Neuropsychology

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Online First Publication, November 14, 2024. https://dx.doi.org/10.1037/neu0000968

AMERICAN PSYCHOLOGICAL ASSOCIATION

Neuropsychology

ISSN: 0894-4105

https://doi.org/10.1037/neu0000968

Affliction Class Moderates the Dementing Impact of Adipokines

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Objective: Biomarker-specific interventions (e.g., for dementia) will necessitate an individualized approach to treatment. We have constructed a psychometric classifier to identify persons adversely impacted by plasma adipokines. ***Method:*** The subjects (N = 1,737) of the Alzheimer's Disease Neuroimaging Initiative were assigned to groups "afflicted" by versus "resilient" against the unique effect of plasma adipokines using a classifier derived by confirmatory factor analysis in a structural equation model framework. The impact of affliction class above and beyond observed biomarker levels and covariates was tested by multivariate regression using CDR "Sum of Boxes" as the dependent variable. The affliction class' moderation of adipokines' effect was tested by chi-square difference. The effect of affliction class on prospective conversion risk was tested by Cox's proportional hazards models. ***Results:*** Seven hundred four out of the 1,737 subjects (40.53%) were assigned to the afflicted class. The afflicted subjects had greater dementia severity, lower (adverse) *Adipokines* factor composite scores (by analysis of variance, $F(1, 1{,}735)$ 2619.68, $p < .001$) and higher observed levels of plasma adipokines (by Tukey's honestly significant difference test, all $p < .001$). *Adipokines'* association with dementia severity was moderated by affliction class. The effect persisted at 48 months. Afflicted cases were more likely to convert to Alzheimer's disease in that timeframe, by Cox's F: $F(234, 286) = 3.89$, $p < .001$. ***Conclusions:*** Our approach could guide precision interventions against specific biomarkers. This classifier could be administered by telephone, making class assignment feasible without direct patient contact or biomarker assessment.

Key Points

Question: Can individuals be distinguished as "afflicted" by versus "resilient" against the unique effect of a single dementia-related biomarker? ***Findings:*** A psychometric classifier derived from a short battery of potentially telephone-administered tests was able to distinguish groups with differing levels of a prespecified dementia-related biomarker (i.e., plasma adipokines). Class assignment explained variance in dementia severity above and beyond plasma adipokine levels and covariates. Adipokine levels were more strongly associated with dementia in the afflicted cases, and initially nondemented afflicted cases were more likely to convert to clinical dementia than their resilient peers. ***Importance:*** Our algorithm could be applied to any dementia-related biomarker using any reasonably comprehensive psychometric battery. Individuals could be assigned to multiple affliction classes by a single administration of the battery and without measuring the biomarker(s) of interest. This approach could facilitate treatment selection for afflicted cases remotely and at scale. Clinical trials could be accelerated by recruitment of afflicted cases. The discrimination of afflicted versus resilient cases could improve outcome prediction within the recently proposed amyloidopathy/tauopathy/neurodegeneration framework for the diagnosis of *Alzheimer's disease*. ***Next steps:*** Significant fractions of patients with confirmed dementia-related biomarkers may be resilient to their effects. Future studies can now examine the mechanisms of resilience and the risk factors for affliction.

Keywords: adipokines, biomarkers, dementia, g, intelligence

Rosemary Fama served as action editor.

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Some data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://adni.loni.usc.edu). ADNI had no role in study design, data collection and analysis, decision to publish, or preparation of the article. However, ADNI investigators contributed to the design and implementation of ADNI and/or provided data. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

This study is supported by the National Institute on Aging, National Institutes of Health (Grant 1R01AG080548-01, principal investigator: Donald R. Royall). Donald R. Royall is also supported by the Julia and Van Buren Parr Endowment to The University of Texas Health Sceince Center at San Antonio.

continued

In the near future, providers of dementia care will need to consult algorithms derived from informatic classifiers. Toward that end, we have been using theory-driven confirmatory bifactor analysis in a structural equation model (SEM) framework to refine dementia's assessment (Royall et al., 2012). This complicated task has been made more urgent by the Food and Drug Administration's recent approval of the anti-amyloid monoclonal antibodies. Not all dementia patients are adversely impacted by beta amyloid, and beta amyloid's assessment is constrained by cost, risk, and access.

We needed first to distinguish functionally salient cognitive impairment (FSCI) from cognitive impairment per se. How disease-specific cognitive changes relate to FSCI and whether FSCI is mediated through familiar cognitive domains are empirical questions that have yet to settled. Next, we needed to identify the biomarkers of FSCI. Since not all individuals who express disease-specific biomarkers have a FSCI, it is again an empirical question whether those biomarkers contribute to the disablement that defines the dementia syndrome. Finally, we needed to accept that dementia severity is likely to be "overdetermined," that is, impacted by multiple statistically independent FSCI-related processes presenting in various combinations. Providers will then need to distinguish individuals who have been adversely impacted by the specific biological process being targeted for intervention regardless of whether it is disease-specific.

We are far along in this work. We first developed a dementia-specific phenotype, that is, "δ," representing FSCI as the variance in cognitive performance that is shared with a measure of instrumental activities of daily living. δ appears to be dementia's essential phenotype. δ is strongly associated with dementia severity but agnostic to etiology. It cannot discriminate between any two dementing conditions but can equate them all on dementia severity (Gavett et al., 2015; John et al., 2016). In contrast, the cognitive changes that do distinguish individual dementing conditions (being orthogonal to δ) are revealed ipso facto to be inessential to dementia and irrelevant to functional disablement.

δ is derived from Spearman's general intelligence factor *g* (Spearman, 1904), not domain-specific cognitive factors (Royall & Palmer, 2014). Both δ and *g* are latent variables derived from multiple cognitive performance measures (i.e., "indicators"), and δ shares *g*'s property of being "indifferent" to its indicators. Thus, δ can be estimated from a wide range of cognitive performance measures, necessitating the distinction of each instance as one of many potential "δ homologs." In genetics, a homolog is a gene descended from an ancestral gene in the same species and which retains the original's function. Similarly, δ homologs may vary with regard to their indicators but all estimate δ by a bifactor model that includes a measure of instrumental activities of daily living (Royall et al., 2012). Eighteen δ homologs have been validated to date. Each is derived from a unique set of cognitive and/or functional status measures (for example, Koppara et al., 2016; Peh et al., 2017).

