

RESEARCH ARTICLE

Selection for depression-specific dementia cases with replication in two cohorts

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Data Availability Statement: The data underlying the results presented in the study are available from TARCC and ADNI. Requests for TARCC data should be made to <http://www.txalzresearch.org/research/>. Requests for ADNI data should be made to adni.loni.usc.edu.

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Abstract

The latent variable “ δ ” (for “dementia”) provides an etiologically “agnostic” omnibus dementia severity metric capable of recognizing the dementing potential of any condition. Depressive symptoms are independent predictors of δ and are thereby implicated as “dementing”. Serum resistin levels partially mediate the association between depressive symptoms and δ . We use a novel “off-diagonal” CHI SQ algorithm to demonstrate our ability to select individuals demented solely by depression’s effect in both the Texas Alzheimer’s Research and Care Consortium (TARCC) (N \cong 3,500), and the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (N \cong 1,750), and demonstrate the higher resistin levels of such cases in TARCC. This approach can be adapted to any δ -related dementia risk factor or biomarker and used identify individuals who might revert back to non-demented states after its successful treatment.

Introduction

Using theory-driven confirmatory bifactor analyses (CFA) in a Structural Equation Model (SEM) framework, we have discovered a transdiagnostic omnibus dementia severity measure (i.e., “ δ ” for “dementia”) [1]. δ represents “the cognitive correlates of functional status”. By definition, it embodies cognition’s association with instrumental activities of daily living (IADL) and it is empirically strongly related to dementia severity [as measured by the Clinical Dementia Rating scale “Sum of Boxes”(CDR-SB)] [2], both cross-sectionally and longitudinally [1, 3–4].

δ ’s strong association with clinical dementia has been independently replicated in the National Alzheimer’s Coordinating Center (NACC)’s Uniform Dataset (UDS) (N = 26,606)

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Competing interests: We have the following potential interests: The authors have disclosed the results of these analyses to the University of Texas Health Science Center at San Antonio (UTHSCSA), which has filed patent applications 61/603,226: "A Latent Variable Approach to the Identification and/or Diagnosis of Cognitive Disorders", 61/671,858: "A Serum Biomarker Screen for the Diagnosis of Clinical and Pre-clinical Alzheimer's Disease in Non-Hispanic Populations", and 62/112,703: "Methods and Approach for Detection and Prediction of Change in Dementia Severity or Clinical Diagnosis over Time" relating to the latent variable δ 's construction and biomarkers. There are no further patents, products in development or marketed products to declare. This does not alter our adherence to all the PLoS ONE policies on sharing data and materials.

[3] and in well characterized European [5] and Austral-Asian [6–7] samples. However, these studies also reveal δ to be "agnostic" to dementia's etiology. δ has a high AUC for the diagnosis of all cause dementia in the NACC (i.e., 0.96) [1], but it cannot distinguish between any two dementia etiologies [8]. Thus, δ does not convey etiologically-salient information. Etiologically-specific information is conveyed instead by domain-specific cognitive factors, residual (and therefore unrelated) to δ . δ cannot distinguish any two dementias because *it* is dementia's essential cognitive impairment.

δ can be "reified" as a factor composite and assigned to individuals as a "d-score". Because d-scores are continuously distributed, δ effectively converts dementia from a *category* to a *dimension*. It can thereby rank order, individuals, even normal controls (NC), with regard to their dementia "severity" and /or equate them for severity across diagnoses. Even slight differences in the d-scores of persons without dementia increases their prospective risk of conversion to clinical dementia [9].

δ is derived from Spearman's general intelligence factor "g" [10]. In consequence, it must be distinguished from domain-specific cognitive performance [i.e., "memory" (MEM) or "executive function" (EF)] [11]. This both undermines the latter's claims of contribution to IADL impairment and implicates a disruption of g as dementia's essential feature.

g manifests in every cognitive performance measure. Since δ is derived from g, it too appears to be estimable from any cognitive battery that contains a measure of IADL. δ can be constructed from a comprehensive battery of formal measures [1, 3, 5–6, 8], from small batteries of formal measures [12–13], from brief batteries of "bedside" measures [14], and even from the items of a single measure [15]. Thus, we must further distinguish between δ i.e., "the cognitive correlates of functional status", and "d" i.e., δ 's "reification" as a composite "d-score" in a specific cognitive battery or analysis. So many batteries are available that we refer to each embodiment as a δ "homolog". In genetics, a homolog is a gene descended from an ancestral gene in the same species and preserving the original's function. All δ homologs (fourteen published to date) share δ 's bifactor construction, target a measure of IADL, exhibit strong associations with dementia severity (e.g., as measured by CDR-SB) and achieve high areas under the receiver operating characteristic curve (AUC /ROC) for the discrimination of various dementias from NC.

