

Please cite the Published Version

Buongiorno, Mariateresa , Sánchez-Benavides, Gonzalo, Marzal-Espí, Clara, Giraldo, Darly Milena, Krupinski, Jerzy , Cullell, Natalia, Grau-Rivera, Oriol, Suárez-Calvet, Marc, Gispert, Juan Domingo and de la Sierra, Alex (2024) Blood-brain barrier permeable -blockers association with Alzheimer's disease cerebrospinal fluid biomarkers levels in non-demented individuals. Journal of Alzheimer's Disease, 102 (4). pp. 975-980. ISSN 1875-8908

DOI: https://doi.org/10.1177/13872877241293812

Publisher: SAGE Publications

Version: Accepted Version

Downloaded from: https://e-space.mmu.ac.uk/637430/

Usage rights: (cc) BY

Creative Commons: Attribution 4.0

Additional Information: This is an author-produced version of the published paper. Uploaded in accordance with the University's Research Publications Policy.

Data Access Statement: The data used in reparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), which is available upon request, and from the EPAD LCS data set V.IMI (doi:10.34688/epadlcs_v.imi_20.10.30). EPAD LCS data is publicly available upon request to the EPAD data access committee.

Enquiries:

If you have questions about this document, contact openresearch@mmu.ac.uk. Please include the URL of the record in e-space. If you believe that your, or a third party's rights have been compromised through this document please see our Take Down policy (available from https://www.mmu.ac.uk/library/using-the-library/policies-and-guidelines)

Blood brain barrier permeable β-blockers association with Alzheimer's disease cerebrospinal fluid biomarkers levels in non-demented individuals

Mariateresa Buongiorno,^{1,2†} Gonzalo Sánchez-Benavides,^{3,4,5†}, Clara Marzal-Espí,⁶ Darly Milena Giraldo,^{1,2} Jerzy Krupinski,^{6,7,8} Natalia Cullell,⁷ Oriol Grau-Rivera^{3,4,5,9}, Marc Suárez-Calvet^{3,4,5,9}, Juan Domingo Gispert,^{3,4,10} Alex de la Sierra,^{7,11} for the Alzheimer's Disease Neuroimaging Initiative* and the European Prevention of Alzheimer's Disease (EPAD) Consortium.

[†]These authors contributed equally to this work.

Author affiliations:

1 Neurology Department, Vall d'Hebron University Hospital, Barcelona, 08035, Spain

2 Neurodegenerative Diseases Research Group, Vall d'Hebron Research Institute, Barcelona, 08035, Spain

3 Barcelonaβeta Brain Research Center (BBRC), Pasqual Maragall Foundation, Barcelona 08005, Spain

4 Hospital del Mar Research Institute, Barcelona 08003, Spain

5 Centro de Investigación Biomédica en Red de Fragilidad y Envejecimiento Saludable (CIBERFES), Madrid 28029, Spain

6 Department of Neurology, Fundació Assistencial Mútua Terrassa, Terrassa 08221, Spain

7 Fundació per a Docència i Recerca, Mútua Terrassa, Terrassa 08221, Spain

8 Faculty of Science and Engineering, Department of Life Sciences John Dalton Building, Manchester Metropolitan University, Chester Street, Manchester, M1 5GD UK

9 Servei de Neurologia, Hospital del Mar, Barcelona 08003, Spain

10 Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Madrid 28029, Spain

11 Internal Medicine Department, University Hospital Mutua de Terrassa, University of Barcelona, Terrassa 08221, Spain

Correspondence to: Mariateresa Buongiorno

Department of Neurology, Vall d'Hebron University Hospital, Pg. de la Vall d'Hebron, 119, 08035 Barcelona, Spain

1

E-mail: mtbuongiorno75@gmail.com

Type of manuscript: Short communication

Word count manuscript body: 1490

Running title: Beta-blockers and CSF AD biomarkers

Keywords: Alzheimer's disease; beta-blockers, blood brain barrier; CSF biomarkers; amyloidb; tau

*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wpcontent/uploads/how to apply/ADNI Acknowledgement List.pdf

ABSTRACT (100 words)

β-blockers that easily cross the blood-brain barrier (BBB) seem to diminish the risk of Alzheimer's disease (AD), hypothetically facilitating waste clearance. However, their effect on AD pathophysiological markers is unknown. We compared CSF AD core biomarkers levels among non-demented individuals taking low, intermediate or high BBB permeable β-blockers in two samples (ADNI:n=216; EPAD:n=79). We found that CSF amyloid-β (Aβ) levels were higher in individuals taking highly permeable β-blockers in the ADNI sample. This result was not replicated in EPAD, in which the diminished levels of pTau181 and tTau were observed. These preliminary data suggest that β-blockers may impact AD pathophysiology.