Like any latent variable, δ can be *reified* as a composite factor score. When a δ homolog is reified, it becomes a *d score*, which can be applied to individuals as a continuously distributed measure of dementia severity. As a continuous measure, the *d* score indicates the severity of FSCI at any point in dementia's evolution, even among normal controls. Receiver operating characteristic curve analysis can establish an empiric threshold for conversion to clinically diagnosable dementia within the *d*-score continuum. All *d* scores published to date are strongly associated with dementia severity as determined by clinicians (i.e., via the Clinical Dementia Rating Scale [CDR]; Hughes et al., 1982) using the CDR "Sum of Boxes" (CDR-SB; O'Bryant et al., 2010) and achieve high areas under the receiver operating characteristic curve (area under the [ROC] curve)s for Alzheimer's Disease (AD)'s discrimination from controls.

The latent variable δ can be leveraged to identify functionally salient and, therefore, dementia-specific biomarkers. Blood-based proteins are of interest. Many have been associated with clinical dementia and may prove useful in its assessment (Teunissen et al., 2022). We have identified several serum protein biomarkers of δ in the Texas Alzheimer's Research and Care Consortium (TARCC; Royall, Bishnoi, et al., 2019; Royall & Palmer, 2015, 2023). We have also published the serum protein mediators of individual δ-related dementia risks (Royall et al., 2016, 2017a, 2017b).

The Alzheimer's Disease Neuroimaging Initiative (ADNI) has offered us an opportunity to replicate TARCC's biomarker findings in a second cohort and a second biofluid (i.e., plasma). ADNI's cognitive battery overlaps substantially with TARCC's, and both studies use similar blood-based biomarker panels processed by a common vendor. To that end, we have constructed and validated the "d TARCC to ADNI" (dT2A) homolog (Royall, Palmer, & the Alzheimer's Disease Neuroimaging Initiative, 2019).

We recently demonstrated significant associations between dT2A and a latent biomarker construct (i.e., *Adipokines*) indicated by eight serum proteins in TARCC, that is, adiponectin, alpha 1 anti-trypsin (A1-AT), interleukin–1 receptor agonist, leptin (Leptin), monocyte chemoattractant protein–1, resistin (Resistin), tumor necrosis factor alpha (TNFa), and vascular endothelial growth factor (Royall & Palmer, 2023). All but interleukin–1 receptor agonist are also available in plasma in ADNI. ADNI additionally has data on plasma complement factor H, which is unavailable in TARCC. Adipokines are proteins released into the blood by adipocytes and thought to engender effects in multiple organs, including the brain (Lehr et al., 2012). Our *Adipokines* construct exhibited a dose-dependent effect on clinical diagnoses in both cohorts/biofluids and was significantly associated with dT2A (i.e., TARCC/serum $r = 0.84$, $p < .001$; ADNI plasma: $r = 0.49$, $p < .001$; Royall & Palmer, 2023).

Although many blood-based proteins can be associated with δ, in isolation or via their contribution to latent constructs, not all individuals are adversely afflicted by any given subset. We recently demonstrated our ability to distinguish individuals who are "afflicted"

Donald R. Royall played a lead role in conceptualization, formal analysis, funding acquisition, and writing–original draft and an equal role in methodology. Raymond F. Palmer played a lead role in data curation and software, a supporting role in writing–review and editing, and an equal role in methodology.

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versus "resilient" against the dementing effects of inflammation by a novel *line of identity* (LOI) algorithm (Royall & Palmer, 2024). Similarly to *Adipokines*, inflammation was estimated by a latent variable (i.e., "*Inflammation*") indicated by multiple blood-based protein biomarkers. The reified *Inflammation* score was shown to be associated with dT2A, across cohorts and biofluids (Royall, Bishnoi, et al., 2019). The LOI algorithm resulted in classifiers that could distinguish individuals afflicted versus resilient to *Inflammation*'s effect (Royall & Palmer, 2024). In ADNI/plasma, 47.1% of subjects were assigned to the afflicted class. There was greater dementia severity in the afflicted class, by analysis of variance (ANOVA): $F(1) = 686.99$, $p < .001$. *Inflammation* scores were significantly higher (more adverse) in afflicted subjects, by ANOVA: $F(1) = 1642.64$, $p = .001$, as were each of its protein indicators (by Tukey's honestly significant difference test, all $p < .001$). In both cohorts/biofluids, nondemented afflicted cases were more likely to convert to AD in the next 4 years, by Cox's F, ADNI/plasma: $F(252, 268) = 3.74$ $p < .001$; TARCC/serum: $F(160, 134) = 3.03$, $p < .001$.

The present analysis is intended demonstrate the generalizability of our approach to the *Adipokines* construct. We hypothesize that the adipokines-afflicted group will have more adverse levels of adipokines-related blood-based biomarkers, greater dementia severity, and greater risk of prospective conversion to clinical AD from nondemented states. If successful, the same approach might be applied to any number of δ's other known or soon-to-be identified biomarkers. Interventions on those δ-related biomarkers might prove more effective in their respective afflicted class.

Method

Subjects

ADNI

ADNI is a well-characterized longitudinal convenience sample developed to validate the magnetic resonance imaging, positron emission tomography, cerebrospinal fluid, and genetic biomarkers of AD (Weiner & Veitch, 2015). Only a subset of ADNI participants have plasma protein biomarkers ($N = 809$) of whom $N = 403$ also had baseline neuroimaging.

Clinical Variables

CDR-SB

The CDR (Hughes et al., 1982) was used to provide a clinician-rated estimate of dementia severity. The CDR assesses a patient's cognitive abilities over six domains—memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Information is collected during an interview with the patient's caregiver. Domain-specific scores are summed to provide the CDR-SB with improved psychometric characteristics relative to the original scoring method (O'Bryant et al., 2010).

