectin density and neuroimaging biomarkers. Two studies found no association between adiponectin and the MRI outcomes examined (e.g., hippocampal integrity or white matter hyperintensities). The other one separated participants according to their sex and reported that, across both sexes, higher adiponectin levels were associated with lower hippocampal volume. Additionally, in men, higher adiponectin levels were associated with lower cortical thickness and glucose uptake. One study ($n = 189$) included a measurement of CSF adiponectin concentrations and found that higher central adiponectin was associated with better hippocampal integrity.

Finally, two studies (pooled $n = 685$) measured AD-related proteins in the CSF and tested their association with blood adiponectin concentrations. One of them reported that higher adiponectin was associated with higher total and phosphorylated tau protein levels in the CSF, and one found no association between adiponectin and beta amyloid or tau protein levels in the CSF. One of these studies ($n = 189$) included a measurement of CSF adiponectin levels and reported that higher central adiponectin was associated with higher beta amyloid concentrations and lower tau protein levels in the CSF.

3.1.4 | Adiponectin: Results of the meta-analyses

Out of 18 studies, 14 compared patients with AD (pooled $n = 940$) and cognitively normal participants (pooled $n = 812$) in blood adiponectin levels and reported sufficient data to be included in the meta-analysis. Patients with AD had marginally significant higher adiponectin levels than cognitively normal participants (combined Cohen's $d = -0.64$; combined standard error = 0.30; 95% CI [−1.20, 0.00]; uncorrected $p = 0.03$; Bonferroni-corrected $p = 0.18$) (Figure 4A). The funnel plot was symmetric (Figure S4A) and the Egger test was not significant ($t = 0.30$, $p = 0.770$). Heterogeneity across studies was high ($I^2 = 96\%$). Moderator analyses showed that mean MMSE scores in patients with AD were significantly influencing group differences in adiponectin. This meant that studies with poorer MMSE scores in AD tended to report that patients with AD had higher adiponectin density than controls whereas studies with better MMSE scores in patients with AD tended to show null differences across groups (beta = 0.64; 95% CI [0.05, 0.28], $p = 0.002$). The other moderators examined (age, sex, and BMI) were not significant (Figure S4B–E).

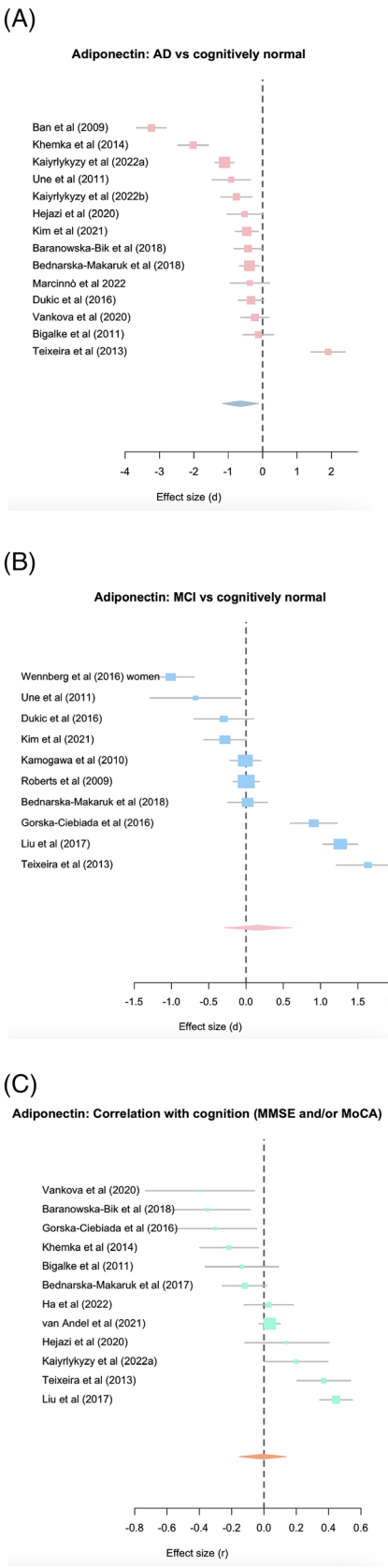

FIGURE 4 Legend on next page.

FIGURE 4 Forest plots of individual effect sizes of studies focusing on blood (serum or plasma) adiponectin. (A) Differences between patients with Alzheimer's disease (AD) and cognitively normal participants in adiponectin. (B) Differences between patients with mild cognitive impairment (MCI) and cognitively normal participants in adiponectin. (C) Associations between adiponectin and dementia screening scores (Mini-Mental State Examination [MMSE] and/or Montreal Cognitive Assessment test [MoCA] tests).

