No relationship between lipoprotein-associated phospholipase A2, proinflammatory cytokines, and neopterin in Alzheimer's disease

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Methods: In total, 59 patients with AD and 38 non-demented individuals were included in the case–control study. Fasting serum concentrations of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), neopterin, and Lp-PLA_2 were determined using ELISA. The associations between AD and each of the variables were analyzed by lo-

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Outline

- Background
- Methods
- Results
- Discussion
- Conclusion and THM
- Future work

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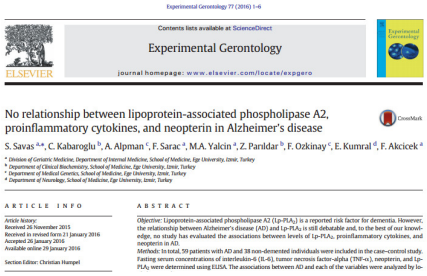

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Background

- AD, most common form of dementia, prevalence growing with increased life expectancy
- progressive neurodegenerative (ND) disorder
- amyloid plaques and neurofibrillary tangles
- arise from abnormal accumulation of amyloid-beta (Aβ) peptides and hyperphosphorylated tau

Musiek & Holtzman, 2015

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The proximal mechanisms underlying AD are complex and poorly understood

- family history, age, *APOE* ε4 allele, high plasma homocysteine; dementia
- unmanaged type 2 DM, high BP, obesity; cognitive decline
- hyperinsulinemia
- chronic inflammation
- increased amyloid load accompanied by marked inflammatory

alterations, at brain parenchyma, barriers of brain

van Himbergen et al., 2012; Luchsinger & Gustafson, 2009; McGeer & McGeer, 2004; S. Dá Mesquita et al.,2016; Attems & Jellinger, 2014; Helman & Murphy, 2015

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The proximal mechanisms underlying AD are complex and poorly understood

it is debatable whether neuroinflammation in aging and AD, together with alterations in peripheral immune system, are responsible for

increased amyloidogenesis, decreased clearance, marked deficits in memory/cognition

AD and vascular dementia were traditionally considered separate disorders, increasing evidence suggests that they may be related

underlying ND mechanisms need to be clarified

van Himbergen et al., 2012; Luchsinger & Gustafson, 2009; McGeer & McGeer, 2004; S. Dá Mesquita et al.,2016; Attems & Jellinger, 2014; Helman & Murphy, 2015

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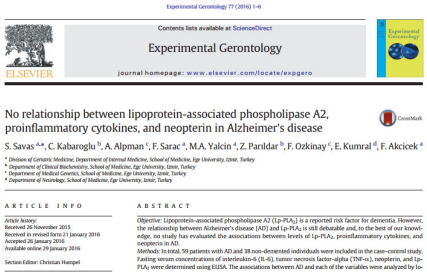

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Methods: In total, 59 patients with AD and 38 non-demented individuals were included in the case–control study. Fasting serum concentrations of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), neopterin, and Lp-PLA2 were determined using ELISA. The associations between AD and each of the variables were analyzed by lo-

Lp-PLA$_2$

- oxidize phospholipids→generates lysophosphatidylcholine and oxidized fatty acids (proinflammatory)
- inflammatory biomarker, expressed in macrophages and foam cells
- circulates in blood associated with LDL-cholesterol
- may hydrolyze PAF in platelets, monocytes, and macrophages
- expression *is* regulated by *inflammatory cytokines*
- high expression is thought to be a predictor of coronary HD
- management of CVS risk factors may reduce cognitive decline
- the impact on development of AD is less certain

MacPhee et al., 1999; Rader, 2000; Rubinstein & Izkhakov, 2011; Stafforini, McIntyre, Zimmerman, & Prescott, 1997; Tselepis et al., 2002; Cao, Stafforini, Zimmerman, McIntyre, & Prescott, 1998; Packard et al., 2000; Ballantyne et al., 2004; Caslake & Packard, 2003; Giordano et al., 2007

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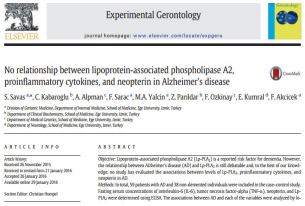
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Methods: In total, 59 patients with AD and 30 non-demented individuals were included in the case-control study. Fasting serum concentrations of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), neopterin, and Lp-PLA2 were determined using ELISA. The associations between AD and each of the variables were analyzed by lo-