The Mini-Mental State Exam

The Mini-Mental State Exam (Folstein et al., 1975) is a well-known and widely used test for screening cognitive impairment. Scores range from 0 to 30. Scores less than 24 reflect cognitive impairment.

dTEL

We used the "dTEL" homolog (Royall & Palmer, 2018a). dTEL has been engineered to facilitate telephone administration. It is indicated by Logical Memory I (LMI) and II (LMII) from the Wechsler Memory Scale (Wechsler, 1977) and Category Fluency (Animals) from the Consortium to Establish a Registry for Alzheimer's Disease battery (Morris et al., 1989). Regardless, in ADNI, these measures were not administered by telephone, so the associations we report here were not achieved by remote administration.

dTEL's Target Indicator

We used the Functional Assessment Questionnaire (FAQ; Pfeffer et al., 1982) as the target functional status indicator. The FAQ is commonly used in dementia studies (Juva et al., 1997) and has been successfully incorporated into δ homologs by other investigators (Gavett et al., 2015; John et al., 2016).

Blood-Based Biomarkers

ADNIs plasma biomarkers were processed by Rules-Based Medicine in Austin, TX. Rules-Based Medicine conducted multiplexed immunoassay via their human multianalyte profile.

Competing Dementia Risks

Age, an apolipoprotein (APOE) ε4 (+) genotype, depressive symptoms, and gender are independently associated with δ. However, the effect of adipokines on δ is independent of their effects (Royall & Palmer, 2023). These dementia risk factors can therefore be considered as competing determinants of dementia severity as measured by δ.

Beta Amyloid Deposition

Central nervous system amyloidosis was estimated by florbetapir positron emission tomography. Regional standardized uptake values were calculated as the mean florbetapir uptake in four neocortical regions (temporal, frontal, parietal, and cingulate) divided by a reference region (cerebellum). Regional standardized uptake values >1.0 have been associated with dementia (Joshi et al., 2012). Further details regarding these biomarkers in ADNI are available at https://adni.loni.usc.edu.

Age

Age was calculated in years from date of birth.

APOE Genotyping

APOE genotyping was conducted in both data sets using standard polymerase chain reaction methods. APOEε4 status was coded dichotomously based on the presence or absence of an ε4 allele.

Depression

Depressive symptoms were assessed in both studies by the Geriatric Depression Scale (Sheikh & Yesavage, 1986). Geriatric Depression Scale scores range from 0 to 30. Higher scores are worse. The Geriatric Depression Scale is valid in persons with dementia (Burke et al., 1989).

Gender

Self-reported gender was scored dichotomously with female = 0 and male = 1.

Statistical Analyses

Approach

Our LOI algorithm has been previously described (Royall & Palmer, 2024). However, here we used the previously validated dTEL homolog (Royall & Palmer, 2018a). dTEL was engineered to allow for the calculation of a *d* score from a set of telephone-administered indicators. However, dTEL's indicators in this analysis were not collected over the telephone by ADNI. This analysis replicates dTEL's association with CDR-SB in a second cohort (ADNI). The latent dTEL factor was reified to produce a composite dTEL score (dTEL).

Next, we reconstructed the previously validated latent *Adipokines* factor (Royall & Palmer, 2023).

Next, we regressed the *Adipokines* factor onto dTEL. This produces a cognitive residual, CR, representing *all* the variance in dTEL (i.e., in dementia severity) not attributable to *Adipokines*. Any and all competing influences on dTEL are captured in that residual. This was confirmed by multivariate regression of the *Adipokines* construct and CR as predictors of dTEL.

Next, we drew an LOI through a CR by dTEL scatterplot. Visual inspection of the scatterplot can test the null hypothesis that adipokines have no effect on dTEL. Cases presenting off the LOI have demonstrably altered dementia severity after *Adipokines'* unique effect is factored out. Cases can be identified as afflicted by adipokines if their CR scores improve relative to dTEL. Otherwise, they are resilient.

We validated the affliction class by testing its effect on baseline clinician-rated dementia severity (CDR-SB), *Adipokines* scores, and observed concentrations of each of *Adipokines'* protein indicators (in plasma; by ANOVA). The specificity of affliction class to the effects *Adipokines* was confirmed by multivariate regression. We formally tested the moderation effect of affliction class on *Adipokines'* association with clinician-rated dementia severity (i.e., CDR-SB). The effect on their association was tested by change in chi-square fit ($\Delta\chi^2$) in constrained versus unconstrained models, stratified by affliction class. Their association was adjusted for age, APOE4, AV45 regional standardized uptake values, and gender. We also estimated time to AD conversion from nondemented baseline diagnosis (i.e., normal controls or mild cognitive impairment). Time to initial AD conversion was calculated, and the effect tested by survival analysis (i.e., Kaplan–Meier and Cox proportional hazards models; ElHafeez et al., 2012).

SEM

These analyses were conducted in a combined sample of ADNI-1, ADNI-2, and ADNI-Grand Opportunities data (N = 1,737; Weiner & Veitch, 2015). The analysis was performed using Analysis of Moment Structures software (Arbuckle, 2006). The maximum likelihood estimator was chosen for these models. Observed indicators were not adjusted for covariates. Covariances between the residuals were allowed to be estimated if they were significant and improved fit.

Missing Data

Analysis of Moment Structures software uses full-information maximum likelihood methods to address missing data in SEM. It yields unbiased parameter estimates, preserves the overall power of the analysis, and is superior to alternative methods (Schafer & Graham, 2002). All other analyses, including correlations, ANOVA, multiple regression, and survival curves were performed in complete cases.

Fit Indices

One advantage of our SEM approach is that the validity of structural models can be assessed by certain statistical tests. A nonsignificant chi-square signifies that the data are consistent with the model (Bollen & Long, 1993). However, the ratio of the chi-square to the degrees of freedom in the model is also of interest. A chi-square divided by degrees of freedom ratio <5.0 suggests an adequate fit to the data (Wheaton et al., 1977). The comparative fit index (CFI), with values ranging from 0 to 1, compares the specified model with a model of no change (Bentler, 1990). CFI values below 0.95 suggest model misspecification. Values of 0.95 or greater indicate adequate to excellent fit. A root-mean-square error of approximation (RMSEA) of 0.05 or less indicates a close fit to the data, with models below 0.05 considered "good" fit, and up to 0.08 as "acceptable" (Browne & Cudeck, 1993). All three should be simultaneously considered to assess the model's fit to the data.

