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# Increased free prostate specific antigen serum levels in Alzheimer's disease, correlation with Cognitive Decline

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ABSTRACT

*Background/aims:* Prostate specific antigen (PSA) is regulated by steroid hormones, such as testosterone, the serum levels of which are altered in patients with Alzheimer's disease (AD).This pilot study compared serum levels of the free (f) PSA between AD, mild cognitive impairment (MCI), and control subjects, and evaluated the relationship between fPSA serum levels and cognitive assessment tests and neuroimaging data. In addition, in a subgroup of AD patients, we correlated fPSA serum levels with the existing data on serum levels of amyloid-beta (Aβ), and iron-related proteins, including hepcidin and ferritin.

*Methods:* Frozen serum samples from the Oregon Tissue Bank were used to measure serum levels of fPSA using enzyme-linked immunosorbent assay.

*Results:* fPSA serum levels calculated as median ± SD were higher in AD males (663.6 ± 821.0 pg/ml) compared to control males (152.0 ± 207.0 pg/ml), $p = 0.003$. A similar Pattern emerged when comparing MCI males (310.7 ± 367.0 pg/ml) to control males ($P = 0.02$). Correlation studies showed a significant association between fPSA and CDR ($r = 0.56$, $P = 0.006$) and CDR-SOB ($r = 0.54$, $P = 0.009$) in AD males.

*Conclusion:* Additional studies in a larger cohort are required for determining whether fPSA can be used as biomarker of AD disease progression and whether it has the potential to identify male subjects at risk of AD dementia.

## 1. Introduction

Alzheimer's disease (AD) is a chronic progressive neurological disease with a prevalence of 10% over age 65 and 40% over age 85, affecting twice as many females compared to males [1]. The hallmarks of the disease are plaques composed mainly of amyloid-beta (Aβ) aggregates and neurofibrillary tangles composed of the hyper-phosphorylated tau protein aggregates. Among risk factors for the late onset sporadic AD is the presence of the e4 allele of apolipoprotein E (APOE4). The allele increases the risk of AD by 12 fold [2].

Mild cognitive impairment (MCI) is the intermediate state where there is an overlap between changes attributed to aging, and those indicative of AD dementia, although it can precede other dementias [3,4]. The rate of conversion from MCI to AD is as low as 5–10% or as high as 25–30%, with the risk factors for conversion being the presence of an APOE4 allele, and the volume of the hippocampus and ventricles, among others [5].

The current AD diagnosis depends on the evaluation of clinical, functional, behavioral, and cognitive assessments that are performed on a routine office visit, which are extended by laboratory and imaging tests, such as MRI. Behavioral and functional measures are needed to exclude Lewy bodies (DLB) dementia, whereas the MRI excludes signs of vascular dementia [6]. However, the definitive diagnosis of AD requires pathological evaluation at the time of autopsy.

MRI, functional MRI, and PET, as well as CSF biomarkers have been studied for their suitability in evaluating brain pathology in AD and MCI, but these approaches are either not routinely available or have limited clinical applications [7]. Serum biomarkers which reflect the AD pathology are ideal for AD diagnosis and for predicting the conversion of MCI to AD.

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Prostate-specific antigen (PSA) is a serine protease and part of the kallikrein superfamily with chymotrypsin-like activity. In circulation, the majority of PSA is 100-kDa complex with various protease inhibitors, mainly with $a_1$-antichymotrypsin (ACT, serpinA3) and to a lesser extent to $a_1$-protease inhibitor (API, serpinA1) and a2-macroglobulin (A2M), while 5–35% of the PSA is in a free form [8]. The free (f) PSA is an enzymatically active form of the protein, although its biological role is not fully clarified.

