Adiponectin, leptin and resistin and the risk of dementia

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Abstract

Background
Adipokines are hormones secreted by adipose tissue with roles in energy homeostasis and regulation of metabolism. Their dysregulation is suggested to contribute to the increased risk of dementia seen with midlife obesity, but longitudinal studies investigating this are scarce. We determined the association between plasma levels of adiponectin, leptin and resistin with the risk of dementia.

Methods
We performed a case-cohort study embedded in the prospective, population-based Rotterdam Study. Plasma levels of the adiponectin, leptin and resistin were measured at baseline (1997-1999) in a random sub-cohort of 945 participants without dementia, and additionally in 177 participants, who were diagnosed with dementia during follow-up (until January 1, 2018).

Results
Higher levels of leptin and resistin were associated with a decreased risk of dementia (adjusted hazard ratio [95% confidence interval] per SD increase of log transformed values: 0.85 [0.72-1.00] for leptin; 0.82 [0.71-0.95] for resistin). The association of leptin with dementia was further modified by body mass index and by APOE ε4 carrier status. Adiponectin levels were not associated with the risk of dementia.

Conclusions
These findings support the hypothesis that adipokines have a role in the pathophysiology of dementia. Future studies are warranted to confirm the findings and to explore the underlying mechanisms.

Keywords: Adipokines – Alzheimer’s Disease – Dementia – Epidemiology – Obesity
Background

Obesity and dementia are both major health concerns that pose a huge burden on societies worldwide. Increasing evidence suggests that overweight or obesity, especially during mid-life, contributes to the susceptibility to develop dementia (1, 2). An increase of adipose tissue, in particular in the abdominal region, and the resulting metabolic and vascular changes, may explain the increased risk of dementia (3). Adipose tissue is recognized as an endocrine organ secreting hormones known as adipokines, such as adiponectin, leptin and resistin, that are involved in regulation of nutrient intake behavior, inflammation and endothelial dysfunction (4). Adipokines interact with nuclei in the brain, such as the hypothalamus and hippocampus, resulting in regulation of metabolism and feeding behavior, as well as synaptic plasticity, neurogenesis and memory consolidation (4, 5). With obesity, a disruption of the homeostasis of those hormones is seen, with increased levels of leptin and often leptin resistance and decreased levels of adiponectin (5).

Adiponectin sensitizes the body to insulin and has anti-inflammatory properties (6). Although adiponectin is suggested to have protective effects on the brain, an increased risk of dementia was found in women in the only longitudinal study that investigated this association (7, 8).

Leptin, considered an anti-obesity hormone by reducing appetite and increasing energy expenditure, is suggested to be protective against neurodegeneration (9). However, studies in human populations on leptin and the risk of dementia are scarce and not all showed this protective effect (10, 11).

A third adipokine, resistin, is involved in obesity-associated inflammation (12) and vascular dysfunction (13), and thereby thought to be a risk factor for dementia, although a potential neuroprotective role has also been described (14). To our knowledge, no longitudinal studies investigated resistin as a risk factor for dementia in humans.

Taken together, existing studies that aimed to determine the role of these adipokines in dementia are predominantly cross-sectional and longitudinal studies are scarce, despite their suggested role in the link between obesity and dementia with potential for prevention (15). Therefore, we determined the association of plasma levels of leptin, adiponectin and resistin with the risk of dementia in a prospective, population-based cohort.
Method

Study Population

This study is embedded within the Rotterdam Study, a prospective population-based cohort designed to study the occurrence and determinants of diseases in the older population, as described previously (16). Briefly, in 1990 all inhabitants aged 55 years or over from the district Ommoord in Rotterdam, the Netherlands, were invited to participate. The initial cohort comprised 7,983 participants and was extended in 2000 with 3,011 participants who had become 55 years of age or moved into the study district. In 2006, the cohort was further extended (RS-III) with 3,932 participants aged 45 years or over. In total, the Rotterdam Study comprises 14,926 participants.

The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus Medical Center and by the board of The Netherlands Ministry of Health, Welfare, and Sports. A written informed consent was obtained from all participants.

Study design

For the present study, we used a case-cohort study design embedded in the initial cohort wave. In this approach, the exposure (i.e., adipokines) is measured in a random subset (N=945) of all participants who were at risk of dementia at the time (i.e., no prevalent dementia; N=3051). For efficiency reasons, this group is enriched with participants who developed dementia during follow-up (N=177), before the study sample was defined (January 1, 2008). To account for overrepresentation of incident dementia cases, results are weighted based on the sampling fraction (945/3051, 31%).