Out of 11 studies, 10 studies comparing patients with MCI (pooled $n = 1109$) and cognitively normal participants (pooled $n = 1944$) in blood adiponectin density presented sufficient data for the meta-analysis. Patients with MCI did not differ from cognitively normal participants in adiponectin (combined Cohen's $d = 0.16$; combined standard error = 0.27; 95% CI [−0.44, 0.77]; uncorrected $p = 0.543$) (Figure 4B). The funnel plot was symmetric (Figure S5A), and the Egger test was not significant ($t = -0.09$, $p = 0.934$). Although the heterogeneity across studies was high ($I^2 = 96\%$), the four moderators examined were not significant: age (beta = −0.15; 95% CI [−0.17, 0.11], $p = 0.639$), sex (beta = −0.36; 95% CI [−0.04, 0.01], $p = 0.167$), BMI (beta = −0.02; 95% CI [−0.24, 0.26], $p = 0.941$), and MMSE scores in the MCI group (beta = 0.06; 95% CI [−1.49, 1.64], $p = 0.896$) (Figure S5B–E).

Out of 14 studies, 12 (pooled $n = 2312$) reported enough data on the associations between blood adiponectin concentration and severity of dementia (MMSE or MoCA scores) and were included in an unregistered and preliminary meta-analysis. There was no correlation between adiponectin and MMSE/MoCA scores (combined r coefficient = −0.01; 95% CI [−0.19, 0.17]; uncorrected $p = 0.928$) (Figure 4C). The funnel plot was asymmetric, indicating the presence of possible publication bias (Figure S6A), but the Egger test was not significant ($t = -1.18$, $p = 0.27$). The heterogeneity across the studies was high ($I^2 = 91\%$). Moderator analyses showed that higher age (beta = 0.66; 95% CI [0.03, 0.05], $p < 0.001$) was associated with a higher correlation value. Higher percentage of females (beta = −0.42; 95% CI [−0.01, 0.00], $p < 0.001$) and higher BMI (beta = −0.32; 95% CI [−0.05, −0.01], $p < 0.001$) were associated with a lower correlation value (Figure S6B–E).

3.1.5 | Resistin: A systematic review

We included five cross-sectional studies published between 2012 and 2023, and all of them measured resistin values in blood (serum or plasma),[47,65,80–82] one of them presented data from three different cohorts ([81]), and one of these cohorts contained available CSF resistin values. Together they analyzed data from 1848 participants (611 females). One study had very low scores in the NOS scale, indicating that the risk of bias was very high in 20% of the studies available (Table S2).

Four datasets compared patients with AD (pooled $n = 241$) and cognitively normal participants (pooled $n = 288$) in blood resistin levels. Two of them reported that patients with AD had higher resistin than cognitively normal participants, one study reported that patients with AD had lower resistin than controls, and one study found no differences between groups. An additional study compared patients with AD ($n = 112$) and cognitively normal participants ($n = 396$) in CSF resistin levels and reported no group differences.

Regarding cognition, the three datasets (pooled $n = 601$) examined the relationship between general screening dementia tests (MMSE or MoCA) and resistin levels. Two of them found that higher resistin levels were associated with lower scores in the MMSE or MoCA while one of them reported no correlation between resistin and the dementia screening test. One study ($n = 333$) examined associations between blood resistin and CDR scores and showed that higher resistin levels were associated with severity of dementia. One study ($n = 138$) examined the associations between resistin levels and performance in specific cognitive functions and found that higher resistin levels were associated with poorer performance in memory, attention, and executive function.

One study ($n = 396$) measured AD-related proteins in the CSF and tested their association with CSF resistin concentrations and reported no associations between the variables.

3.1.6 | Ghrelin: a systematic review

We included five cross-sectional studies published between 2012 and 2021. All of them measured total ghrelin values in blood (serum or plasma), and one of them provided an additional measure of acylated ghrelin.[44,58,59,83,84] They included 1316 participants, 674 of them were women. Two studies obtained very low scores in the NOS scale (0 or 1), indicating that 40% of the studies available were at a very high risk of bias (Table S2).

Two studies compared patients with AD (pooled $n = 57$) and cognitively normal participants (pooled $n = 46$) in total ghrelin levels. Neither study showed group differences in ghrelin levels between patients with AD and cognitively normal participants.