INTRODUCTION

Recent epidemiological research conducted in almost 70.000 individuals reported compelling evidence suggesting that those β -blockers (β -adrenergic antagonists) that easily cross the blood-brain barrier (BBB) diminish the risk of Alzheimer's disease as compared to less permeable β-blockers.¹ Such protective effect seems to be dose-dependent based on BBB permeability, and specific to Alzheimer's disease, since the associations were not identified when all-cause dementia was used as an outcome. These findings support the hypothesis that highly BBB permeable β-blockers protect against Alzheimer's disease by promoting the clearance of brain metabolite waste. The reduction of norepinephrine signaling in the CNS has been related to a reduction of glial cell volume, which would increase the interstitial space, lowering the resistance to parenchymal flow, and facilitating the clearance.² However, there is no evidence of the effect of highly permeable β -blockers on Alzheimer's disease pathophysiological biomarkers. We aimed to further explore the suggested protective effect of highly BBB permeable β -blockers in Alzheimer's disease by studying their effect on Alzheimer's disease cerebrospinal fluid (CSF) core biomarker (amyloid-\beta-42 [A\beta42], phosphorylated tau-181 [pTau181], and total tau [tTau]) in non-demented individuals. We hypothesize that participants treated with highly BBB permeable β-blockers would have lower AD pathology as measured by CSF biomarkers.

METHODS

We leveraged on the data collected in the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study³ (ID NCT02804789), from which we selected non-demented individuals (Clinical Dementia Rating [CDR]<1) treated with β -blockers for at least one year and with CSF biomarkers data available at baseline (ADNI:*n*=216; EPAD:*n*=79). Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI)

database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org. See Supplementary material for further EPAD study details. Following the same approach as Beaman *et al.*¹, we classified β blockers by their BBB permeability as low [atenolol, bisoprolol, sotalol], intermediate [metoprolol] or high [propranolol, carvedilol]. CSF biomarkers were measured using the Roche cobas Elecsys. A positivity was defined using the cut-off A β_{42} < 976.6 pg/ml in ADNI⁴ and $A\beta_{42} < 1000 \text{ pg/ml}$ in EPAD.³ Participants were classified as cognitively normal (Clinical Dementia Rating (CDR)=0) or mildly impaired (CDR=0.5). EPAD-LCS inclusion and exclusion criteria can be found in Supplementary Table 1. We used linear models with logtransformed CSF biomarkers (A β_{42} , pTau181, tTau) as dependent variables, β -blockers group permeability as the predictor of interest, and age, sex, and global CDR as covariates. Standardized estimates (β coefficients) and 95% confidence intervals were calculated. The interaction terms β-blocker group*Aβ status, β-blocker group*CDR and β-blocker group*APOEE4 status were also explored. We also performed binary logistic regressions to predict A β status (+/-) using β -blockers group permeability as the predictor of interest, and age, sex, and global CDR as covariates.

RESULTS

Descriptive data by BBB permeability β -blocker groups is shown in Table 1. We found a main effect of β -blocker permeability groups on CSF A β_{42} levels in the ADNI sample (p=0.007) but not in EPAD (p=0.495). Pairwise comparisons in the ADNI sample showed significantly higher levels of CSF A β_{42} (indicating less amyloid pathology) in the high permeability β -blocker group as compared to the low (β = 0.144, 95% CI 0.019–0.269, p=0.007) and intermediate permeability groups (β = 0.165, 95% CI 0.042–0.287, p=0.002), see Figure 1 and Table 2. Regarding CSF pTau181 and tTau, there were not main effect of β -blocker permeability groups in ADNI (p=0.483, p=0.542), but significant differences were found in the EPAD sample (p=0.047, p=0.021). In pairwise comparisons, pTau181 (β =-0.311, CI 95% -0.578–-0.043, p=0.023) and tTau levels (β =-0.303, CI 95% -0.422–-0.063, p=0.018) were lower in the high permeability β -blocker group as compared to the low permeability one.