Measurement of adiponectin, leptin and resistin

Fasting blood samples were collected during the third visit (1997-1999). Plasma was isolated and immediately put on ice and stored at −80 °C. Citrate plasma (200 μL) was sent in July 2008 to Rules-Based Medicine (Myriad RBM), where adipokine levels were assessed using multiplex immunoassay on a custom-designed human multianalyte profile. The intra-assay variability was less than 4%, and the inter-assay variability, tracked by recording the control values generated on each plate of samples over time (using the Levy-Jennings methodology), was less than 13%.

Dementia assessment

Participants were screened for dementia at baseline and subsequent center visits with the Mini-Mental State Examination and the Geriatric Mental Schedule organic level. Those with a Mini-Mental State Examination score <26 or Geriatric Mental Schedule score >0 underwent further investigation and informant interview, including the Cambridge Examination for Mental Disorders of the Elderly. In addition, the entire cohort was continuously under surveillance for dementia through electronic linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental health care. Available information on clinical neuroimaging was used when required for diagnosis of dementia subtype. The final diagnosis was established by a consensus panel led by a consultant neurologist, according to standard criteria for dementia (using Diagnostic and Statistical Manual of Mental Disorders III-revised) and Alzheimer’s Disease (AD) (using National...
Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association).

Covariates

During home interviews, participants provided information on educational level, smoking status, and alcohol use. Educational level was categorized as primary education, lower, intermediate, or higher. Smoking status was classified into never, current, or former. Alcohol use was categorized as no use or any use. At the research center, height and weight were measured from which the body mass index (kg/m²) was computed. Blood pressure was measured in the sitting position on the right arm using a random-zero sphygmomanometer. Serum concentrations of total cholesterol, high-density lipoprotein cholesterol, triglycerides, and creatinine were measured in fasting blood samples. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (17). Chronic kidney disease was defined as eGFR less than 60 mL/min/1.73 m². APOE was genotyped by polymerase chain reaction and participants were categorized as carrier or non-carrier of the ε4 allele. Diabetes was defined as fasting blood glucose >7.0 mmol/L, use of antidiabetic medications or self-reported as having diabetes. Depressive symptoms were considered as a score of 16 or higher on the validated Center for Epidemiology Depression Scale (18).

Statistical Analyses

Given the right-skewed distribution of the adipokine levels, we used a natural logarithmic transformation to achieve a roughly normal distribution and better fitting models (Supplementary Figure 1). Z-scores were computed by dividing the difference between the individual values and the population mean by the population standard deviation. In addition, adipokines were analyzed in quartiles. We used Cox proportional hazards models to assess the association with the risk of dementia with modification of the standard errors based on robust variance estimates. Since cases were overrepresented, we weighted the random subcohort by the inverse of the sampling fraction from the source population (945/3051, 31%). Follow-up started when blood was drawn and ended at the date of dementia diagnosis, date of death, or end of the study period (January 1st, 2018), whichever came first.

All analyses were adjusted for age, sex, educational attainment, smoking status, alcohol use and APOE ε4 carrier status (model 1). Model 2 additionally adjusted for known metabolic risk factors of dementia, namely systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, triglycerides and eGFR. In model 3, the estimates were also adjusted for levels of the other two adipokines.

We repeated the analyses after stratifying the study population by sex, age (<70 and ≥70 years), BMI (<25, 25-30 and ≥30 kg/m²) and by APOE ε4 carriership, after excluding participants with diabetes, participants with CKD, and after excluding the first 5 years of follow-up.

Missing data in covariates (maximum of 4%) were imputed using multiple imputation with give imputed datasets based on other covariates and the outcome, using the package “mice”. Statistical analyses were performed in R Studio Version 3.6.3. Statistical testing was performed two-sided with p<.05.
Results

Baseline characteristics of the study population are shown in Table 1 and by adipokines quartiles in Supplementary Table 1. Participants with lower levels of adiponectin and higher levels of leptin generally had a more unfavorable profile of cardiovascular risk factors, including higher BMI, blood pressure, triglycerides and more diabetes at baseline, as could be expected given their strong association with overweight/obesity. Levels of adiponectin and leptin were higher among women. There were no large differences in baseline characteristics by resistin levels, except for slightly more diabetes and higher creatinine in participants with higher resistin. During a median follow-up of 11 years [IQR 5-17], 360 participants were diagnosed with dementia, of whom 269 had AD.