Given δ 's unique association with dementia, dementia's risk factors must be associated with δ and δ 's biomarkers are likely to mediate dementing processes. Age, depression, and the apolipoprotein E (APOE) e4 allele are independently associated with δ [16]. We have reported the serum protein biomarkers that mediate each of their unique associations with δ [17–19]. Independently of those risk factors, δ is associated with additional pro- and anti-inflammatory serum protein biomarkers, [16, 20–22]. It is unclear how these might relate to traditional Alzheimer's Disease (AD)-specific biomarkers, but it is more clear that unless the latter can also be associated with δ , their effects on cognitive performance will not be dementing.

It seems increasingly likely then that dementia severity, as estimated by δ homologs, represents the summed effects of multiple independent δ -related processes. There may be interindividual variability with regard to which specific processes are responsible for the observed d-score in an individual patient. Each process may have its own unique set of biomarkers and yet explain only a portion of δ 's variance. It becomes desirable then to intervene on the processes that are most amenable to treatment and /or contribute most to the individual's d-score. In individual patients, the treatable subset may be entirely responsible for the observed d-score, or only a minor component. Thus, the impact of successful intervention may depend on the targeted process' contribution to the observed d-score. Ideally, we would want to intervene on patients who might revert back across the d-score threshold for "clinical" dementia into δ 's non-demented range. The goal is to select patients who are not merely afflicted by the targeted

dementing process, but who have been pushed over the d-score threshold for clinical dementia solely by that process. Moreover, such cases will have to be identified as individuals so that they can be targeted precisely for treatment.

Approach to case selection

We propose the following algorithm to detect individuals most likely to respond to an intervention against any pre-specified dementing process (e.g., depressive symptoms in the present analysis). By definition, all dementing processes must impact δ . While any δ homolog might be employed, we chose the recently validated “dT2A” (TARCC to ADNI) homolog. “ADNI” refers to the Alzheimer’s Disease Neuroimaging Initiative (ADNI). dT2A was specifically engineered to replicate across the TARCC and ADNI studies [23]. We chose this homolog because we intend to validate the cases selected by this approach on the basis of certain blood-based protein biomarkers (e.g., resistin) which we have previously shown to mediate the unique association between δ and depressive symptoms [19]. The dT2A homolog (Fig 1) has been reported to have excellent fit in both datasets [TARCC: CHI SQ = 73.6 (20), $p < 0.001$; CFI = 0.996; RMSEA = 0.028; ADNI: CHI SQ = 12.464 (7), $p < 0.001$; CFI = 0.999; RMSEA = 0.019], to correlate strongly with CDR-SB in both datasets [TARCC: $r = 0.99$, $p < 0.001$; ADNI: $r = 0.96$, $p < 0.001$], and to achieve a high AUC for AD’s discrimination from NC [TARCC: AUC = 0.981 (0.976–0.985); ADNI: AUC = 1.0 (0.995–1.00)] [23].