In males, PSA is produced by the prostate gland and increased PSA serum levels is used as a marker of prostate cancer [9]. In females, the breast is the main source of PSA production, and albeit in much lower concentrations, PSA is also detected in sera from women [10]. However, PSA has been shown to be produced in tissues other than prostate and breast, both in physiological and pathological circumstances [11]. PSA expression in male is upregulated by androgens and regulated by the androgen receptor at the transcriptional level through three different androgen receptor binding elements in the promoter of the PSA gene [12,13]. Similarly, PSA production in females is under the control of both androgen and progestin [10].

In prostate cancer patients, the medical castrations is used to halt the progression of the disease; this strategy reduces both androgens and PSA serum levels [14]. However, medical castration has been shown to adversely affect cognitive function indicated by reduction in the performance on tasks of spatial and short-term memory capacity and language ability [15,16]. Testosterone levels are also reduced in normal aging, and this reduction is also accompanied by cognitive impairment [17]. Also the level of testosterone is much lower in females compared to males, the same age-related patterns occurs in females due to aging [18]. Supplementation of the major androgen, testosterone, significantly improve cognitive function in testosterone-deficient males [19].

Serum testosterone levels are higher in AD patients compared to control subjects [20]. Since testosterone regulates PSA production, we hypothesized that AD subjects may also present with alterations in the serum levels of the enzymatically active form of PSA, the fPSA, and correlated between fPSA serum levels and patients' clinical and neuroimaging data.

## 2. Materials & methods

### 2.1. Population

The study relied on frozen serum samples obtained from Oregon Brain Tissue Bank. The samples represented 33 AD, patients (22 males), age 70.1 ± 10.3 years, 22 MCI (14 males), age 70.8 ± 10.6 years, and 20 controls (7 males), age 69.5 ± 8.0 years. Autopsy was performed in 26 (16 males) patients which confirmed the diagnosis of pure AD in 14 patients (7 males). The term “pure AD” refers to those subjects who present with brain pathology indicative of AD, without the presence of additional pathology related to other neurodegenerative diseases, the latter often termed “mixed dementia”. The group of pure AD also included 5 MCI patients (2 males), who underwent autopsy (Table 1A). The 12 remaining patients had mixed dementia, including combination of AD/vascular dementia ($n$ = 5), AD/*Lewy body dementia* (n = 5), AD/hippocampal sclerosis (1), AD/Parkinson (1) We excluded one AD patient, two MCI patients and one control subject due to the documented diagnosis of prostate cancer.

All participants in the study (both AD and Controls) were outpatients with an unremarkable general medical exam and complete blood count with no evidence of sepsis, anemia, or any other acute illness.

### 2.2. Materials and measurements

Enzyme-linked immunosorbent assay (ELISA) kit was used to measure fPSA serum levels (Raybiotech, Cat # ELH-PSAfree-1, detection range 45 pg/ml-12,000 pg/ml, and sensitivity of 45 pg/ml. fPSA serum levels were correlated with patients' cognitive assessment test results, including mini-mental state examination (MMSE) test, clinical dementia rating (CDR), and CDR-sum of boxes (SOB); and neuroimaging data, including total CNS volume, ventricular CSF volume, hippocampal volume, subarachnoid volume, and white matter hyper-intensity volume. In addition, we correlated fPSA with data on $A\beta_{40}$ and $A\beta_{42}$, and with iron related proteins, hepcidin, ferritin, serum iron, transferrin (measured indirectly as total iron binding capacity (TIBC), and percent transferrin saturation. This data was available from previous study [21] for 25 (17 males) patients.

### 2.3. Statistical analysis

Non-parametric tests were used to compare AD and the subgroups, MCI, and controls, adjust for differences in autopsy status and post-autopsy diagnosis. The fPSA was calculated and compared between AD patients and controls, pure AD patients and controls, MCI and controls, and between AD and MCI, and $P \leq 0.05$ was indicated as statistically significant. *Pearson* correlation was used to test the relationship between fPSA and cognitive assessment test results, neuroimaging data and clinical data (Aβ and iron-related proteins). Because we were testing a priori hypotheses on fPSA levels, rather than engaging in exploratory statistical analyses, the correlation analysis was not corrected for multiple tests.