Higher levels of adiponectin were not associated with the risk of dementia in the total study group (Table 2), although a non-significantly increased risk was seen among men, among participants with BMI <25kg/m² and after excluding the first five years of follow-up (Figure 1). Participants with higher leptin levels were at lower risk of dementia (hazard ratio (HR) 0.85 (95% CI 0.72-1.00; P=.056) per SD increase in model 3) and of AD (HR 0.77 (95% CI 0.64-0.92); Table 2), especially among participants with BMI ≥25kg/m² and among APOE ε4 carriers (Figure 1). Analyzed in quartiles, no statistically significant association of leptin with incident dementia was observed (Supplementary Table 2). Higher levels of resistin were also associated with a decreased risk of dementia (HR 0.82 (95% CI 0.71-0.95) in model 3) and of AD (HR 0.80 (95% CI 0.68-0.93); Table 2), and this effect was consistent over the subgroups. The risk of dementia was lowest for participants with resistin levels in the highest quartile (HR 0.54 (95% CI 0.36-0.80) in model 3), compared to participants with levels in the lowest quartile (Supplementary Table 2). Additional adjustment for BMI did not substantially change the results (data not shown).
Discussion

In this study, we found that higher plasma levels of the adipokines leptin and resistin, but not of adiponectin, were associated with a decreased risk of dementia and AD later in life.

This is the first study to investigate the adipokine resistin as a risk factor for dementia, showing a potential protective effect independent of other cardiovascular risk factors and consistent over the studied subgroups. Resistin is implicated in pathological processes such as insulin resistance, inflammation, endothelial dysfunction and atherosclerosis and is primarily secreted from macrophages rather than adipocytes (19). Increased serum levels of resistin were previously found in persons with AD in cross-sectional studies and were suggested to contribute to AD pathology (12, 20). However, neuroprotective effects of resistin have been observed in in vitro models of AD and resistin was suggested to attenuate oxidative stress induced by amyloid-β (14). The decreased risk of dementia in persons with higher resistin levels may also be explained by a higher risk of mortality in those persons due to other age-related diseases. An increased risk of all-cause mortality, independent of traditional cardiovascular risk factors, was indeed reported by previous studies, suggestively due to involvement of resistin in inflammatory processes (21). In the present study, however, resistin was not associated with mortality in a post-hoc analysis (data not shown).

Our finding that leptin was associated with a decreased risk of all-cause dementia, although borderline significant, and AD was consistent with a previous longitudinal study and with its implicated beneficial role in brain functioning (10). Namely, beside its well-documented role in regulating appetite and energy expenditure via binding receptors in the hypothalamus, leptin is thought to facilitate long-term potentiation via receptors in the hippocampus (22). Leptin is also shown to increase hippocampal neurogenesis and may reduce amyloid-β levels and inhibit tau phosphorylation, two hallmarks of AD (5). Moreover, leptin interacts with several other hormones including insulin and glucagon-like-protein that may mediate effects of leptin on the brain (4, 23). A protective effect of leptin on late-life dementia was not found in a study among women in mid-life with up to 32 years of follow-up, suggesting that leptin may mainly be protective in late-life (11).

Interestingly, we observed a protective effect of leptin in persons with BMI ≥25 kg/m², particularly in those with BMI ≥30, but not in persons with BMI <25. This finding may, in part, be explained by the frequently observed drop in body weight in persons with dementia years before diagnosis and in older persons in the last years of life, thereby concealing any potential, protective effect of leptin. Alternatively, the effect of leptin, particularly its role in, and the transportation into, the brain, may indeed differ with BMI, for example via leptin resistance in obesity, but this remains largely unclear. In addition, there might be larger variability in leptin levels among persons with obesity, which could explain why our finding in this subgroup were not in accordance with that from a previous study (10).

Although a protective effect of adiponectin on the brain has also been suggested (5), we found no association between plasma levels of adiponectin and the risk of dementia. In fact, higher adiponectin was non-significantly associated with an increased risk in part of the subgroup analyses. In contrast to leptin, it is a matter of debate whether peripheral adiponectin crosses the blood-brain barrier. Consequently, plasma measurements of adiponectin may poorly correlate with levels in the
brain, which could explain why no association with dementia incidence was found in this study and exclusively in women in a previous study based on plasma measurements (8).

Limitations of the current study include the predominantly white race and the relatively old age of participants at the time of adipokine measurement, while obesity particularly during midlife seems to affect the risk of dementia. Nevertheless, we found similar results in participants below the age of 70, albeit with wider confidence intervals. Second, interpretation of the effects of adipokines is complicated because levels may be affected by a drop in body weight due to prodromal dementia or comorbidities. Repeated measurement of the adipokines could help to identify certain patterns. Third, we cannot rule out confounding from unmeasured variables, for example from other lifestyle factors. Fourth, there is a possibility of missed dementia diagnoses, for example due to health care avoidance. Finally, given that we intended to explore biological mechanisms, this study has no direct clinical implications.