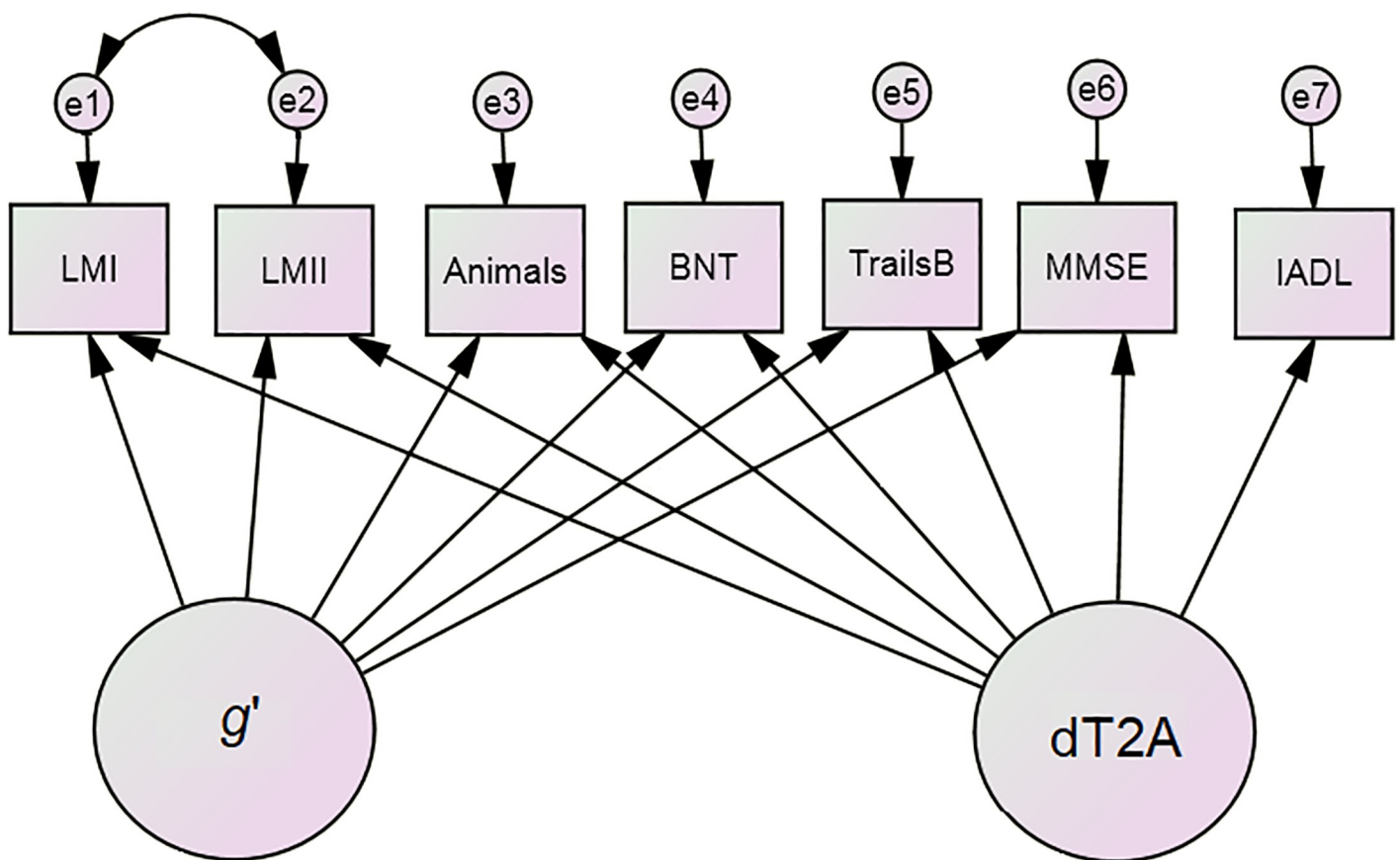


Fig 1. dT2A.

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For the present analysis, we chose depressive symptoms as the δ -related risk factor of interest because of the widespread availability of effective antidepressant treatments. We propose to identify individuals in TARCC who have converted to clinical dementia, nominally “AD”, solely by the effect of depressive symptoms on their d-scores, and to validate the selected cases on the basis of biomarkers known to mediate that specific association.

First, we must reconstruct dT2A in both cohorts. No covariate adjustments are applied to the raw data. Next, we adjust dT2A for depressive symptoms. To that end, we constructed a dichotomous dummy variable (GDS-di) coding scores $\geq 11/30$ on the GDS, i.e., at the GDS’ recommended threshold for “clinical depression” [24]. This divides both samples into cases with higher and lower burdens of depressive symptoms. By adjusting only for depressive symptoms, the variance related to all other δ -related dementia risks remains in the composites.

Next, we identify the thresholds for dementia conversion by both the adjusted and unadjusted composites, in both datasets, by ROC analysis. The thresholds are all set at Specificity = 0.85. Next, we dichotomize each cohort into “demented” and “non-demented” cases, by both the adjusted and unadjusted composites.

Since the adjusted and unadjusted composites differ only with regard to the variance related to depressive symptom burden, they are expected to be highly correlated, *but not identical*. To confirm this, we regress the adjusted and unadjusted dT2A composites. Because they are not identical, there is expected to be some discrepancy in the classifications derived from these composites. By comparing the resulting adjusted and unadjusted classifications in a CHI-SQ table, “off-diagonal” cases can be recognized as individuals. These represent individuals whose classification changes when depression’s unique effect on δ is considered. The group which reverts back to a non-demented d-score after the GDS’ impact has been adjusted can be considered to have been demented solely on the basis of their depressive symptom burden. To confirm this conclusion, we contrast serum (TARCC) and plasma (ADNI) resistin levels across the off-diagonal groups. This approach also allows us to estimate the fraction of so-called “AD” cases who have been demented (i.e., pushed across dT2A’s threshold for clinical conversion) by a GDS score ≥ 11 in both the TARCC and ADNI cohorts.

Materials and methods

The samples and methods employed in dT2A’s construction and in the present analysis are identical to Royall & Palmer, 2018 [23] and reiterated here for the convenience of the reader.

Subjects

The present study is a secondary analysis of data collected by TARCC and ADNI. Informed consent was obtained from all participants (or their legally authorized proxies) before data collection, and both studies are approved by their respective Institutional Review Boards (IRB).

TARCC. Subjects included N = 3502 Texas Alzheimer’s Research and Care Consortium (TARCC) participants [25]. TARCC is a longitudinally followed convenience sample of elderly persons with Alzheimer’s disease (AD) (n = 1275), “Mild Cognitive Impairment” (MCI) (n = 732), or normal cognition (NC) (n = 1445) (and 58 “others”) recruited from five Texas medical schools. Each participant underwent a standardized annual examination that included a medical evaluation, neuropsychological testing, and clinical interview. Categorical clinical diagnoses of “AD”, “MCI” and “NC” were established through consensus. The diagnosis of AD was based on National Institute for Neurological Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria [26]. The diagnosis of MCI was based on site-specific consensus-based clinical diagnoses derived from all available information but without reliance on specific neurocognitive tests and /or cut-

scores. “All available information” included the results of TARCC’s entire neuropsychological battery, clinical evaluations, informant interviews, and any available outside medical records. We could not easily use cut-scores because normative Mexican-American (MA) scores are not available for many measures.