### 2.4. Human subjects

The study was approved by the Internal Review Board of the State University of New York at Buffalo. The collection of data and samples was approved by the Oregon Health and Science University Internal Review Board.

## 3. Results

### 3.1. Group comparison in fPSA um levels

Table 1A presents demographics of patients and controls. The ages

**Table 1**
Patients' demographics (1A) and cognitive assessment tests. The values are mean ± SD. $P$ values ≤0.05 are statistically significant.

| *A-Demographics* | AD | Pure AD | MCI | CTL | $P$ (AD/CTL) | $P$ (MCI/CTL) |
|---|---|---|---|---|---|---|
| Sample size | 33 (22 M) | 14 (7 M) | 22 (14 M) | 20 (7 M) | | |
| Age ± SD (Years) | 70.0 ± 10.5 | 70.0 ± 14.7 | 70.8 ± 10.6 | 69.5 ± 8.0 | > 0.05 | > 0.05 |
| APOE4 (1 copy) | 25 (17 M) | 9 (5 M) | 10 (7 M) | 7 (0 M) | 0.01 | 0.8 |
| *B-Cognitive Assessment Tests* | | | | | | |
| MMSE | 18.7 ± 5.8 | 21.9 ± 7.2 | 27.8 ± 1.9 | 29.4 ± 1.0 | < 0.001 | 0.002 |
| CDR | 1.0 ± 0.4 | 0.65 ± 0.5 | 0.18 ± 0.24 | 0.0 ± 0.0 | < 0.001 | 0.004 |
| CDR-SOB | 6.8 ± 2.7 | 4.3 ± 3.2 | 0.76 ± 1.1 | 0.0 ± 0.0 | < 0.001 | 0.01 |

Abbreviations: AD: Alzheimer's disease, APOE: apolipoprotein E, CDR: clinical dementia rating, CTL: control, MCI: mild cognitive impairment. MMSE: mini mental state examination, SOB: sum of boxes.

of the groups did not differ significantly (all $P > 0.05$). In addition, consistent with the APOE4 allele being a risk factor for AD, 75% of AD patients had at least one copy of the APOE4 allele; while percentages were 45% and 35% in MCI and control subjects respectively (AD compared to controls $P = 0.01$; MCI compared to controls, $p = 0.8$).

Table 1B presents the severity of dementia in AD patients, MCI patients, compared to control subjects, indicated by MMSE, CDR, and CDR-SOB. The data is presented as mean ± SD. MMSE scores were significantly lower in AD patients compared to controls (18.7 ± 5.8 vs. 29.4 ± 1.0, $P < 0.001$), and MCI patients compared to controls (27.8 ± 1.9 vs. 29.4 ± 1.0, $P = 0.002$). The CDR was significantly higher between AD patients and controls (1.0 ± 0.4 vs. 0.0 ± 0.0, $P < 0.001$), and MCI patients and controls (0.18 ± 0.24 vs. 0.0 ± 0.0, $P = 0.004$). Similarly, CDR-SOB was significantly higher between AD patients and controls (6.8 ± 2.7 vs. 0.0 ± 0.0, $P < 0.001$), and MCI patients and controls (0.76 ± 1.1 vs. 0.0 ± 0.0, $P = 0.01$).

Among AD patients, 86% were on acetylcholinesterase inhibitors, 26% were on Memantine, 80% on cardiovascular drugs, and 72% were on psychotropic drugs. Among MCI patients, 49% were on acetylcholinesterase inhibitors, 10% were on Memantine, 60% on cardiovascular drugs, and 23% were on psychotropic drugs. Among control subjects, 84% were on cardiovascular drugs and 26% were on psychotropic drugs.

Table 2 compares fPSA serum levels between AD patients and control subjects (A), Pure AD patients and control subjects (B), MCI and control subjects (C), and between AD and MCI (D), stratified by gender. The results are presented as median ± SD.