Transparency and Openness

This article provides appropriate citation for data and materials. Data and methods are appropriately cited. This is a secondary analysis of data obtained from ADNI. ADNI data are available to qualified users from https://adni.loni.usc.edu. The protocol and study design have not been preregistered.

Results

Descriptive statistics of the ADNI sample are presented in Table 1.

dTEL

In this sample, dTEL had excellent fit ($\chi^2 = 2.76$, $df = 2$; CFI = 1.00, RMSEA = 0.02) and exhibited a strong association with CDR-SB ($r = -0.78$, $p < .001$), as reported in its original ADNI validation (Royall & Palmer, 2024). That inverse association, and dTEL's inverse association with FAQ, suggests that higher dTEL scores are salutary.

dTEL was strongly associated with each of its indicators, ranging from Animals ($r = 0.63$, $p < .001$) to LMII ($r = 0.86$, $p < .001$). The FAQ was associated moderately with CDR-SB, independently of dTEL and its cognitive indicators. This unique effect is likely to represent clinician bias, that is, a misattribution of cognition-independent instrumental activities of daily living impairment to *dementia severity* as rated by the CDR. dTEL's indicator paths were fixed, and it was then reified as a composite dTEL score.

The Adipokines Factor

In ADNI/plasma, *Adipokines* factor also had excellent fit ($\chi^2 = 3.24$, $df = 2$; CFI = 0.978, RMSEA = 0.02) as previously reported (Royall & Palmer, 2023). The *Adipokines* indicators were

Table 1
Descriptive Statistics by Adipokine Affliction Class

Variable	All cases $N = 1{,}737$ *M* (*SD*)	"Resilient" above the LOI $n = 1{,}033$ *M* (*SD*)	"Afflicted" below the LOI $n = 704$ *M* (*SD*)	*t*(1,735)	*p*[b]
Age (years)	73.77 (7.20)	72.9 (6.82)	75.01 (7.55)	−5.98	<.001
Animals	17.15 (5.93)	19.48 (5.42)	13.73 (4.89)	22.60	<.001
APOE ε4 allele (%)	56.81	47.13	71.18	−7.47	<.001
CDR-SB	1.64 (1.79)	0.65 (0.81)	3.12 (3.39)	−38.10	<.001
EDUC (years)	15.91 (2.86)	16.37 (2.74)	15.22 (2.89)	8.36	<.001
FAQ	4.26 (6.26)	1.67 (3.38)	8.06 (7.45)	−24.30	<.001
GDS_{30}	1.42 (1.40)	1.27 (1.34)	1.65 (1.46)	−5.71	<.001
Gender (%♂)	55.10	54.70	55.68	−0.41	.69
MMSE	27.17 (2.67)	28.34 (1.79)	25.46 (2.82)	26.04	<.001
WMS LMI[a]	9.28 (4.83)	11.54 (4.24)	5.96 (3.55)	28.72	<.001
WMS LM II[a]	7.07 (5.23)	9.59 (4.88)	3/38 (3.49)	29.03	<.001

Note. LOI = line of identity; Animals = animal naming; APOE = apolipoprotein; CDR-SB = Clinical Dementia Rating scale "Sum of Boxes"; EDUC = education; FAQ = Functional Abilities Questionnaire; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Exam; WMS LM I = Weschler Memory Scale: Immediate Logical Memory; WMS LM II = Weschler Memory Scale: Delayed Logical Memory.
[a] Scaled scores. [b] By *t* test across LOI class.

all significantly inversely associated with the construct, ranging from Leptin ($r = -0.16$, $p < .001$) to A1-AT ($r = -0.37$, $p < .001$; Figure 1).

Once the *Adipokines* construct was reified, it correlated moderately and positively with dTEL ($r = 0.31$, $p < .001$; Figure 1) and strongly inversely with dementia severity by the CDR-SB (in complete cases; $r = -0.61$, $p < .001$). These findings suggest that higher *Adipokines* factor scores are salutary and, because the construct is inversely associated with its indicator proteins, that higher concentrations of those adipokine proteins in plasma are adversely associated with functionally salient cognitive performance.

The *Adipokines* construct explained variance in dementia severity (CDR-SB) independently of its indicators' factor-adjusted observed concentrations, which were also significant (Table 2). This suggests that each adipokines indicator protein can be associated with dementia either via their shared variation (i.e., via the *Adipokines* construct as a systems level biomarker) or independently of both the adipokines construct, *and of each other*. Those latter effects might either be part of competing systems level factors involving yet other cytokines or biomarkers (e.g., Inflammation, which is also indicated by TNFa; Royall, Bishnoi, et al., 2019) or represent direct effects on dementia severity, independent of any other biomarker constellation.

The *Adipokines* Factor's CR

Figure 1 also demonstrates the derivation of the CR factor via regression in SEM. The residual e1 is constrained to zero variance to force dTEL's residual variance into CR, that is, the variance residual to the adipokines construct's effect. CR sequesters the variance in observed dementia severity (i.e., dTEL) due to any and all influences, excepting *Adipokines*. That is confirmed by the finding that CR and adipokines explain 100% of dTEL's variance, by multivariate regression: $F(2, 1{,}734) = 868E^{15}$, $p < .001$. $R^2 = 1.00$.

Derivation of the Affliction Classes From LOI Analysis

Figure 2 presents the LOI analysis. The adjusted (i.e., CR) and unadjusted (i.e., dTEL) composites were strongly correlated (i.e., $r = 0.99$, $p < .001$). Because dTEL is inversely associated with CDR-SB, lower scores are more adverse. Cases with CR scores above the LOI have relatively improved dementia severity after the *Adipokines* factor's unique effect have been accounted for. They are afflicted. The remaining cases are resilient to the effect of the *Adipokines* construct.