ADNI. ADNI is a well-characterized longitudinal convenience sample developed to validate the magnetic resonance, positron emission tomography (PET), cerebrospinal fluid (CSF), and genetic biomarkers of AD [27]. The initial 5-year study, ADNI-1, enrolled cognitively normal, mild cognitive impairment (MCI) and AD subjects, and subsequent studies (ADNI-GO and ADNI-2) added early- and late-MCI cohorts. ADNI has provided a framework for similar initiatives worldwide, including TARCC. In its combined sample ($N = 1738$), $N = 342$ were diagnosed with AD, $N = 978$ with MCI and $N = 417$ as NC. For this analysis, all MCI subtypes were combined, including ADNI-GO participants with “Subjective cognitive impairment (SCI)”.

Clinical variables

dT2A, a δ homolog for ADNI. dT2A is indicated by observed cognitive measures that are common to both TARCC and ADNI, including the Boston Naming Test (BNT) [28], Category Fluency (Animals) [29], Logical Memory I (LMI) and II (LMII) [30], the Mini-Mental State Examination (MMSE) [31], and Trail-Making Part B (TrailsB) [32]. All are available in TARCC in Spanish translation.

Boston Naming Test (BNT) [28]: The BNT is a confrontation naming test that requires the subject to verbally name line drawings of objects associated with words of increasingly lower frequency in the target language. TARCC uses 30 item BNT. ADNI uses 60 item BNT.

Categorical Fluency (Animals) [29]: This test of verbal fluency asks subjects to verbally generate as many animal names as they are able in one minute.

Logical Memory II (LMII) [30]: Immediately (LMI), and following a thirty minute delay (LMII), the subject recalls two paragraphs read aloud.

Mini-Mental Status Examination (MMSE) [31]: The MMSE is a well-known and widely used test for screening cognitive impairment.

Trail Making Part B (Trails B) [32]: Trails B is a timed test of attention, speed, and mental flexibility that requires the subject to alternately connect between numbers and letters. TARCC reports Trails B as scaled scores.

dT2A’s target indicators. In TARCC, we used informant-rated Instrumental activities of daily living (IADLs) [33] as dT2A’s target indicator. Unfortunately, IADL is not available in ADNI, and so the Functional Assessment Questionnaire (FAQ) [34] was used instead. The FAQ has been successfully incorporated into δ homologs by other investigators [10–11].

Instrumental Activities of Daily Living: IADL was assessed using Lawton’s method [33]. This involves a structured clinical interview that provides informant-reported information on seven IADLs. Each item is scored on a four point Likert scale with 0 signifying “no impairment”.

The Functional Activities Questionnaire (FAQ) [34]: The FAQ is an informant-rated measure of a participant’s ability to be perform IADLs. The FAQ is commonly used in dementia evaluations [35–36].

Observed clinical measures. Observed clinical measures are often used as covariates or to provide external validation. The following measures are available in both TARCC and ADNI.

Self (informant)-reported age, and gender are self-explanatory. Education was measured in years. Ethnicity is coded dichotomously according to self-reported Hispanic affiliation. TARCC has a substantial number of MA participants. MA ethnicity has pronounced effects on

serum protein biomarkers in TARCC [22, 37]. There are no racial distinctions in TARCC, and no reported racial effects on plasma protein biomarkers in ADNI.

The Clinical Dementia Rating Scale “Sum of Boxes” (CDR-SB) [2]. The CDR is used to evaluate dementia severity. The rating assesses the patient’s cognitive ability to function in 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 and their caregiver (15 minutes).

Geriatric Depression Scale (GDS): Depressive symptoms were assessed in both studies by the Geriatric Depression Scale (GDS) [24, 38]. GDS scores range from zero-30. Higher scores are worse. The GDS is valid in persons with dementia [39].

Statistical analyses

These analyses were conducted in TARCC’s most recent dataset ($N = 3502$) and in a combined sample of ADNI-1, ADNI-2, and ADNI-GO data ($N = 1737$). The analysis was performed using Analysis of Moment Structures (AMOS) software [40]. The maximum likelihood estimator was chosen for these models. Covariances between the residuals were allowed to be estimated if they were significant and improved model fit.

The observed variables were fit to a linear confirmatory bifactor model. Measurement errors are assumed uncorrelated and the latent variables means and variances were fixed to 0 and 1 respectively allowing all loadings to be freely estimated.

Missing data. We used Full Information Maximum Likelihood (FIML) methods to address missing data. FIML uses the entire observed data matrix to estimate parameters with missing data. In contrast to listwise or pairwise deletion, FIML yields unbiased parameter estimates and preserves the overall power of the analysis [41–42].