No significant interactions β -blocker group*A β status, β -blocker group*CDR, β -blocker group**APOE* ϵ 4 were observed (p>0.1).

Logistic regressions outcomes showed that taking high permeable β -blockers relates to lower probability of A β positivity as compared to taking low permeable β -blockers (OR= 0.312, 95% CI 0.116– 0.843, p=0.022) in the ADNI sample. No significant prediction was observed in the EPAD sample (p=0.470).

DISCUSSION

Our results, although preliminary, cast relevant insights on the mechanisms underpinning the reduction of risk of Alzheimer's disease attributed to highly BBB permeable β -blockers. The main finding suggests that the use of β -blockers with high BBB permeability relates to lower levels of amyloid pathology, as reflected by higher levels of CSF A β_{42} , and maybe to lower levels of CSF pTau and tTau, although the results were inconsistent across the samples analyzed.

We found higher levels of CSF A β_{42} associated to the use of β -blockers that easily pass the BBB (propranolol and carvedilol) as compared to the use of less BBB permeable β -blockers in the ADNI sample. Moreover, the odds of being classified as A β + in this sample is 68.8% lower for participants treated with high permeable β -blockers than those treated with low permeable

drugs. However, this result was not replicated in the EPAD cohort, in which we only observed lower levels of CSF pTau181 and tTau associated to highly permeable β -blockers. While the discrepant results on A β_{42} may be explained by lack of statistical power associated to the smaller sample size in EPAD, the findings in pTau and tTau are more intriguing. Although we adjusted for demographic variables and clinical staging, samples were different in age (participants were roughly 5 years older in ADNI) and in the distribution of CDR groups (CDR=0.5 was more frequent in ADNI). Such differences in sample characteristics, and other unknown, may underlie the observed discrepancies. Despite the lack of replication of the main results, we acknowledge the findings observed in ADNI over EPAD due to the larger sample size in ADNI, especially in the high permeability group, which is three times larger. Under this rationale, the pTau and tTau findings in EPAD may be considered as potential Type II errors. However, we think that the possible impact of β -blockers that easily cross the BBB on downstream AD pathology deserves further investigation.

The hypothetical protective role of β -blockers has been suggested to rely on its ability to facilitate the removal of waste proteins by the glymphatic system. The glymphatic system is a sophisticated clearance pathway composed of perivascular spaces, astrocytes, and aquaporin-4 channels that manage brain waste and nutrient delivery. Astrocytes, through their endfeet, surround blood vessels and drive the exchange of CSF with interstitial fluid through aquaporin-4 channels (see ⁵ for a thorough review). This dynamic flow, which is more active during sleep, removes neurotoxic substances such as A β and tau proteins.^{6,7} The volume fraction and the tortuosity of the extracellular space is critical for determining the concentration of solutes and limits the rate at which they can arrive and leave the compartment.⁵ Moreover, the volume of extracellular space dynamically changes as a function of cell volume and neural activity, being adrenergic signaling an important factor in modulating both cortical neuronal activity and the volume of the extracellular space.⁶ Specifically, the stimulation of astroglial β -adrenergic

receptors produces cellular expansion (with increments of up to 30-50% in cell perimeter), and antagonists such as propranolol block this expansion.⁸ Thus, both the physiological well-known reduction of adrenergic stimulation during sleep,⁹ or pharmacological treatments such as the use of β -blockers, would increase the interstitial space volume, lowering the resistance to parenchymal flow and promoting waste clearance. Therefore, it is plausible that a sustained treatment with propranolol or carvedilol facilitates amyloid clearance and led to higher levels of CSF A β_{42} as a result. This finding supports the epidemiological data that highly permeable BBB β -blockers may prevent AD¹ by providing, for the first time, pathophysiological proof.