The fPSA was significantly higher in AD males compared to control males (663.6 ± 821.0 pg/ml vs. 152.0 ± 207.0 pg/ml, $p = 0.003$). Among males approximately 70% had fPSA serum levels above the median value of 152 pg/ml observed in control males, and in 52% of patients, the fPSA serum levels were 3SD higher than the levels in controls. However, fPSA tended to be lower in AD females compared to control females (8.8 ± 4.6 pg/ml vs. 12.2 ± 28.3 pg/ml, $p = 0.13$).

AD males who were diagnosed having pure AD upon autopsy had 55% higher fPSA serum levels than control males (237.8 ± 525.2 pg/ml vs. 152.0 ± 207.0 pg/ml, $p = 0.18$), but no differences between pure AD females and control females were apparent (11.7 ± 13.5 pg/ml vs. 12.2 ± 28.3 pg/ml, $p = 0.52$).

Comparison between MCI and controls showed two times higher fPSA serum levels in MCI males than control males (310.7 ± 367.0 pg/ml vs. 152.0 ± 207.0 pg/ml, $p = 0.02$), with no differences between MCI females and control females (11.6 ± 26.9 pg/ml vs. 12.2 ± 28.3 pg/ml, $p = 0.89$).

We then compared fPSA between AD patients and MCI patients. AD males had as much as 80% higher fPSA serum levels compared to MCI males (663.6 ± 821.0 pg/ml vs. 310.7 ± 367.0 pg/ml, $p = 0.12$), whereas AD females tended to have lower fPSA compared to MCI females (8.8 ± 4.6 pg/ml vs. 11.6 ± 26.9 pg/ml, $p = 0.18$). None of the analysis reached statistical significance.

**Table 2**
f-PSA serum levels in AD, pure AD, MCI, and CTLs. The values are median ± SD

| Groups | M | F |
|---|---|---|
| AD | 663.6 ± 821.0 | 8.8 ± 4.6 |
| Pure AD | 237.8 ± 525.2 | 11.7 ± 13.5 |
| MCI | 310.7 ± 367.0 | 11.6 ± 26.9 |
| CTL | 152.0 ± 207.0 | 12.2 ± 28.3 |
| *P* | | |
| AD/CTL | 0.003 | 0.13 |
| Pure AD/CTL | 0.18 | 0.52 |
| MCI/CTL | 0.02 | 0.89 |
| AD/MCI | 0.12 | 0.18 |

Abbreviations: As in Table 1, and F: female, fPSA: free prostate specific antigen., M: male
P values ≤0.05 are statistically significant.

The box graph (Fig. 1) presents fPSA serum levels in male AD, pure AD, MCI and controls. The graph is presented only for males, since many of the fPSA values determined in the females, especially AD females, were below the optimal range for accurate determination for our assay. Female AD and MCI subjects clearly did not show the same absolute increase in fPSA values as observed for male subjects (~400 pg/ml for AD vs control). Further, if female AD subjects had exhibited the same ~4-fold increase over controls that we observed in males we believe that our assay would have detected such an increase. Therefore, it does not appear that fPSA levels are correlated robustly with pathology of AD in female patients as it may be correlated in male patients. Therefore, the additional statistical analyses were conducted only for male gender.

### 3.2. Correlation studies

Correlation analysis between fPSA and indicators of AD disease severity in AD males showed a significant association between fPSA and CDR ($r = 0.56$, $P = 0.006$) and CDR-SOB ($r = 0.54$, $P = 0.009$) (Fig. 2), but not with MMSE ($r = -0.18$, $P = 0.39$). We observed an inverse association between fPSA and APOE4 in controls ($r = -0.92$, $P = 0.003$), but not in AD patients ($r = -0.196$, $P = 0.36$). No correlation between fPSA and age and fPSA and neuroimaging data was observed in either AD subjects or controls. Furthermore, in a subgroup of 17 CE males, for whom the data was available for analysis, we did not observe a correlation between fPSA and Aβ, and between fPSA and iron- related proteins (results not shown).