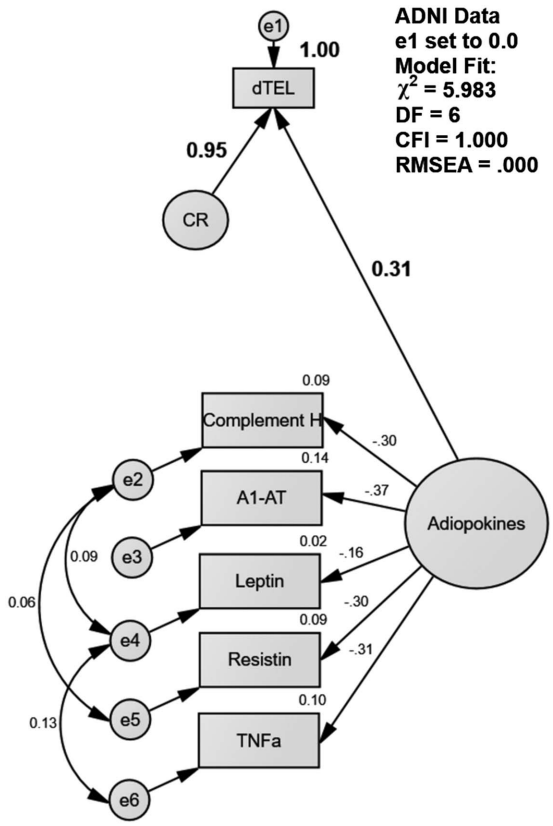
Seven hundred four of 1,737 (40.53%) of ADNI's subjects were adversely impacted by the *Adipokines* construct. Afflicted cases presented across dTEL's entire range. Table 1 presents descriptive statistics by affliction class. Adversely impacted cases were significantly more likely to be ε4 carriers, more impaired on multiple cognitive measures, and were significantly less well-educated. They had higher levels of informant-reported disability and were more likely to be depressed. They were not distinguished by gender.

Validation of the Affliction Classes

CDR-SB scores were significantly higher in the afflicted LOI class, by ANOVA: $F(1, 1{,}735) = 693.54$, $p < .001$. Affliction class adds variance to CDR-SB independently of the *Adipokines* construct and competing dementia risks (Table 3). *Adipokines* scores (in plasma) were significantly lower (adverse) in afflicted subjects, by ANOVA: $F(1, 1{,}735)$ 2619.68, $p < .001$, as were observed levels of each of adipokines' serum protein indicators (i.e., by Tukey's honestly significant difference test, all $p < .001$).

As expected, LOI class membership is largely determined by *Adipokines* construct scores. These are near-normally distributed. $N = 731$ (42.1%) ADNI participants had below average scores ($Z < 0.0$). Six hundred ninety-three (94.80%) of those subjects are afflicted, while 98.91% ($n = 995$) of $N = 1{,}006$ subjects with above-average adipokines scores are resilient. This finding supports the ability of our algorithm to assign affliction class membership relative to a prespecified biomarker. Moreover, Table 4 shows that LOI class fully attenuates the effects of all the observed adipokine biomarkers on CDR-SB (except TNFa, which is also an indicator of *Inflammation*; Royall, Bishnoi, et al., 2019; and presumably associated with δ through its effect). This makes the more inconvenient assessment of the biomarkers themselves irrelevant as no information is provided by

Figure 1
Cognitive Residual Factor (ADNI)



Note. A1-AT = alpha 1 antitrypsin; ADNI = Alzheimer's Disease Neuroimaging Initiative; CFI = comparative fit index; CR = Cognitive Residual factor; Complement H = complement factor H; DF = degrees of freedom; RMSEA = root-mean-square error of Approximation; TNFa = tumor necrosis factor alpha.

observed biomarker values independent of affliction class. Nevertheless, class membership was only moderately associated with a clinical diagnosis of "AD" (Spearman rank correlation = 0.49, $p < .05$). This suggests that AD's clinical diagnosis is influenced by factors other than adipokines (i.e., via CR's effect). The effect of plasma adipokines on δ may merely be one of many biomarker-mediated processes contributing to the observed dementia severity of ADNI subjects. Regardless, those afflicted by *Adipokines* can now be recognized and triaged for adipokine-specific intervention.

Figure 3a presents the baseline moderation model. The moderation effect was significant, $\Delta\chi^2 = 26.66$ ($\Delta DF = 1$), $p < .001$. The adipokines construct explained fourfold more variance in CDR-SB in the afflicted class (Figure 3b) relative to the resilient class (Figure 3c). There is little change in the total explained variance in CDR-SB. This suggests that the covariate effects are relatively attenuated by *Adipokines* in the affliction class, raising the possibility of adipokine mediation effects on one or more of the covariates.

Baseline affliction class continues to impact CDR-SB at 48 months, by ANOVA: $F(1, 614) = 77.14, p < .001$. Baseline affliction class also had a significant effect on 4-year (48 months) prospective conversion to clinical AD from nondemented states, Cox's $F(234, 286) = 3.89$, $p < .001$; Figure 4.

Discussion

These findings recapitulate earlier findings from TARCC and ADNI (Royall, Bishnoi, et al., 2019; Royall & Palmer, 2023). A latent *Adipokines* factor can be associated with δ, and now with a second homolog, that is, dTEL. We also demonstrate that this biomarker affects dTEL scores across dTEL's entire distribution, that is, the entire range of dementia severity, including nondemented ADNI participants. Its effect persists at 48 months and contributes to the prospective conversion risk of initially nondemented subjects.

This analysis also suggests that the *Adipokines'* effects on δ are independent of multiple competing dementia risks, including central nervous system amyloidosis by positron emission tomography, that is, an AD-specific biomarker. Affliction class explains additional variance in dementia severity independently of covariates and observed plasma biomarker concentrations and latent *Adipokines* scores; affliction class also moderates *Adipokines'* independent effect on dementia severity by a factor of four.