Fit indices. The validity of structural models was assessed using two common test statistics. A non-significant chi-square signifies that the data are consistent with the model [43]. However, with large samples chi-square will often be significant, even for models which fit the data well. Therefore, the ratio of the chi-square to the degrees of freedom in the model is also of interest. A CMIN/DF ratio < 5.0 suggests an adequate fit to the data [44]. The comparative fit index (CFI), with values ranging from between 0 and 1, compares the specified model with a model of no change [45]. 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” [46]. All three fit statistics should be simultaneously considered to assess the adequacy of the models to the data.

Results

Descriptive statistics are presented by group in Table 1. Cohen’s d and t tests of significance are reported in Table 1, where estimable, for TARCC vs. ADNI. These samples differed significantly on all measures. ADNI appears to have a relatively high fraction of MCI cases, which were recruited explicitly into ADNI-2 and ADNI-GO. TARCC has a much higher prevalence of MA participants.

Descriptive statistics by diagnosis are provided for TARCC and ADNI (respectively) in Tables A and B in S1 File.

dT2A’s unadjusted model had excellent fit in both cohorts as previously reported [17]. The GDS adjusted models also fit well [i.e., TARCC: CHI SQ = 50.9 (7), $p < 0.001$; CFI = 0.998; RMSEA = 0.042; ADNI: CHI SQ = 71.7 (7), $p < 0.001$; CFI = 0.994; RMSEA = 0.064]. The GDS-adjusted composites achieved high Areas Under the Receiver Operating Characteristic

Table 1. Descriptive statistics by sample (raw scores except where indicated).

	TARCC Total N = 3502	ADNI N = 1738
	Mean (SD)	Mean (SD)
AD cases	1275 (37.0%)	342 (19.7%)
MCI cases	723 (21.0%)	978 (56.3%)
NC	1445 (41.9%)	417 (24.8%)
Gender (%♀)	61.6	55.1
Ethnicity (%MA)	35.7	3.4
	Mean (SD)	Mean (SD / d1)
Age	70.8 (9.6)	73.8 (7.19 / 0.35 [‡])
Education	13.3 (4.3)	15.91 (2.86 / 0.71 [‡])
MMSE	25.6 (4.7)	27.17(2.67 / 0.42 [‡])
Animals	14.9 (5.5)	17.15 (5.93 / 0.39 [‡])
BNT*	7.9 (4.3)	25.97 (4.51 / **)
CDR-SB	2.4 (3.3)	1.64 (1.79 / 0.28 [‡])
GDS30	5.6 (5.2)	1.42 (1.40 / 1.09 [‡])
LMI	7.9 (4.2)	9.28 (4.83 / 0.30 [‡])
LMII	8.2 (4.6)	7.07 (5.33 / 0.22 [‡])
Trails B (sec)	144.24 (84.05)	122.23 (75.78 / 0.27 [‡])

d1 = Cohen’s d vs. TARCC’s entire sample.

*Scaled scores.

**TARCC uses 30 item BNT, ADNI uses 60 item BNT.

[‡] p <0.001

ADNI = Alzheimer’s Disease Neuroimaging Initiative; Animals = Animal Naming; BNT = Boston Naming Test; CDR-SB = Clinical Dementia Rating scale “Sum of Boxes”; GDS = 30 item Geriatric Depression Scale; LMI = Wechsler Logical Memory immediate recall; LMII = Wechsler Logical Memory delayed recall; MA = Mexican-American; MMSE = Mini-mental State Exam; SD = standard deviation; TARCC = Texas Alzheimer’s Research and Care Consortium; Trails B = Trail Making Test Part B.

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Curve (AUC /ROC) for AD’s discrimination from NC [i.e., TARCC: AUC = 0.964 (0.976–0.985); ADNI: AUC = 0.988 (0.983–0.993)]. At a threshold of -0.0441, the adjusted composite had a sensitivity of 0.974 and a specificity of 0.845 for AD’s diagnosis in TARCC. In ADNI, a threshold of -0.068 on the adjusted composite had a sensitivity of 0.959 and a specificity of 0.845 for AD’s diagnosis.

The GDS-adjusted and unadjusted composites were strongly correlated in both datasets (i.e., TARCC: r = 0.987, p <0.001; ADNI: r = 0.998, p <0.001). Both regressions exhibit GDS effects on dT2A. Fig 2 presents the TARCC data. A high GDS score effectively left-shifts δ’s association with its GDS adjusted composite along their entire range. This suggests that depressive symptoms even increase the “dementia severity” of persons without dementia by placing them closer to δ’s critical threshold for dementia conversion. Similar results are seen in ADNI (data not shown).