Proinflammatory cytokines

- risk factors such as dyslipidemia and oxidative stress promote the accumulation of damage signals, which may be earliest triggering event in AD
- microglia are activated
- TNF-α, IL-6, some trophic factors released
- cytokine network complex, biologically labile, rapidly disappear from circulation
- neopterin an indicator of peripheral immune responses
- enables effective monitoring
- increased neopterin found in patients with AD

Maccioni, Rojo, Fernández, & Kuljis, 2009; Licastro et al., 2000; Fuchs, Weiss, & Wachter, 1993; Akgül et al., 2013; Leblhuber et al., 1999

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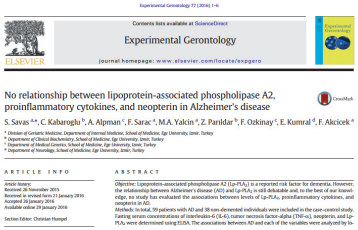

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?

- relationship between *chronic inflammation* and AD is of great interest and understanding the mechanisms that mediate this relationship may provide a basis for preventative methods and novel therapies

- we hypothesized that there is a relationship between Lp-PLA_2, cytokines, and neopterin

- these relationships may explain the inconclusive results regarding the role of Lp-PLA_2 in AD

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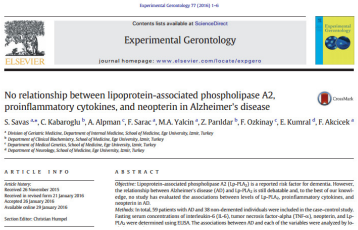

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Methods

- 59 patients with AD
- 38 non-demented individuals case-control study
- ELISA
  - IL-6
  - TNF-α
  - Neopterin
  - Lp-PLA_2
- The associations between AD and each of the variables were analyzed by logistic regression
- Ege University Ethical Committee

National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (Morris et al., 1989)
Turkish Mini-Mental State Examination (MMSE) (Güngen, Ertan, Eker, Yaflar, & Engin, 1999)
Enzyme-linked immunosorbent assays (ELISA) (DIA Source, Louvain-la-Neuve, Belgium; Thermo Scientific, Waltham, MA, USA, DRG Instruments GmbH, Marburg, Germany; diaDexus, Inc., San Francisco, CA, USA, respectively). The lower detection limits were 2 pg/mL for IL-6, 15.6 pg/mL for TNF-α, 0.2 ng/mL for neopterin, and 0.34 ng/mL for Lp-PLA2. Neopterin values were expressed as nmol/L.
(Modular Analytics, Roche Diagnostics, Basel, Switzerland)

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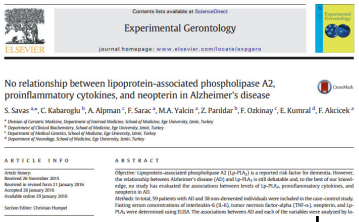

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Subjects with AD ≥65 years
Neurology Department of the School of Medicine of Ege University
N=80

EXCLUSION
MMSE< 10
N = 3

MMSE

between ≥10 and ≤24

EXCLUSION
history of cerebrovascular disease
coronary revascularization
Dialysis
liver disease
Malignancy
congestive heart failure
Acute-chronic inflammatory
no informed consent
N = 18

Subjects with AD ≥65 years

N=59

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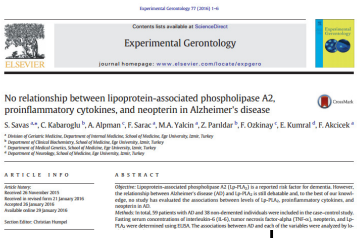

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bjects with non-specific complaints ≥65 years
ternal Medicine Department of the School of Medicine of Ege University
N=70

EXCLUSION
MMSE< 10
N= 2

MMSE

>24

EXCLUSION

history of cerebrovascular disease
coronary revascularization
Dialysis
liver disease
Malignancy
congestive heart failure
Acute-chronic inflammatory
no informed consent
N= 30

Non-demented control subjects ≥65 years

N=38

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Socio-demographic characteristics and clinical data for patients with Alzheimer's disease and the control group

Characteristics	Patients with AD ($n = 59$)	Control group ($n = 38$)	OR (95% CI)
Age[a], y [± SD; range]	75 ± 6.4 (58–85)	72 ± 5.9 (65–85)	
Female, *n* (%)	39 (66)	22 (58)	1.42 (0.61–3.28)
Living alone, *n* (%)	21 (36)	10 (26)	1.55 (0.63–3.79)
Education <5 years, *n* (%)	41 (70)	18 (47)	2.53 (1.09–5.89)
DM, *n* (%)	17 (29)	7 (18)	1.79 (0.66–4.85)
HT, *n* (%)	28 (48)	14 (37)	1.55 (0.67–3.57)
Hypercholesterolemia[b], *n* (%)	23 (47)	23 (61)	0.58 (0.24–1.36)
Hypertriglyceridemia[b], *n* (%)	11 (22)	11 (29)	0.71 (0.27–1.88)
High LDL-C[b], *n* (%)	33 (73)	31 (84)	0.53 (0.18–1.59)
Low HDL-C[b], *n* (%)	10 (23)	4 (11)	2.28 (0.65–8.02)
High hs-CRP[b], *n* (%)	24 (62)	25 (70)	0.70 (0.27–1.84)

Y, years; DM, diabetes mellitus; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; AD, Alzheimer's disease.