Two studies compared patients with MCI (pooled $n = 134$) and cognitively normal participants (pooled $n = 136$) in total ghrelin levels. One of them reported that patients with MCI had lower total ghrelin than controls, while one of them showed no group differences in total ghrelin levels between participants with MCI and cognitively normal participants. One of these studies additionally presented results in acylated ghrelin concentrations. In this study, patients with MCI ($n = 22$) had higher acylated ghrelin than cognitively normal participants ($n = 30$).

With regard to cognitive function, three studies examined the relationship between general dementia screening scores and total ghrelin (pooled $n = 1060$). Two studies found no correlation between total ghrelin levels and MMSE scores, while one study reported that higher total ghrelin was associated with higher MoCA scores. Moreover, three studies (pooled $n = 1168$) examined specific cognitive domains using neuropsychological tests. The three studies examining the correlation between total ghrelin and memory reported a positive, a negative, and a null association between ghrelin and this cognitive domain, respectively. One study found that higher total ghrelin was associated with lower attention and executive function performance while another paper reported no correlation between total ghrelin and these domains. Finally, one study

including acylated ghrelin ($n = 52$) reported that higher acylated ghrelin was associated with lower performance in memory and language functions.

3.2 | Results of the longitudinal studies

Due to the small number of studies available and their heterogeneity with regard their dependent/outcome variable (e.g., prospective risk for AD diagnosis vs. longitudinal change in MMSE scores), no meta-analysis was performed in this section.

3.2.1 | Leptin and prospective cognitive decline: A systematic review

We included nine prospective studies published between 2009 and 2022. All of them measured blood leptin (in serum or plasma).[57,59,85–91] Overall, they included 5758 participants, 4033 of whom were women. Their mean follow-up period was between 14.5 and 384 months, with five of them having a follow-up period inferior to 40 months. None of the studies obtained very low scores in the NOS scale (0 or 1) (Table S3).

Five papers (pooled $n = 4222$) examined the relationship between baseline levels of blood leptin and the prospective incidence of general dementia or AD. Two studies found that higher baseline leptin levels were associated with lower prospective risk of general dementia, AD, and MCI. Two other papers reported that baseline leptin levels did not have any association with risk of developing dementia. An additional study separated participants according to weight status and reported that, in normal-weight individuals, leptin at baseline was associated with lower risk of developing dementia or MCI, while the association between leptin and the incidence of dementia was absent in overweight and individuals with obesity. Of note, these studies differ in terms of age: the three studies finding longitudinal associations between leptin and risk of dementia tested participants with a baseline age between 72 and 83 years. In the two studies finding null effects, the age of the participants at baseline was 47 and 74 years.

Four studies (pooled $n = 1537$) tested the links between baseline leptin and cognitive decline, as measured using repeated administrations of the MMSE test. None of the studies found significant associations between baseline leptin levels and longitudinal change or decline of MMSE scores.

One study ($n = 785$) included an examination of the association between baseline leptin and neuroimaging outcomes. They reported that higher baseline leptin was associated with higher total brain volume.

3.2.2 | Adiponectin and longitudinal cognitive decline: A systematic review

We included seven longitudinal studies published between 2013 and 2022 that measured blood adiponectin (serum or plasma).[59,70,74,85,88,92,93] Overall, they included 4128 participants, 2291 of them were women. Their mean follow-up period was between 14.5 and 156 months, with four of them having a follow-up period inferior to 40 months. None of the studies obtained very low scores in the NOS scale (0 or 1) (Table S3).

Four studies (pooled $n = 2559$) examined the association between adiponectin levels and the incidence of dementia and reported that baseline adiponectin levels were not associated with the longitudinal incidence of dementia, AD, or MCI.

One paper ($n = 205$) investigated the link between adiponectin and repeated measurements of the MMSE and found no association between baseline adiponectin and decline in MMSE scores. With regard to specific cognitive functions, another study ($n = 496$) found no association between baseline adiponectin levels and longitudinal decline in memory and executive function after a short follow-up period. Finally, another study divided participants by sex and found that in women ($n = 484$), higher baseline adiponectin was associated with lower delta (change) scores in a composite index that included MMSE and memory-related scores whereas no association between baseline adiponectin and delta scores was reported for men ($n = 414$).

3.2.3 | Resistin and prospective cognitive decline: A systematic review

There is one longitudinal study available on plasma resistin density, published in 2021.[88] It included 785 participants (490 women). Its average follow-up period was 132 months (Table S3).

This study reported that higher baseline resistin levels were associated with lower prospective risk of dementia and AD.

3.2.4 | Ghrelin and prospective cognitive decline: A systematic review

We included one study on total serum ghrelin levels, published in 2021.[59] It was performed in 898 participants, 484 of whom were women. The follow-up period was short (36 months) (Table S3).