Our study contributes to previous studies that found associations between adipokines and dementia. Future studies are warranted to confirm these findings and to extend knowledge of underlying mechanisms. However, the limitations of our study mean that our results should be interpreted with a degree of caution.
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Author contributions

S.S.M. conceived the idea, designed the study, conducted the analyses, interpreted the results and drafted the manuscript. M.K.I and M.A.I. contributed to the interpretation of the results and revised the manuscript for intellectual content.

Conflict of Interest

None declared.
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Table 1. Baseline characteristics of the study population

| Characteristic          | Women (N=640) | Men (N=482) |
|------------------------|--------------|-------------|
| Age, years             | 74.0 (7.5)   | 73.0 (7.2)  |
| Educational attainment |              |             |
| Primary                | 140 (22)     | 58 (12)     |
| Lower                  | 326 (52)     | 155 (32)    |
| Intermediate           | 141 (22)     | 195 (41)    |
| Higher                 | 26 (4)       | 72 (15)     |
| APOE ε4 carrier        | 170 (28)     | 153 (32)    |
| History of diabetes    | 78 (12)      | 65 (13)     |
| Body mass index, kg/m² | 27.1 (4.4)   | 26.1 (3.1)  |
| Adiponectin, μg/mL     | 4.2 [3.1-5.8]| 2.6 [1.9-3.7]|
| Leptin, ng/mL          | 14.3 [8.4-22.6]| 4.2 [2.5-6.8]|  
| Resistin, ng/mL        | 0.4 [0.3-0.6]| 0.4 [0.3-0.6]|  

Note. APOE, apolipoprotein E, eGFR, estimated glomerular filtration rate. Numbers are means (standard deviation) or numbers (percentages), unless specified otherwise.

a Numbers are median [interquartile range].
Table 2. Associations of adiponectin, leptin and resistin with the risk of dementia and Alzheimer’s Disease

|                      | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) |
|----------------------|---------------------|---------------------|---------------------|
| Adiponectin          |                     |                     |                     |
| All-cause dementia   | 1.06 (0.90-1.24)    | 1.07 (0.89-1.29)    | 1.04 (0.86-1.26)    |
| Alzheimer’s Disease  | 1.00 (0.84-1.20)    | 1.00 (0.81-1.24)    | 0.96 (0.77-1.19)    |
| Leptin               |                     |                     |                     |
| All-cause dementia   | 0.85 (0.73-0.98)    | 0.85 (0.72-1.00)*   | 0.85 (0.72-1.00)*   |
| Alzheimer’s Disease  | 0.81 (0.69-0.95)    | 0.78 (0.65-0.93)    | 0.77 (0.64-0.93)    |
| Resistin             |                     |                     |                     |
| All-cause dementia   | 0.82 (0.72-0.95)    | 0.82 (0.71-0.95)    | 0.82 (0.71-0.95)    |
| Alzheimer’s Disease  | 0.80 (0.69-0.92)    | 0.80 (0.68-0.93)    | 0.80 (0.68-0.93)    |

Note. HR, hazard ratio; CI, confidence interval. Hazard ratios for all-cause dementia (n=360, N=1122) and for Alzheimer’s Disease (n=269) per standard deviation increase of log transformed values of the adipokines.

Model 1: adjusted for age, sex, educational attainment, smoking status, alcohol use and APOE ε4 carrier status.

Model 2: additionally adjusted for systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, triglycerides and estimated glomerular filtration rate.

Model 3: additionally adjusted for levels of the other two adipokines.

* P-values of the association of leptin with all-cause incident dementia were .047 for model 2 and .056 for model 3.
Figure 1.

Associations of adiponectin, leptin and resistin with the risk of all-cause dementia in subgroups, per standard deviation increase of log transformed values of the adipokines. Unless specified differently, all estimates were adjusted using Model 3. BMI, body mass index; APOE, apolipoprotein E; CKD, chronic kidney disease.
Figure 1

| Subgroups             | Adiponectin | Leptin | Resistin |
|-----------------------|-------------|--------|----------|
| Women                 | 233/640     |        |          |
| Men                   | 127/482     |        |          |
| Aged <70 years        | 73/406      |        |          |
| Aged ≥70 years        | 287/716     |        |          |
| BMI <25 kg/m²         | 127/386     |        |          |
| BMI 25-30 kg/m²       | 173/533     |        |          |
| BMI ≥30 kg/m²         | 58/195      |        |          |
| APOE ε4 non-carrier   | 210/752     |        |          |
| APOE ε4 carrier       | 134/323     |        |          |
| No diabetes           | 308/979     |        |          |
| No CKD                | 286/900     |        |          |
| First 5 years excluded| 202/839     |        |          |

0.40  1.0  1.7 (HR (95% CI))