Since this is our second demonstration of psychometric biomarker affliction classification, it seems likely that the effects of other biomarkers on dTEL might be determined by the same approach. If so, then an individual might be assigned to multiple affliction

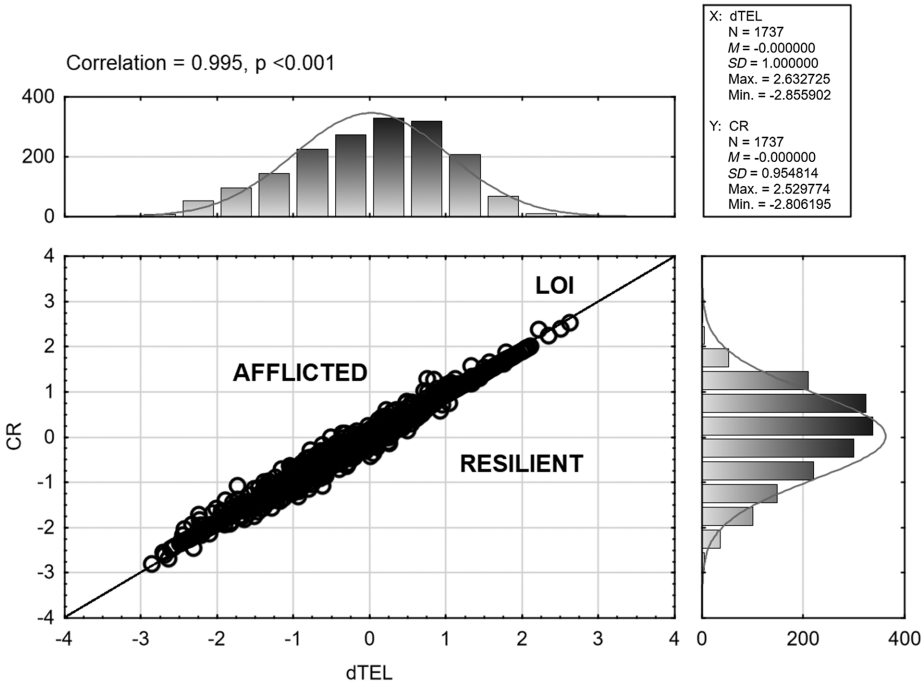
Table 2
The Adipokines Construct Is Associated With CDR-SB Independently of Its Indicators

Predictor	b[a]	*SE* of b[a]	b	*SE* of b	$t(1,730)$	p
Intercept			21.367	0.552	38.693	<.001
A1-AT[a]	−0.533	0.020	−17.718	0.660	−26.846	<.001
Complement H[b]	−0.370	0.018	−0.001	<0.001	−21.077	<.001
Leptin[c]	−0.106	0.015	−0.795	0.112	−7.088	<.001
Resistin[c]	−0.379	0.018	−7.310	0.337	−21.687	<.001
TNFa[d]	−0.461	0.018	−5.168	0.201	−25.700	<.001
Adipokines	−1.534	0.0298	−6.383	0.122	−52.157	<.001

Note. $N = 1{,}737$. Regression summary for dependent variable CDR-SB: $R = 0.802$; $R^2 = 0.643$; adjusted $R^2 = 0.642$; $F(6\ 1{,}730) = 518.73$, $p < .001$. CDR-SB = Clinical Dementia Rating scale "Sum of Boxes"; *SE* = standard error; A1-AT = alpha 1 antitrypsin; Complement H = complement factor H; TNFa = tumor necrosis factor alpha.
[a] mg/ml. [b] μg/ml. [c] ng/ml. [d] pg/ml.

Figure 2

Scatterplot of Adipokine-Adjusted (CR) × Unadjusted (dTEL) Composite Scores With LOI (ADNI)



Note. CR = Cognitive Residual factor; LOI = line of identity; ADNI = Alzheimer's Disease Neuroimaging Initiative; Max = maximum; Min = minimum.

classes after a single administration of dTEL's indicators. Since our algorithm might be applied to any other δ-related biomarker or risk factor, our approach could be leveraged to diagnose affliction by imaging and/or cerebrospinal fluid biomarkers and without the need for their expensive, potentially hazardous, difficult to acquire, and/or difficult to perform assessment.

Our analysis has replicated the existence of individuals who are resilient against certain δ-related blood-based biomarkers, that is, inflammatory cytokines (Royall & Palmer, 2024) and now adipokines. Those findings calls into question studies that try to relate observed concentrations of blood-based proteins to cognitive performance, as class membership may moderate their associations, as it moderates *Adipokines'* association with CDR-SB in Figure 3.

In the case of these adipokines, resilience is largely attributable to the cross-class differences in observed baseline adipokines factor scores but not the observed values of individual biomarkers (Table 4). This suggests that the integrated actions of adipokine biomarkers may be more salient to dementia's severity than their observed concentrations. Such interactions can be quantified through latent variables and are a strength of our approach.

Regardless, affliction class explains variance in dementia severity independently of even the *Adipokines* construct. Class membership

Table 3

Affliction Class Adds Variance to CDR-SB Independently of Adipokines and Competing Dementia Risks

Predictor	β	*SE* of β	*b*	*SE* of *b*	*t*(1,717)	*p*
Intercept			−1.129	0.402	−2.810	.005
Age	−0.037	0.019	−0.009	0.005	−1.981	.056
APOE4	0.071	0.020	0.190	0.053	3.628	<.001
AV45	0.248	0.021	2.411	0.207	11.669	<.001
GDS	0.086	0.018	0.110	0.023	4.765	<.001
Gender	0.047	0.018	0.169	0.065	2.601	.009
Adipokines	−0.433	0.029	−1.802	0.119	−15.139	<.001
Affliction class	0.074	0.029	0.269	0.106	2.551	.01

Note. $N = 1{,}725$. Regression summary for dependent variable CDR-SB: $R = 0.68$; $R^2 = 0.46$; adjusted $R^2 = 0.46$; $F(7, 1{,}717) = 206.75$, $p < .001$. CDR-SB = Clinical Dementia Rating scale "Sum of Boxes"; *SE* = standard error; APOE4 = the number of apolipoprotein E ε4 alleles; AV45 = florbetapir PET; GDS = Geriatric Depression Scale; PET = positron emission tomography.