The results of this study suggest that total ghrelin does not have an effect on longitudinal change (delta scores) in general cognitive function.

4 | DISCUSSION

Adipokines are molecules secreted by the adipose tissue that can have effects on homeostatic control, cardiovascular health, and in some cases, cognitive performance. Our work provides a comprehensive view of three adipokines and an additional gastrointestinal hormone that have the potential to become preclinical markers of dementia and AD: leptin, adiponectin, resistin, and ghrelin. Our results strongly suggest that blood leptin levels are diminished in participants with AD. Alterations in leptin are also negatively correlated with cognitive performance, meaning that lower leptin concentrations are associated

with a more pronounced cognitive deterioration. Although longitudinal studies are still scarce, it might be possible to establish a temporal relationship between alterations in leptin and cognitive impairment, because independent studies have shown that higher baseline leptin in late adulthood is associated with lower risk of developing general dementia, AD, and MCI. Results in resistin are still scarce and preliminary but suggest that this adipokine might be elevated in patients with AD. Across different analyses, age, sex, BMI, and severity of cognitive impairment have emerged as moderating factors on the associations between adipokine levels and neurodegeneration.

4.1 | Leptin

Our cross-sectional results show that patients with AD, but not patients with MCI, have lower blood leptin concentrations relative to cognitively normal participants. Moreover, prospective studies in late adulthood have shown that higher blood leptin at baseline is associated with lower longitudinal risk of dementia.[87,88] We can regard these results in two different ways. First, weight loss, and its consequent decrease in leptin levels, is often interpreted as a preclinical sign[4] or risk factor[5] of dementia. This matches our results on the moderator effect of BMI well because we found that the higher the global BMI of the participants, the lower the differences in leptin across patients with AD and cognitively normal participants. As such, body weight should be considered an important source of heterogeneity across studies. Second, beyond its role in energy homeostasis, leptin supports synaptic function in the hippocampus, facilitating hippocampus-related memory processes.[18] Moreover, cellular studies have shown that leptin can lower amyloid-beta pathology, by modulating its production, clearance, and degradation.[94] This suggests that leptin might have some neuroprotective effects against AD-related protein accumulation, thus affecting the progression of AD.[94] Perhaps as a reflection of the role of leptin in facilitating hippocampal function and in altering AD-related protein deposition, our results also show that decreases in leptin density are accentuated with increases in the severity of dementia (i.e., MMSE or MoCA scores). Alternatively, our results could also indicate that, with increased severity of dementia, additional symptoms that might result in malnutrition, like lack of appetite or dysphagia, are more likely to occur,[95] causing alterations in leptin and other adipokines in patients with AD.

4.2 | Adiponectin

Animal studies have highlighted the neuroprotective properties of adiponectin and have hypothesized that reductions in adiponectin might be one pathological mechanism driving neuroinflammation and amyloid beta accumulation in AD.[21] In contrast, our meta-analysis showed that patients with AD had marginally higher blood levels of adiponectin than cognitively normal participants. We did not find a meta-analytic association between adiponectin levels and dementia severity scores. Likewise, prospective studies mostly found no link between baseline adiponectin and prospective cognitive decline. Peripheral blood levels of adiponectin might not necessarily translate to CSF adiponectin. In agreement with this, a study included in this systematic review found opposite directionality of results between serum and CSF adiponectin: While serum adiponectin density was elevated in patients with AD compared with controls, CSF adiponectin levels were diminished in patients with AD relative to controls.[76] Another paper that compared between AD and participants with amnestic MCI showed that patients with AD had higher serum adiponectin, while no group differences were found regarding adiponectin CSF levels.[96] Of note, in this last study, the correlation strength between serum and CSF adiponectin was moderate (~0.5), indicating that some collinearity between the two variables is expected.

4.3 | Resistin

With regard to resistin, the available literature was scarce, which limits the generalization of the results. Cross-sectional results suggest that patients with either AD or MCI have higher levels resistin than cognitively normal participants. Moreover, higher resistin seems to be associated with the severity of dementia (e.g., Wang et al.[80]). This is in agreement with studies showing that resistin is involved in inflammatory processes that can potentially cause vascular damage to the CNS.[97] By contrast, the only prospective study available on resistin suggests the opposite result, that is, higher resistin density is related to a lower risk of dementia/AD.[88] While more studies are needed in this area, it is possible that weight loss associated with the development AD might be driving this result.[4]