It is noteworthy that data on hippocampal and subarachnoid volumes in the control group was available for only 3–5 controls patients, and therefore underpowered for statistical analysis. In addition, the exclusion of two MCI male patients who were diagnosed as having AD upon autopsy from the correlation analysis led to a weak association between fPSA serum levels and hippocampal volume ($r = 0.47$, $P = 0.038$).

## 4. Discussion

Our study show higher fPSA serum levels in AD, MCI, and pure AD of male gender. fPSA serum levels correlated with disease severity, indicated by CDR and CDR-SOB which have been shown to be more precise measurement of disease severity than the MMSE scores [22]. In our best knowledge this is the first study comparing serum levels of fPSA between AD and controls. In addition, there are no published studies linking fPSA serum levels to any other neurodegenerative disease. The increase in fPSA serum levels in AD, Pure AD, and MCI suggests a role of fPSA in AD pathology.

However, we did not observe a correlation between fPSA and neuroimaging data and between fPSA and Aβ. The absence of a correlation between fPSA and clinical/neuroimaging biomarkers of AD makes the findings questionable. These results should be repeated in a larger cohort before a conclusion is reached. Furthermore, this cross-sectional findings should be followed by longitudinal studies, determining the dynamics of the association between fPSA and AD clinical and neuroimaging markers, as the disease progresses.

Mulder et al. [23] did not find differences in total PSA serum levels between AD, MCI, and controls, suggesting that AD alterations in PSA may be limited to the enzymatically active free form of the protein. Nevertheless, Sattkeckar et al. [24], using SOMAscan assay for quantifying 1001 proteins in blood samples from AD, MCI, and controls, reported a strong association between PSA complexed to ACT and AD diagnosis.

The exact source of fPSA in the serum is unknown. Although non-prostatic sources of PSA have been reported [11], there is no documentation of PSA production in the peripheral immune cells and