Table 4
Affliction Class Attenuates Multiple Observed Adipokine Biomarker Effects on CDR-SB

Predictor	β	*SE* of β	*b*	*SE* of *b*	*t*(1,730)	*p*
Intercept			2.373	0.466	5.093	<.001
A1-AT[a]	−0.023	0.022	−0.766	0.738	−1.038	.299
Complement H[b]	0.003	0.021	<0.001	<0.001	0.126	.900
Leptin[c]	−0.016	0.021	−0.123	0.156	−0.790	.430
Resistin[c]	−0.039	0.022	−0.754	0.419	−1.800	.072
TNFa[d]	−0.088	0.022	−0.990	0.246	−4.034	<.001
Affliction class	0.592	0.026	2.162	0.094	22.901	<.001

Note. N = 1,737. Regression summary for dependent variable CDR-SB: $R = 0.543$; $R^2 = 0.295$; adjusted $R^2 = 0.292$; $F(6\ 1{,}730) = 120.51$, $p < .001$. CDR-SB = Clinical Dementia Rating scale "Sum of Boxes"; *SE* = standard error; A1-AT = alpha 1 antitrypsin; Complement H = complement factor H; TNFa = tumor necrosis factor alpha.
[a] mg/ml. [b] µg/ml; [c] ng/ml; [d] pg/ml.

fully attenuates the effects of observed plasma biomarkers on dementia severity, while the *Adipokines* construct does not (Tables 3, 4). These findings suggest that affliction class informs *Adipokines*-specific effects on dementia severity independently of both unique and integrated biomarker effects. So, ironically, psychometric assessment may be essential to the interpretation of biomarkers, which were introduced, in part, as a means of circumventing the perceived weaknesses of psychometric measures.

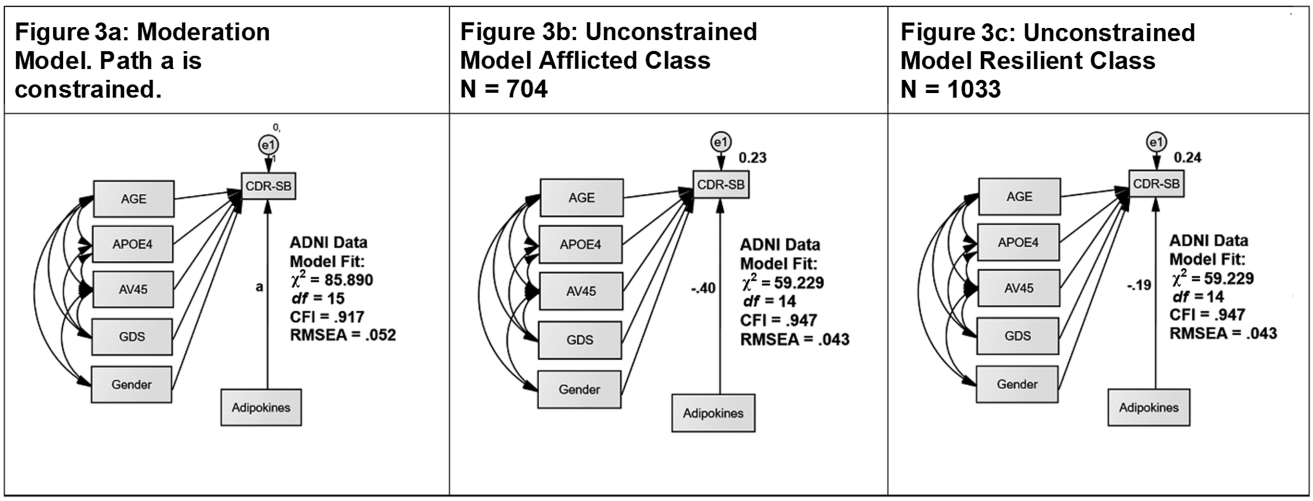
This may have implications for the Alzheimer's Precision Medicine Initiative, which aims to facilitate a "precision medicine" approach to dementia-related interventions in preclinical cases (Hampel et al., 2017; O'Bryant et al., 2023). Our findings suggest that the psychometric recognition of biomarker-afflicted cases has cross-sectional and longitudinal clinical impacts above and beyond the biomarkers themselves and that a sizable fraction of nondemented subjects at risk for dementia may be resilient against a biomarker's effect. The integration of affliction class assessment into precision medicine initiatives might improve study power and prevent unnecessary risk of adverse outcomes in the resilient class.

The fraction of observed dementia severity that is specifically attributable to plasma adipokine biomarkers may be amenable to intervention in afflicted cases. Raising plasma *Adipokines'* construct scores should have a salutary impact on δ, and the construct's impacts are likely to be independent of multiple better known dementia risks. Interestingly, treatment with donepezil has been shown to modulate two of the adipokines construct's indicators, leptin and adiponectin (Pákáski et al., 2014). Serum adiponectin has been associated with δ in TARCC (Royall & Palmer, 2020). We have been recently funded by the National Institute on Aging to investigate the *Adipokines* construct as a potential mediator of donepezil's effect on δ (Grant 1R01AG080548-01, principal investigator: Donald R. Royall).

Our results do not preclude direct effects of individual plasma adipokines on δ independent of their interactions represented by the adipokines construct. All *Adipokines* indicators are associated with CDR-SB independently of the latent construct (Table 2), and TNFa is associated with CDR-SB independently of LOI class (Table 4). So, these plasma proteins might impact dementia severity either directly or indirectly via one or more latent biomarker factors. These paths are amenable to description in an SEM framework but are indiscernible from observed biomarker values.