The TARCC cases were significantly distributed (by CHI SQ: F = 3324.75 (1), p <0.001). The vast majority were “on-diagonal” given both studies’ selection against clinically depressed cases (Table 2) (Phi Coefficient = 0.957). Regardless, n = 36 TARCC participants, 2.82% of that study’s “AD” cases, were identified as being demented by their depressive symptom burdens. Resistin levels rise significantly across clinical diagnostic groups (Fig 3). The adversely affected off-diagonal group had significantly higher resistin levels in TARCC (by ANOVA, F = 11.33,

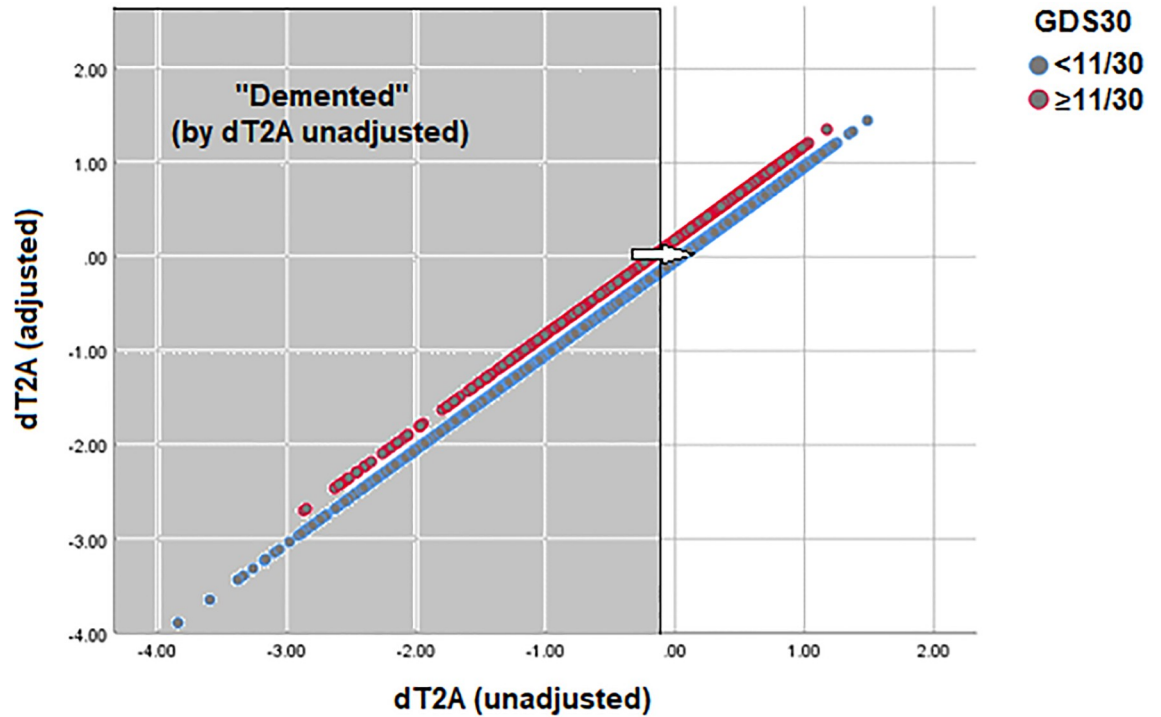


Fig 2. Scatterplot of GDS-adjusted vs. unadjusted dT2A scores (Grouped by GDS $\geq 11/30$). * Note right shifted distribution (away from dementia) in non-depressed cases. GDS = Geriatric Depression Scale; GDS Scores have been dichotomously split at GDS $\geq 11/30$.

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$p = 0.006$) (Fig 4). $n = 5$ (0.8%) of ADNI’s “AD” cases were demented by depression (CHI SQ: $F = 1689.1$ (1), $p < 0.001$). Plasma resistin levels could not be replicated in ADNI because of the small number of off-diagonal cases.

Discussion

This analysis supports the hypothesis that clinical “AD” arises from multiple interacting disease processes [47]. Even in the presence of AD-specific biomarkers, dementia yet arise by other means. This may explain the interindividual variability reported in disease-specific biomarkers among cases matched to clinical dementia severity and contribute to so-called “cognitive reserve” [48]. Since the key cognitive factor (i.e., δ) is an aspect of g , this would also explain the salience of measures of intelligence to that construct [49].

The present analysis provides proof of concept for an algorithm designed to identify patients converted to dementia by any pre-specified condition or biomarker, and offers a foundation for precision anti-dementia therapy. 1–3% of well-characterized “AD” cases are hereby

Table 2. “Off-Diagonal” selection of target cases (TARCC).

	- Unadjusted	+ Unadjusted
- Adjusted	2323	36 Target cases* \cong 3% of demented participants
+ Adjusted	36	1239

*Target cases revert back to a non-demented d-score when the effect of the GDS score is considered. Such cases are presumed to have traversed the threshold for dementia solely by the effect of their of depressive symptoms.