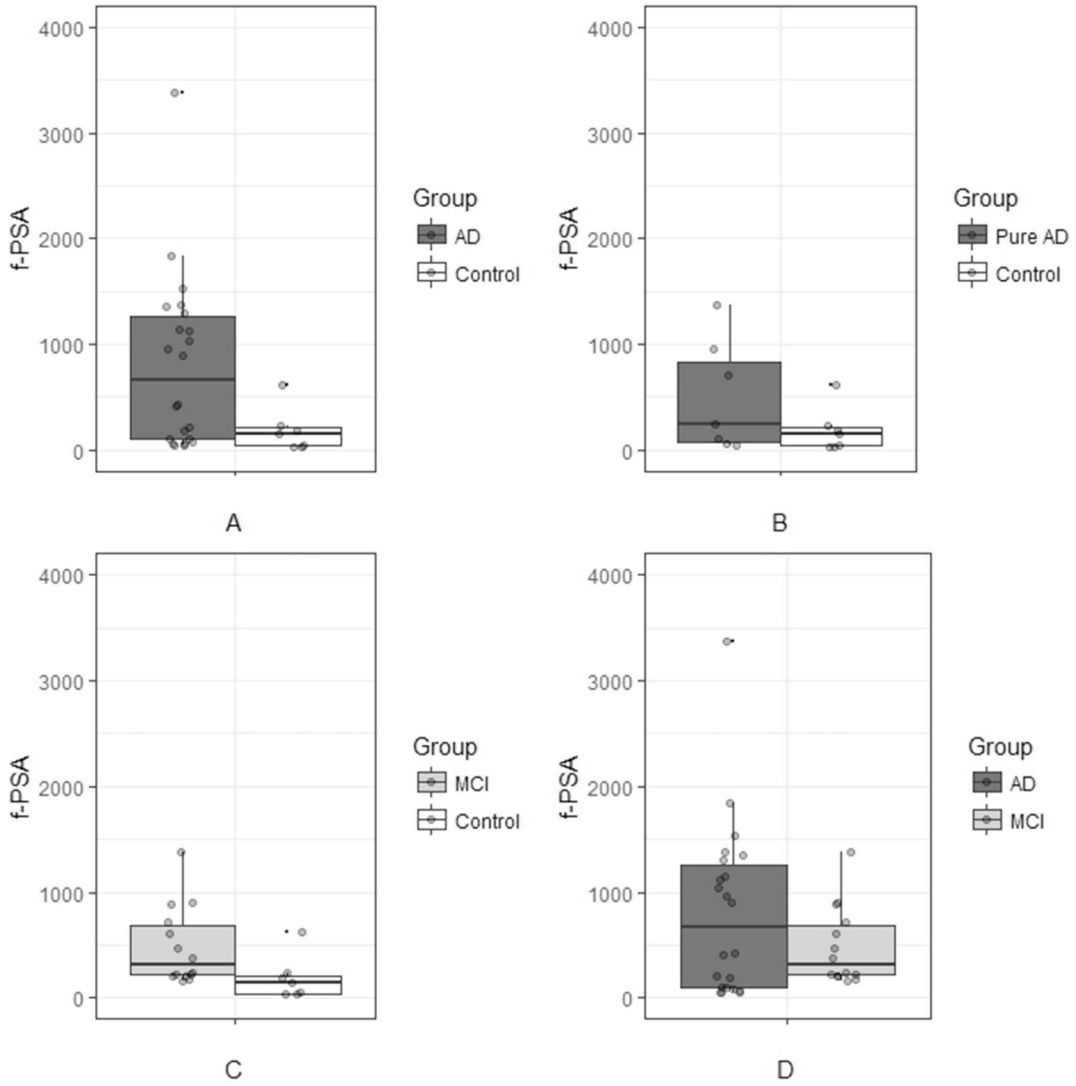


**Fig. 1.** *Comparison of fPSA serum levels between AD, pure AD, MCI, and controls.*
Abbreviations: AD: Alzheimer's disease; fPSA: Free prostate specific antigen; MCI: Mild cognitive impairment.

release into the circulation. Since PSA is an acute phase reactant, its release is expected to be enhanced during inflammatory processes.

PSA has been detected in the CSF [25] and in postmortem hippocampus and temporal cortex specimens [23], brain areas heavily affected in AD, suggesting a local production of PSA in the brain, which could be enhanced due to AD-related inflammatory processes. fPSA can then leak into the serum due to its relatively small size (~33-kDa) and monomeric form; This process may be enhanced in AD patients due to a compromised blood brain barrier (BBB) integrity [26], resulting in higher PSA levels in the serum. However, such scenario is unlikely to significantly influence PSA serum levels, since PSA levels in the CSF are known to be 25 to 150 folds lower compared to the levels in the serum [27].

The PK/PD dynamics of PSA binding to ACT in the serum is unknown. Although ACT plasma levels are enhanced in AD patients compared to controls [28], the levels are known to be reduced as disease severity increases [29]. The reduction in serum ACT may result in an increase in fPSA serum levels as the disease progresses; an assumption that is consistent with our observed results. Nevertheless, neither the leakage through the BBB, nor alteration in serum ACT levels could explain the fPSA elevation being limited to male gender.

The most likely explanation for the fPSA elevation in AD males is the upregulation of testosterone [20]. The reason for the upregulation of testosterone in AD males is unknown, but testosterone is known to promote hippocampal neurogenesis [30] and synaptic plasticity [31]. Therefore, it's likely that the increase in fPSA mediated by enhanced testosterone represents a compensatory response to halt the progression of AD pathology. Our results have also clinical implications in the treatment of patients with prostate cancer, since a population-based study reports a correlation between AD and prostate cancer (OR = 1.53, 95% CI: 1.04 ~ 2.22) [32].