The results presented here should be taken with caution due to relevant limitations of the study. The main one is the relatively small sample size of the individuals taking highly permeable β -blockers. This limitation is driven by the scarcity of data with both AD biomarkers and information on β -blocker medication available. The small sample sizes analyzed may have contributed to both Type I and Type II errors, as indicated by the divergent results observed between the ADNI and EPAD samples. In addition, in the data used, the prescription reason is in many cases unknown or ambiguous, and related comorbidities (vascular risk factors) have not been considered and may have affected the results. Comorbidities and lifestyle factors (such as sleep quality, exercise, etc.) can affect AD biomarker levels and protein clearance, and may have significantly influenced the observed results, potentially explaining the discrepancies. More thorough studies that account for these variables are needed to clarify their effects. Moreover, most of the participants in the available samples were White/Caucasian (95% in ADNI and virtually 100% in EPAD), which limits the generalizability of the findings. Future research using larger, better phenotyped, and more diverse samples is necessary to confirm the observed beneficial effects of β -blocker that easily pass to the CNS.

The data presented provide preliminary pathophysiological support for the hypothesis of enhanced glymphatic function and improved protein clearance potentially influenced by norepinephrine signaling, and consequent reduction of astrocytic size, produced by β -blockers able to pass the BBB. Future studies to confirm or refute the observed associations and deepen the knowledge of the underlying mechanisms are warranted. Such knowledge might contribute to the development of new Alzheimer's disease prevention strategies.

ACKNOWLEDGMENTS

We would like to thank ADNI and EPAD-LCS volunteers for their generous participation. The investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators be found http://adni.loni.usc.edu/wpcan at: content/uploads/how to apply/ADNI Acknowledgement List.pdf. We would also acknowledge the investigators within the EPAD LCS and EPAD Consortium, that contributed to the design and implementation of EPAD and/or provided data but did not participate in analysis or writing of this report. A complete list of EPAD Investigators can be found at: http://ep-ad.org/wp-content/uploads/2020/12/202010 List-of-epadistas.pdf

FUNDING

Data collection and sharing for the Alzheimer's Disease Neuroimaging Initiative (ADNI) is funded by the National Institute on Aging (National Institutes of Health Grant U19 AG024904). The grantee organization is the Northern California Institute for Research and Education. In the past, ADNI has also received funding from the National Institute of Biomedical Imaging and Bioengineering, the Canadian Institutes of Health Research, and private sector contributions through the Foundation for the National Institutes of Health (FNIH) including generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. This work also used data from the EPAD project which received support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking EPAD grant agreement n° 115736 and an Alzheimer's Association Grant (SG21-818099-EPAD). Gonzalo Sánchez-Benavides is supported by the Instituto de Salud Carlos III (ISCIII) through the project CP23/00039 (Miguel Servet contract).

CONFLICT OF INTEREST

Gonzalo Sánchez-Benavides worked as a consultant for Roche Farma, S.A. Marc Suárez-Calvet has served as a consultant and at advisory boards for Roche Diagnostics International Ltd and has given lectures in symposia sponsored by Roche Diagnostics, S.L.U, Roche Farma, S.A and Roche Sistemas de Diagnosticos, Sociedade Unipessoal, Lda.

Gonzalo Sánchez-Benavides is Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review. All other authors have no conflict of interest to report.

DATA AVAILABILITY

The data used in reparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), which is available upon request, and from the EPAD LCS data set V.IMI (doi:10.34688/epadlcs_v.imi_20.10.30). EPAD LCS data is publicly available upon request to the EPAD data access committee.

SUPPLEMENTARY MATERIAL

EPAD study details and EPAD-LCS inclusion and exclusion criteria can be found in the supplementary material available in the electronic version of this article.

REFERENCES

- Beaman EE, Bonde AN, Larsen SMU, et al. Blood-brain barrier permeable β-blockers linked to lower risk of Alzheimer's disease in hypertension. *Brain* 2023; 146: 1141– 1151.
- Sherpa AD, Aoki C, Hrabetova S. Noradrenaline Drives Structural Changes in Astrocytes and Brain Extracellular Space. In: Vardjan N, Zorec R (eds) Noradrenergic Signaling and Astroglia. Elsevier, pp. 241–255.
- Solomon A, Kivipelto M, Molinuevo JL, et al. European Prevention of Alzheimer's Dementia Longitudinal Cohort Study (EPAD LCS): study protocol. *BMJ Open* 2018; 8: e021017.
- Suárez-Calvet M, Morenas-Rodríguez E, Kleinberger G, et al. Early increase of CSF sTREM2 in Alzheimer's disease is associated with tau related-neurodegeneration but not with amyloid-β pathology. *Mol Neurodegener* 2019; 14: 1.
- Rasmussen MK, Mestre H, Nedergaard M. Fluid transport in the brain. *Physiol Rev* 2022; 102: 1025–1151.
- Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science 2013; 342: 373–377.
- Holth JK, Fritschi SK, Wang C, et al. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science (80-)* 2019; 363: 880–884.
- 8. Vardjan N, Kreft M, Zorec R. Dynamics of β-adrenergic/cAMP signaling and