[a] Values are expressed as means ± SD.

[b] Missing data.

marital status (married/living with spouse or living alone/not married/widow)
level of education (≥5 years or <5 years)

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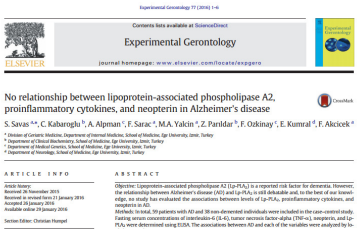

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Results

- The median Lp-PLA_2 levels in AD and controls similar (P = 0.29)
- Median serum neopterin and IL-6 levels significantly higher in patients with AD than in controls (P = 0.0001 and P = 0.03)

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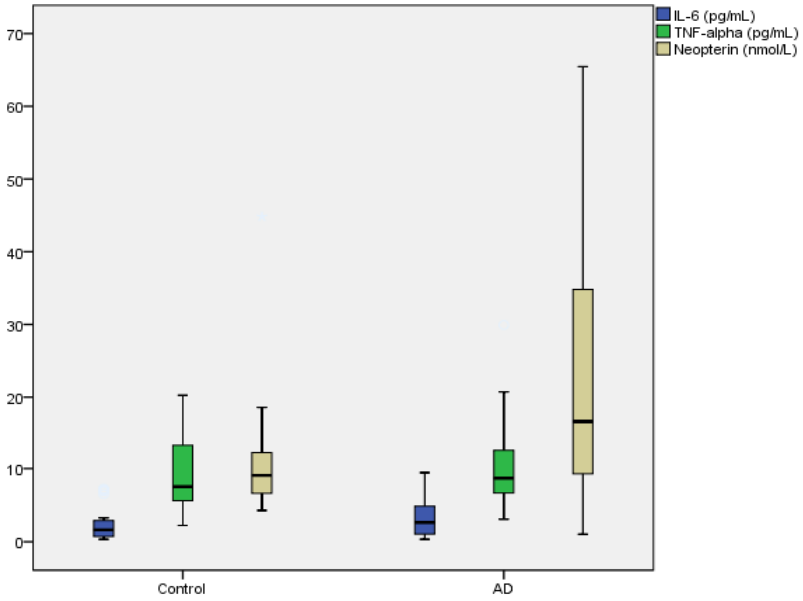
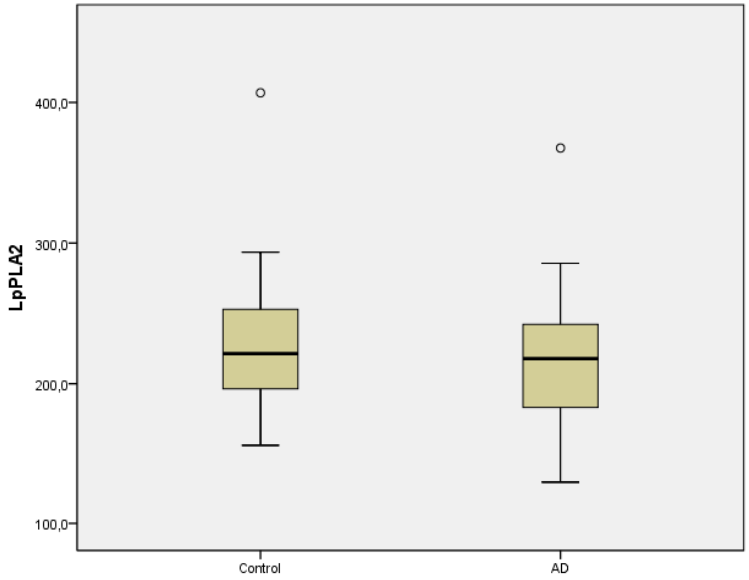
Lipoprotein-associated phospholipase A_2, proinflammatory cytokine, and neopterin levels in patients with Alzheimer's disease and the control group





Factor[a]	Patients with AD	Control group	Significance
Lp-PLA_2 (ng/mL)	217.89 (60.8)	221.42 (62)	$P = 0.29$
IL-6 (pg/mL)	2.82 (4.3)	1.55 (2.2)	$P = 0.03$
TNF-α (pg/mL)	9.42 (6.4)	8.01 (9.5)	$P = 0.48$
Neopterin (nmol/L)	17.37 (30.1)	8.89 (6.1)	$P = 0.0001$

Lp-PLA_2, Lipoprotein-associated phospholipase A_2; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor-alpha; AD, Alzheimer's disease.