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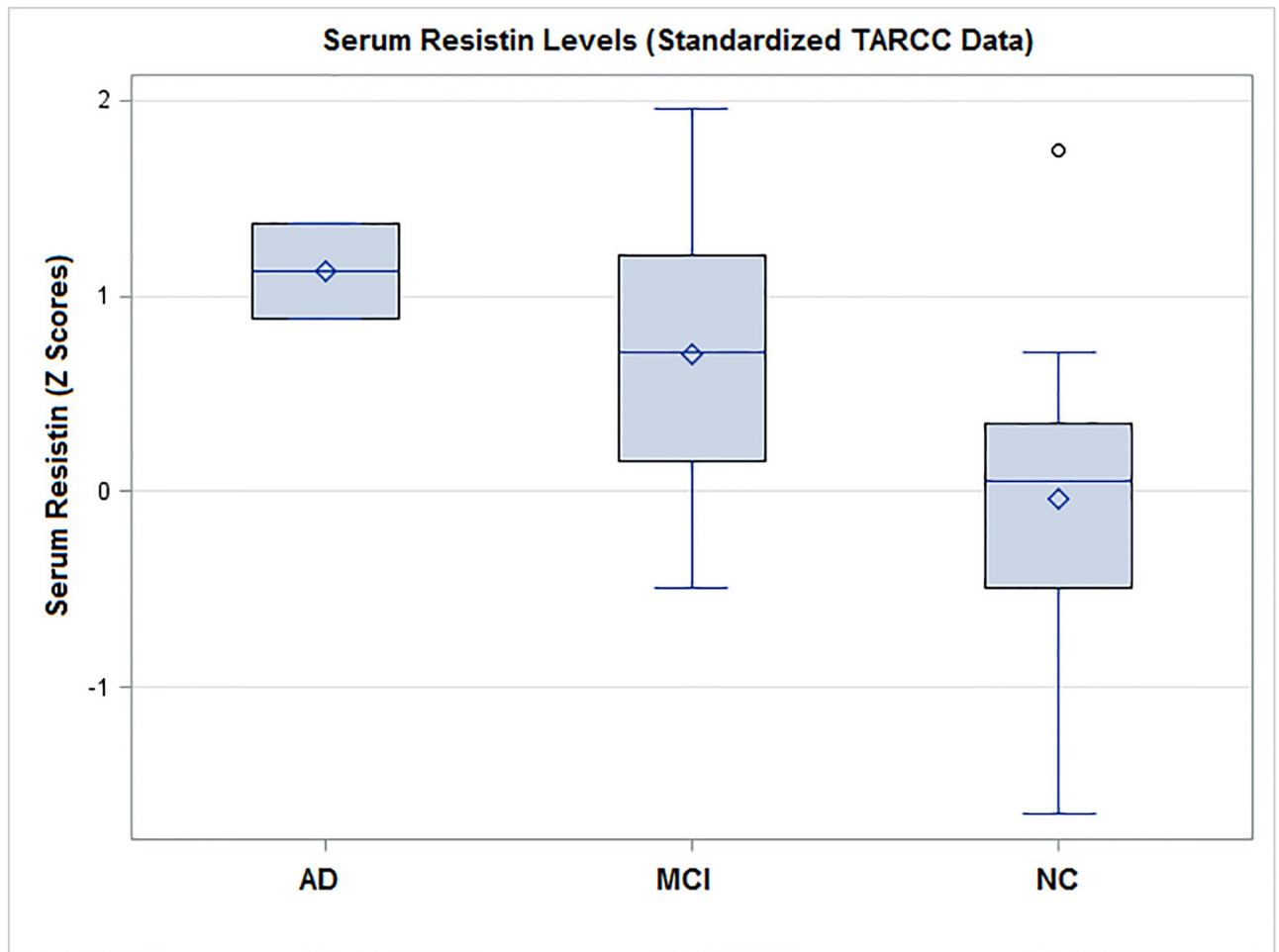


Fig 3. Serum resistin levels are elevated in AD cases (TARCC). * AD = Alzheimer's Disease; MCI = Mild Cognitive Impairment; NC = Normal Controls; TARCC = Texas Alzheimer's Research and Care Consortium.

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estimated to be demented solely by the effect of depressive symptoms. This might translate into \cong 150,000 "AD" cases in the United States (US) [50]. However, our estimates may be lowered by systematic TARCC and ADNI's selection biases against the recruitment of clinically depressed subjects into their cohorts. The prevalence of such cases in unselected community or primary care dementia cases is likely to be higher than reported here [51].

Our approach can identify cases converted to dementia through depression as individuals. Once appropriate GDS-adjusted and unadjusted d-score thresholds are validated in a well-characterized cohort, they can be applied to an individual's calculated d-scores by a simple algorithm, e.g., coded for a mobile device app. If the δ homolog being used is indicated by simple bedside measures, or even items of a single test [52], large numbers of patients might be effectively screened. Although infrequently encountered, cases converting to dementia through depression might possibly revert back to non-demented states with treatment of depression's specific effect. Moreover, this approach identifies only cases who would not be demented without depression's unique and independent contribution to the δ score. Specific treatment of depressive symptoms broadly in persons with dementia might also improve dementia severity in the far larger fraction of "on-diagonal" dementia cases with depressive



Fig 4. Serum resistin levels are elevated in off-diagonal target cases. *GDS = Geriatric Depression Scale (30 item); TARCC = Texas Alzheimer's Research and Care Consortium.

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symptoms. However, they would not be expected to revert, most likely because they are too impaired by other δ -related dementia risks.