morphological changes in cultured astrocytes. *Glia* 2014; 62: 566–579.

 Aston-Jones G, Bloom FE. Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J Neurosci* 1981; 1: 876–886.

	β-blocker permeability groups			
	Low	Intermediate	High	
ADNI	n=80	n=109	n=27	
Age, years M±SD	73.8±7.0	75.5±7.5	74.0±7.6	
Sex, females n(%)	41(51.3%)	36(33.0%)	15(55.5%)	
APOE <i>e</i> 4 carriers n(%)	38(47.5%)	50(45.9%)	2(7.4%)	
CDR 0.5 n(%)	50(62.5%)	74(67.9%)	14(51.9%)	
Aβ+ n(%)	43(53.8%)	71(65.1%)	7(25.9%)	
$CSF \ A\beta_{42} \ pg/ml \ M\pm SD$	1081±603	1001±574	1501±707	
CSF pTau181 pg/ml M±SD	25.6±11.3	28.6±14.2	20.6±12.6	
CSF tTau pg/ml M±SD	270±104	294±125	261±101	
EPAD	n=58	n=13	n=8	
Age, years M±SD	70.1±7.2	68.4±6.5	68.2±6.8	
Sex, females n(%)	24(41.4%)	6(46.2 %)	3(37.5%)	
APOE <i>e</i> 4 carriers n(%)	26(44.8%)	6(46.2%)	2(25.0%)	
CDR 0.5 n(%)	27(46.6%)	5(38.5%)	3(37.5%)	
Aβ+ n(%)	30(51.7%)	8(61.5%)	3(37.5%)	
$CSF \ A\beta_{42} \ pg/ml \ M\pm SD$	1200±566	1134±675	1077±416	
CSF pTau181 pg/ml M±SD	22.4±9.8	19.0±8.9	15.2±4.8	
CSF tTau pg/ml M±SD	248±94	208±93	173±49	

Table 1. Descriptive data of the samples by β -blocker permeability groups

APOE: apolipoprotein E; CDR: Clinical Dementia Rating; MMSE: Mini-Mental State Examination; A β : Amyloid-beta; A β + was defined as A β_{42} < 976.6 pg/ml in ADNI and A β_{42} <1000 pg/ml.