[a] Values are expressed as medians (interquartile range).

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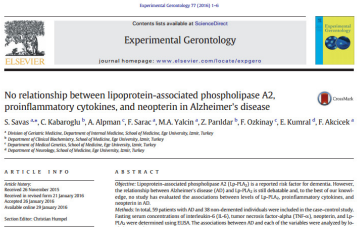

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Results

- There was no relationship between Lp-PLA$_2$ and either inflammatory cytokines or neopterin, as well as hs-CRP and age in both groups and the whole population

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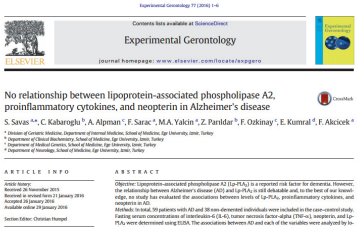

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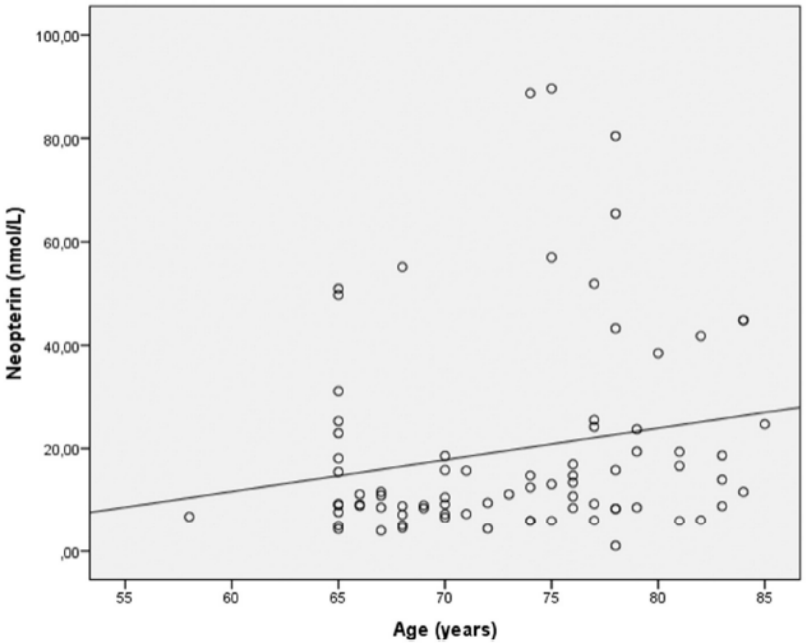
Neopterin levels are associated with age



in the whole population age

- positively correlated with neopterin (r = 0.235, P = 0.035)
- negatively correlated with both TC and LDL-C (r = -0.262, P = 0.014 and r = -0.292, P = 0.008)
- neopterin higher in the ≥75 years old group (P = 0.012)

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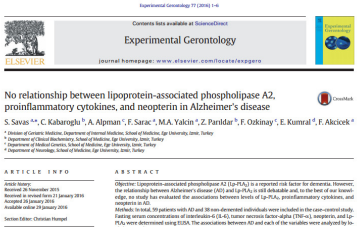

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ABSTRACT

Objective: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a reported risk factor for dementia. However, the relationship between Alzheimer's disease (AD) and Lp-PLA2 is still debatable and, to the best of our knowledge, no study has evaluated the associations between levels of Lp-PLA2, proinflammatory cytokines, and neopterin in AD.
Methods: In total, 59 patients with AD and 38 non-demented individuals were included in the case-control study. Fasting serum concentrations of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), neopterin, and Lp-PLA2 were determined using ELISA. The associations between AD and each of the variables were analyzed by lo-

Results

- neopterin (OR, 31.44, 95% CI 3.59–275.28, *P* = 0.002)
- lower education level (OR, 4.35, 95% CI 1.13–16.61, *P* = 0.032)
- female gender (OR, 7.25, 95% CI 1.88–28.00, *P* = 0.004)

significantly associated with AD when compared with controls

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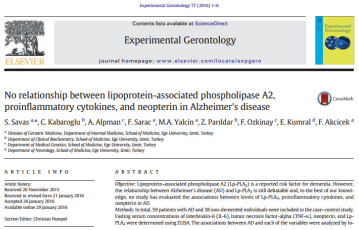