4.4 | Ghrelin

There is no conclusive evidence that total ghrelin is associated with the incidence of general dementia, AD, or MCI, neither in cross-sectional nor in longitudinal studies. The literature available was scarce, with a high proportion of studies scoring very low in the NOS scale. Previous studies have shown that the distinction between unacylated and acylated ghrelin might be useful because acylated ghrelin, with its ability to cross the BBB, is considered the functional form of ghrelin.[31,32] Although the link between ghrelin and AD is still unclear, it might be interesting to focus on the acylated form of ghrelin in the future, especially so because a study included in the review found that this form of ghrelin is increased in patients with MCI compared with control participants.[83]

There are some common limitations across the studies included in this systematic review. With regard to the cross-sectional studies, very few of them provided information that allows the reader to judge the representativeness of either the patients with AD or MCI, or the cognitively normal participants. This might be an issue, because patients volunteering to participate in the studies might be healthier, wealthier, and more motivated than what is expected. With regard to the prospective studies, two factors that might critically influence the

results are the baseline age of the participants and the time of the follow-up. In most of the studies (see Gustafson et al.[86] for an exception), baseline data were taken from participants in their late adulthood. It would be relevant to expand the number of studies recruiting middle aged participants to test the possible long-term effects of midlife obesity and its subsequent impact on adipokine concentrations and risk of neurodegeneration. Second, follow-ups tended to be shorter than 3 years. This poses the problem that only a small fraction of participants might develop cognitive impairment of dementia during the time of the study.[38] When longer follow-ups were available, sometimes the range of the follow-up period varied starkly between individuals of the same cohort (see, e.g., Lieb[87]), which might also affect the validity of the results.

Our systematic review also has some limitations that we would like to acknowledge. First, all the meta-analyses performed showed high heterogeneity across the results of the studies. We have attempted to provide an account of four possible sources of this heterogeneity: age, sex distribution, BMI, and severity of cognitive impairment in patients with MCI or AD. However, there are other factors that are known to affect the phenotype of patients with AD and MCI, such as socioeconomic status, cognitive reserve, or APOE-ε4 genotype (e.g., Yasuno et al.[98] and Cacciaglia et al.[99]), to name a few. Second, we did not differentiate between amnestic versus non-amnestic MCI, despite the fact it is well established that the first of these subtypes is more likely to convert to AD.[100] Nor did we differentiate patients with stable MCI from other patients. While studies providing this fine-grained information were very scarce, grouping patients with MCI together has the risk of losing nuances with regard to the characteristics and prognosis of these patients.

The advancement of clinical trials testing for treatments that are aimed at modifying AD brings renewed interest in finding biomarkers that can inform clinicians of which patients are at high risk of developing dementia.[101] In this context, the finding that low blood leptin concentration is associated with AD and with the risk of development of AD can have implications for early disease detection. In order to get a fine-grained characterization of brain atrophy and neurodegeneration, future lines of research might benefit from incorporating neuroimaging data because studies that have acquired any type of neuroimaging data are still very scarce. There is also a need for longitudinal studies on younger participants, to test whether alterations in adipokine concentrations during middle age have prospective value for late-life AD.

5 | CONCLUSIONS

In this study, we comprehensively evaluate the link between four adipokine and gastrointestinal hormones, leptin, adiponectin, resistin, and ghrelin, and their cross-sectional and longitudinal associations with general dementia, MCI, and AD. Our meta-analysis shows that blood leptin levels are reduced in patients with AD, and our systematic review indicates that late-life alterations in blood leptin density might be predictive of the subsequent development of AD. Similarly, and although the number of studies available are fewer by comparison, blood resistin levels seem to be higher in patients with AD compared with cognitively normal participants Results on the other molecules examined are heterogeneous, and more research is needed taking into account potential moderators such as age, sex, obesity or BMI, and degree of cognitive impairment. Our work might contribute to the identification of possible new biomarkers for the early detection of MCI and AD.

AUTHOR CONTRIBUTIONS

Marina Fernández-Andújar, Natalia García-Casares, and Isabel García-García, were responsible for the study conceptualization. Formal analysis was conducted by Isabel García-García. Methodology was carried out by Marina Fernández-Andújar, Natalia García-Casares, and Isabel García-García. Supervision was provided by Marina Fernández-Andújar, Natalia García-Casares, Manuel Narváez, and Isabel García-García. Visualization and writing of the original draft were performed by was provided by Marina Fernández-Andújar and Isabel García-García. Writing-review and editing was carried out by Manuel Narváez and Natalia García-Casares. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

Isabel García-García is currently employed at *Clinique la Prairie*. This company had no role in conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript. The rest of the authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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