Although the results in AD females cannot be conclusive due to the suboptimal sensitivity of the ELISA kit, the tendency to lower fPSA in AD females may stem from elevation in the serum levels of the sex hormone binding globulin (SHBG) [33]. Produced by the liver, SBHG binds to sex hormones, including testosterone and render them biologically inactive, hence reducing PSA production. Serum fPSA in AD females warrants further investigations and should be repeated in larger cohort, using an ultra-sensitive fPSA EKISA kit.

## 5. Study limitations

Although our study results are interesting one should note the study limitations, one of which is a relatively small sample size, especially when patients are stratified by gender. In addition we do not have the data for total PSA serum levels, which would enable us to determine

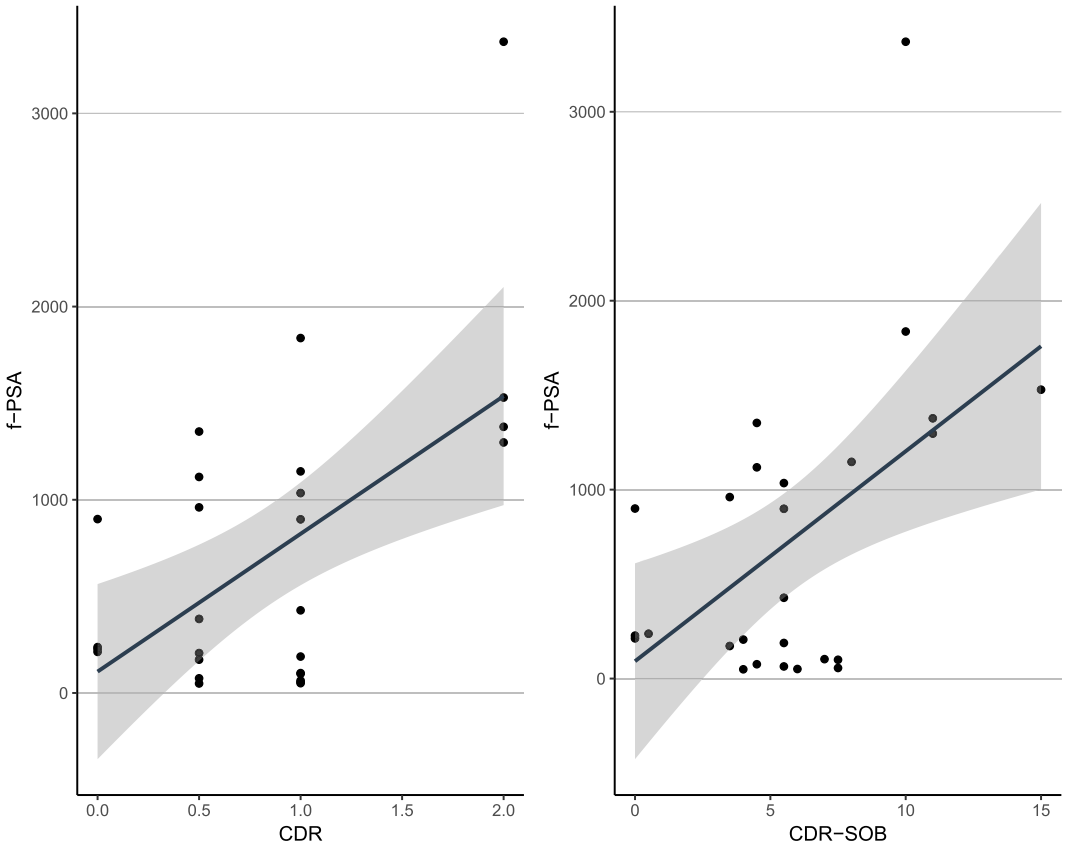


**Fig. 2.** *Correlation between fPSA serum levels and cognitive assessment tests in male AD.*
Abbreviations: Fig. 1 And CDR: Clinical dementia rating; SOB: Sum of boxes.

whether the higher fPSA observed in AD males is secondary to the alterations in the ratio of fPSA/T(total)PSA or unrelated.

## Authors' declaration

Authors have no conflict of interest to declare.

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