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Discussion

Lp-PLA_2

- associated with risk of stroke, independent of CVS risk factors
- risk factor for dementia independent of CVS and inflammatory factors in the Rotterdam study
- not associated with dementia or AD in Framingham Heart Study
- inconclusive results in AD

Oei et al., 2005; Fitzpatrick et al., 2014; van Oijen et al., 2006; van Himbergen et al., 2012;

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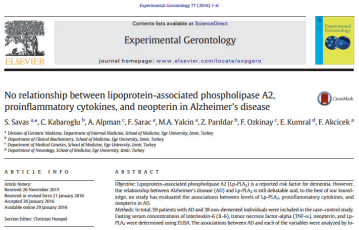

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Discussion

IL-6, TNF-α

- Framingham study: higher spontaneous production of IL-1 / TNF-α by peripheral blood mononuclear cells→ increased risk of developing AD
- prospective cohort study (mild to severe AD)→ high baseline TNF-α → cognitive decline
- increased peripheral levels of IL-6 in AD
- hs-CRP associated / not associated, with cognitive decline, risk of dementia
- meta-analysis of 40 studies of peripheral blood and 14 studies of cerebrospinal fluid cytokines → higher IL-6, TNF-α, IL-1β, TGF-β, IL-12, and IL-18 in AD

Tan et al., 2007; Holmes et al., 2009; Singh & Guthikonda, 1997; Licastro et al., 2000; Yaffe et al., 2003; Noble et al., 2010; Engelhart et al., 2004; Kravitz, Corrada, & Kawas, 2009; Tan et al., 2007; van Himbergen et al., 2012; Swardfager et al., 2010,

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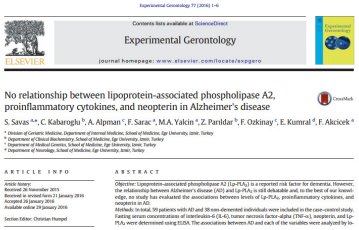

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Discussion

Neopterin

- increased serum neopterin in AD vs MCI/control or lower levels in AD
- inconclusive

Leblhuber et al., 1999; Parker et al., 2013; Licastro et al, 2000;

- Lp-PLA_2 associated with inflammatory cytokines, IL-6 and oxidized LDL, in women with metabolic syndrome
- no strong correlations between Lp-PLA2 and cerebrospinal fluid markers of AD
- Few studies of relationship between neopterin and Lp-PLA_2 ; no relationship of Lp-PLA_2, neopterin, IL-6, fibrinogen, and hs-CRP)

Chae et al., 2011; Davidson et al., 2012; Kabaroğlu et al., 2013; Launer et al., 1999

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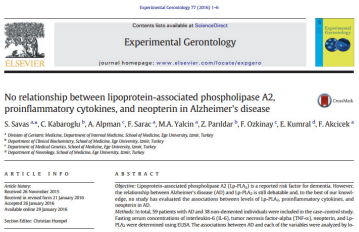

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Conclusions and THM

- This study reports on relationship between Lp-PLA2 and immune activation biomarkers in patients with AD
- Lp-PLA_2 a reported risk factor for dementia, and an inflammatory marker
- Relationship between AD & Lp-PLA_2 is still debatable
- No study on the associations between serum levels of Lp-PLA_2, proinflammatory cytokines, and neopterin in AD
- Median Lp-PLA_2 levels in AD and controls were similar in this study
- Neopterin and IL-6 levels were significantly higher in AD patients
- We determined that Lp-PLA_2 is not associated with either AD or levels of proinflammatory cytokines and neopterin
- Neopterin, low level of education, and female gender were associated with AD
- Elevated neopterin levels may be used as an inflammatory marker in patients with AD

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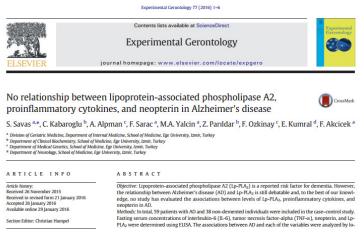

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Future Work

- Further studies of neopterin as a biomarker of diagnosis / monitoring of disease progression
- Larger studies investigating the relationships between AD and Lp-PLA_2 , cytokines, neopterin
- Genes that encode PLA_2 enzymes could play a role in disease susceptibility
- Polymorphisms in genes that act as regulatory factors of strategic molecules like cytokines and Lp-PLA_2

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