ADNI	[Standardized β	95%CI	P value		
CSF Aβ ₄₂						
	High vs Low permeability	0.144	0.019–0.269	0.007		
	High vs Intermediate permeability	0.165	0.042-0.287	0.002		
	Intermediate vs Low	-0.021	-0.091–0.050	0.564		
CSF p	Tau181					
	High vs Low permeability	-0.010	-0.089–0.070	0.812		
	High vs Intermediate permeability	-0.037	-0.115-0.040	0.348		
	Intermediate vs Low	0.028	-0.026-0.081	0.312		
CSF tTau						
	High vs Low permeability	-0.002	-0.091-0.077	0.962		
	High vs Intermediate permeability	-0.003	-0.093-0.042	0.458		
	Intermediate vs Low	0.024	-0.023-0.071	0.313		
EPAD						
EPAI)	Standardized β	95%CI	P value		
EPAD CSF A) Δβ ₄₂	Standardized β	95%CI	P value		
EPAL CSF A) Aβ ₄₂ High vs Low permeability	Standardized β -0.047	95%CI -0.191–0.097	P value		
EPAI CSF A) Aβ ₄₂ High vs Low permeability High vs Intermediate permeability	Standardized β -0.047 0.017	95%CI -0.191–0.097 -0.154–0.188	P value 0.515 0.848		
EPAD CSF A	Aβ ₄₂ High vs Low permeability High vs Intermediate permeability Intermediate vs Low	Standardized β -0.047 0.017 -0.063	95%CI -0.191–0.097 -0.154–0.188 -0.181–0.053	P value 0.515 0.848 0.281		
EPAD CSF A	Aβ ₄₂ High vs Low permeability High vs Intermediate permeability Intermediate vs Low Tau181	Standardized β -0.047 0.017 -0.063	95%CI -0.191–0.097 -0.154–0.188 -0.181–0.053	P value 0.515 0.848 0.281		
EPAL CSF A	 Aβ₄₂ High vs Low permeability High vs Intermediate permeability Intermediate vs Low Tau181 High vs Low permeability 	Standardized β -0.047 0.017 -0.063 -0.311	95%CI -0.191-0.097 -0.154-0.188 -0.181-0.053 -0.5780.043	P value 0.515 0.848 0.281 0.023		
EPAL CSF A	Aβ ₄₂ High vs Low permeability High vs Intermediate permeability Intermediate vs Low Tau181 High vs Low permeability High vs Low permeability	Standardized β -0.047 0.017 -0.063 -0.311 -0.159	95%CI -0.191-0.097 -0.154-0.188 -0.181-0.053 -0.5780.043 -0.481-0.162	P value 0.515 0.848 0.281 0.023 0.327		
CSF A	Aβ ₄₂ High vs Low permeability High vs Intermediate permeability Intermediate vs Low Tau181 High vs Low permeability High vs Low permeability Intermediate vs Low	Standardized β -0.047 0.017 -0.063 -0.311 -0.159 -0.152	95%CI -0.191-0.097 -0.154-0.188 -0.181-0.053 -0.5780.043 -0.481-0.162 -0.376-0.073	P value 0.515 0.848 0.281 0.023 0.327 0.183		
EPAD CSF A CSF p	Aβ ₄₂ High vs Low permeability High vs Intermediate permeability Intermediate vs Low Tau181 High vs Low permeability High vs Low permeability High vs Low permeability Intermediate vs Low Tau181 High vs Low permeability Intermediate vs Low Tau181 High vs Intermediate permeability Intermediate vs Low Tau	Standardized β -0.047 0.017 -0.063 -0.311 -0.159 -0.152	95%CI -0.191-0.097 -0.154-0.188 -0.181-0.053 -0.5780.043 -0.481-0.162 -0.376-0.073	P value 0.515 0.848 0.281 0.023 0.327 0.183		
EPAL CSF A CSF p	Aβ ₄₂ High vs Low permeability High vs Intermediate permeability Intermediate vs Low Tau181 High vs Low permeability High vs Low permeability Intermediate vs Low Tau181 High vs Low permeability Intermediate vs Low Tau High vs Low permeability High vs Low permeability	Standardized β -0.047 0.017 -0.063 -0.311 -0.159 -0.152 -0.303	95%CI -0.191-0.097 -0.154-0.188 -0.181-0.053 -0.5780.043 -0.481-0.162 -0.376-0.073 -0.4220.063	P value 0.515 0.848 0.281 0.023 0.327 0.183 0.018		
EPAD CSF A CSF p	Aβ ₄₂ High vs Low permeability High vs Intermediate permeability Intermediate vs Low Tau181 High vs Low permeability High vs Low permeability Intermediate vs Low Tau181 High vs Low permeability Intermediate vs Low Tau High vs Low permeability High vs Low permeability Intermediate vs Low Tau High vs Low permeability High vs Low permeability	Standardized β -0.047 0.017 -0.063 -0.311 -0.159 -0.152 -0.303 -0.137	95%CI -0.191-0.097 -0.154-0.188 -0.181-0.053 -0.5780.043 -0.481-0.162 -0.376-0.073 -0.4220.063 -0.422-0.148	P value 0.515 0.848 0.281 0.023 0.327 0.183 0.018 0.343		

Table 2. Effect of β -blockers permeability groups on CSF biomarkers

Models were adjusted by age, sex and CDR.

Figure 1. Boxplots showing CSF biomarker levels (adjusted by age, CDR, and sex) by β blockers permeability groups. Dashed line depicts the threshold for A β positivity in each cohort (ADNI < 976.6 pg/ml; EPAD <1000 pg/ml).



15