The significance of this may come out when an intervention is proposed. If a biomarker is associated with dementia only via its integrated action with others, then an intervention that alters the observed level of that single biomarker cannot modulate the outcome of interest, as the change would be residual to the latent factor. Interventions may have to modulate *all* of the *Adipokines* construct's indicators to change the adipokines construct score and thereby modulate dementia severity. The single exception might be

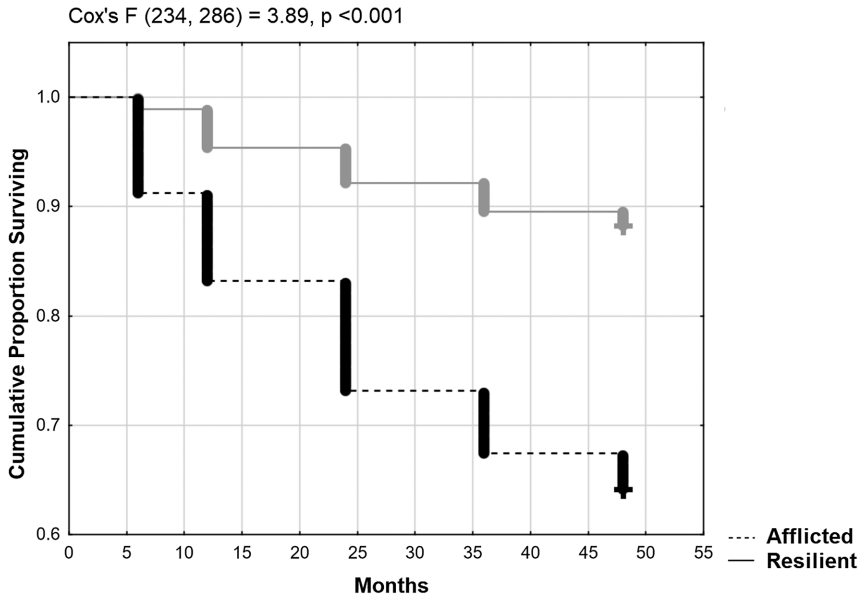
Figure 3
Moderation Effect



Note. APOE4 = the number of apolipoprotein E ε4 alleles; AV45 = florbetapir; GDS = Geriatric Depression Scale; CDR-SB = Clinical Dementia Rating Scale "Sum of Boxes"; ADNI = Alzheimer's Disease Neuroimaging Initiative; DF = degrees of freedom; CFI = comparative fit index; RMSEA = root-mean-square error of approximation; PET = positron emission tomography.

Figure 4

48-Month Prospective Conversion to Clinical AD From Nondemented Baseline Diagnoses (NC + MCI) as a Function of Adipokines Affliction Class (ADNI)



Note. AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; NC = normal controls; MCI = mild cognitive impairment.

TNFa, whose association with CDR-SB was found to survive adjustment for the LOI class in Table 4. TNFa may also impact dementia through its integration with inflammatory cytokines (Royall & Palmer, 2024). We can now begin to appreciate how a single protein biomarker (e.g., TNFa) might impact dementia either via *Inflammation*, via *Adipokines*, or via both factors, depending on the biomarker milieu in which it is operating. In this sense, our latent variable approach is exploring systems effects, not merely the effects of individual biomarkers in isolation from each other. Any study that relates the unique effects of one or more observed biomarkers with dementia may be blind to effects mediated via their interactions.

Some significant caveats may limit our approach. First, since ADNI is a convenience sample, it remains to be seen if parameter weights derived from it can be generalized to newly assessed cases. Another caveat is that since ADNI is neither ethnically nor racially diverse, it remains to be seen if our classifier can be generalized to demographics other than non-Hispanic Whites. However, our *Inflammation* classifier was replicated in TARCC's more diverse sample and its Mexican American participants (Royall & Palmer, 2024).

Second, this is an ad hoc panel of adipokines of unestablished biological validity. Over 600 proteins have been identified as potential adipokines by proteomic methods. However, that list includes all of our construct's indicators (Lehr et al., 2012).

Regardless, our use of a latent variable approach is conceptually novel. We are not associating observed concentrations of adipokine biomarkers with dementia. We are, instead, associating a latent factor representing their concerted interaction with that syndrome. That the effect of *Adipokines* on CDR-SB is independent of its indicators' observed levels suggests that their shared variance, captured by the latent construct, contributes independently to dementia severity. It is their shared variance (i.e., the *Adipokines* score) that is also relevant to the LOI class's effect on dementia, as most *Adipokines* indicators have no independent effect on CDR-SB (Table 4).

Finally, our analysis does not address domain-specific cognitive variance. The *Adipokines* construct might relate to such domains or not. Even if they were related, the effect of adipokines on domain-specific constructs would be incapable of explaining variance in dementia severity, as domain-*specific* factors are orthogonal to δ (Royall & Palmer, 2014, 2019). We emphasize "specific" because so-called "domain-specific" factors in the literature are rarely adjusted for *g*'s effect and remain intercorrelated through it.

Future Directions

Since most of the *Adipokines* construct's indicators do not predict dementia severity independently of LOI class (Table 4), knowledge of the LOI class may obviate biomarker assessment. While we used biomarker data to generate dTEL and CR parameter weights in this reference sample (i.e., ADNI), affliction class *is determined only by the difference in dTEL and CR scores*. Both are latent variables, and neither is indicated by adipokine proteins (Figure 1). CR has a single indicator, that is, dTEL. Once a dTEL score is calculated from its *psychometric* indicators, CR can be calculated from it, and their difference will determine the LOI class.

It would be inconvenient to take an unknown case and have Analysis of Moment Structures software calculate their CR scores by treating them as ADNI subjects with missing biomarker data. However, we have developed SEM methods, not used here, that can predict biomarkers from cognitive assessment (Royall & Palmer, 2018b, 2018c). If those were directed toward CR's estimation,

affliction class might be assigned from dTEL's indicators alone, without knowledge of adipokine biomarker values and without any additional statistical manipulation. Since that might be repeated for any δ-related biomarker, individuals might be assigned to any number of affliction classes after a single administration of dTEL's indicators. Since those can be potentially administered remotely or by telephone, individuals might be screened for multiple dementia-related biomarkers without any personal contact. Afflicted cases could then be referred for biomarker-specific interventions (a precision medicine approach). One significant obstacle to that program would be the generalizability of parameter weights derived in a convenience sample (i.e., ADNI) to the general population. Regardless, future models derived in even relatively small well-characterized *representative samples* might overcome that limitation.

Conclusions

Biomarker-specific psychometric classifiers can be constructed by an LOI approach applied to reified δ homologs. Our *Adipokines* classifier selects individuals with prespecified biomarker profiles and predicts prospective conversion to AD from nondemented states. Our approach also distinguishes individuals resilient to individual biomarker effects, allowing for more accurate prediction and precision intervention.

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Received February 7, 2024
Revision received May 6, 2024
Accepted June 7, 2024 ■