Depression's unique effect on cognitive performance does not appear to be mediated through neurodegenerative pathologies [53–54]. Instead, the GDS' association with dementia severity, as measured by δ , can be shown to be mediated through a small set of serum protein biomarkers [19]. Resistin is among those biomarkers, and can be shown to fully attenuate MCI's 5-year prospective dementia conversion risk in TARCC [55]. Our approach has demonstrably selected for cases with significantly higher serum resistin levels relative to off-diagonal cases "protected" from a dementia diagnosis, i.e., by a GDS score ≤ 10 .

Competition among independent δ -related processes may contribute to "cognitive reserve" among persons at risk for "AD", and explain depression's association with reserve. A low GDS score increases the change in δ necessary to effect dementia conversion by any other δ -related process, including AD-specific neurodegeneration. AD-specific neurodegenerative changes have been previously associated with δ [56]. A higher GDS score effectively erodes reserve and might lower the amount of AD-specific pathology required to effect a demented state. Because δ is derived from g , this model might also explain reserve's association with estimators of intelligence.

Our off-diagonal approach might be applied to the effects of age, gender or any other δ -related dementia risk. In their aggregate, these might explain a considerable fraction of so-

called “AD” cases and specify which of those comorbidities need to be addressed in individual patients. If all the models were nested over a single cognitive battery (set of indicators), dementia conversions by a number of unique processes could be screened simultaneously by a single cognitive assessment. In all, 20% of well-characterized “AD” cases appear to be demented in the absence of AD-specific biomarkers [57–59]. Their inclusion in clinical trials directed specifically at AD might weaken statistical power to detect effects. The current approach might be applied proactively, i.e., to identify individuals demented uniquely by a biomarker of interest, e.g., amyloidopathy by Positron Emission Tomography (PET), or restrictively, i.e. to exclude cases demented by competing processes.

We have also replicated an earlier report of elevated resistin levels in clinically diagnosed “AD” cases [60]. However, our analysis makes clear that some cases may be pushed into δ 's demented range by resistin's effect on depressive symptom burden. Although the present algorithm might be used to select individual candidates for anti-dementia therapy by antidepressants, it is currently unknown whether “effective” antidepressant treatment has effects on either δ or resistin. However, cholinesterase-inhibitors have been reported to lower serum resistin [61] and might therefore have a role in the treatment of depressed “AD” cases. Alternatively, their apparent utility in “AD” cases may depend on depressive symptom burden. It is also worth noting that effecting a change in δ will necessitate changes to intelligence. Improvement in domain-specific cognitive performance is orthogonal to g/δ by definition and is therefore unlikely to effect improvements in dementia severity or functional status [10].

Our study has certain limitations. First, we were limited to the dT2A homolog by our desire to replicate the analysis in ADNI's data. δ appears to be unlimited by the battery in which it is assessed, but the GDS' association with those measures might impact its association with the resulting δ homolog composite, and might alter the fraction of off-diagonal cases selected. Second, despite the use of similar biomarker assays by a common vendor, TARCC and ADNI do not overlap precisely either with regard to the biomarkers on their panels or the biomarkers lost to technical issues. We could not attempt replications of all the depression-related mediators identified in reference [19]. Despite their large baseline sample sizes, neither study collected these biomarkers in multiple waves. This restricted us to modeling off-diagonal effects at baseline, temporally close to biomarker measurement, but also to *a priori* selection against clinically recognized cases of depression. Incident depressive symptoms emerging in later waves might have had stronger effects on dT2A (which is available in multiple waves), but in smaller samples (due to attrition) and temporally distant from baseline biomarker assessment. Another limitation is that TARCC's biomarkers (at least) are associated with batch effects. We can account for that by the introduction of a BIAS construct in SEM [62], but this approach is conducted outside of SEM (which cannot handle ROC analysis). Similarly, we cannot use a BIAS construct to account for differences in the biofluids in which the biomarker is assessed. TARCC is also more affected by ethnicity (ADNI is less diverse). Moreover, some biomarkers are known to have strong ethnicity effects in TARCC (but not resistin) [16, 22].

In summary, we have shown depressive symptoms to uniquely explain dementia conversion in a small fraction of clinically diagnosed “AD” cases from two large well-characterized cohorts. We did so by a novel “off-diagonal” approach using the omnibus transdiagnostic dementia severity measure δ . This analysis provides a means to identify individuals most likely to revert back to non-demented states by the modulation of any pre-specified biomarker or risk factor. The cases selected by this approach, which could be easily automated and /or adapted to brief and convenient cognitive assessments, might then be triaged to specific therapies. The approach can be adapted to any δ -related dementia risk and appears to select for individuals with distinguishable biomarker profiles. We have also replicated an earlier association of clinical “AD” with serum resistin levels and clarified that they may be related through

the effect of depressive symptoms on dementia, most likely independently of AD-specific neurodegenerative changes.

Supporting information

S1 File. (Table A) Descriptive statistics by diagnosis (TARCC). (Table B) Descriptive statistics by diagnosis (ADNI). (DOCX)

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