

Investigating 2-arachidonoylglycerol (2-AG) as a biomarker of agitation in Alzheimer's disease



Hui Jue Wang^{1,2}, Giovanni Marotta^{1,3}, Amer M. Burhan^{4,5}, Zahinoor Ismail⁶, Sanjeev Kumar⁷, Tuoyo Awani^{8,9}, Corinne E. Fischer^{4,10}, Damien Gallagher^{1,4,11}, Mark J. Rapoport^{1,4,11}, Gayla Tennen^{4,11}, Kate Survilla¹, Danielle Vieira¹, Krista L. Lanctôt^{1,2,4,11}



Geriatric Psychopharmacology Research Group, Sunnybrook Research Institute¹; Department of Pharmacology and Toxicology, University of Toronto²; Geriatric Medicine Division, Sunnybrook Health Sciences Centre³; Department of Psychiatry, University of Toronto⁴; Ontario Shores Centre for Mental Health Sciences⁵; Departments of Psychiatry, Clinical Neurosciences, and Community Health Sciences, University of Calgary⁶; Geriatric Psychiatry Division, Centre for Addiction and Mental Health⁷; Division of Geriatric Psychiatry, Western University⁸; Department of Geriatric Psychiatry, London Health Sciences Center⁹; Keenan Research Centre for Biomedical Science, St. Michael's Hospital¹⁰; Department of Psychiatry, Sunnybrook Health Sciences Centre¹¹

Background

- Agitation is a prevalent and challenging neuropsychiatric symptom (NPS) of Alzheimer's disease (AD) associated with reduced quality of life and increased risk of mortality
- Dysregulation of the endocannabinoid system (ECS) has been implicated in neuroinflammation, oxidative stress, and neurotransmitter imbalances, all of which may be linked to agitation in AD
- Prior studies have suggested that increased ECS signaling may be associated with favourable cognitive and psychiatric outcomes
 - Higher 2-AG levels correlated with better memory and attention, as well as decreased depressive and anxiety-like symptoms
- 2-AG may be a mechanistically relevant blood-based biomarker for agitation in AD, but this has yet to be investigated

Objectives

This study aimed to assess the cross-sectional relationship between plasma 2-AG and agitation in individuals with moderate-to-severe AD

- Primary: lower plasma 2-AG will be associated with higher CMAI total score at baseline
- Secondary: lower plasma 2-AG will be associated with higher CMAI physical non-aggression, physical aggression, and verbal aggression at baseline
- Exploratory: relationships between 2-AG and agitation outcomes will be moderated by other co-occurring NPS

Methods

- Data were collected from two randomized controlled trials investigating cannabinoids for agitation in AD
 - NAB-IT**: 9-week, phase 3, double-blind, placebo-controlled, parallel group study of nabilone
 - CALM-IT**: 23-week, phase 2, double-blind, placebo-controlled, cross-over study of cannabidiol
- Participants had Major Neurocognitive Disorder (DSM-5) due to AD or mixed AD/vascular, standardized Mini-Mental State Examination (sMMSE) ≤ 24 , and clinically significant agitation per IPA criteria
- Agitation was assessed with the Cohen-Mansfield Agitation Inventory (CMAI), NPS with the Neuropsychiatric Inventory-Nursing Home version (NPI-NH), and cognition with the sMMSE
- Plasma 2-AG concentrations quantified with liquid chromatography-tandem mass spectrometry (LC-MS/MS)
- Linear regression assessed associations between 2-AG and agitation outcomes; exploratory analyses assessed interactions between 2-AG and co-occurring NPS

Results

Table 1 Baseline demographics and clinical characteristics

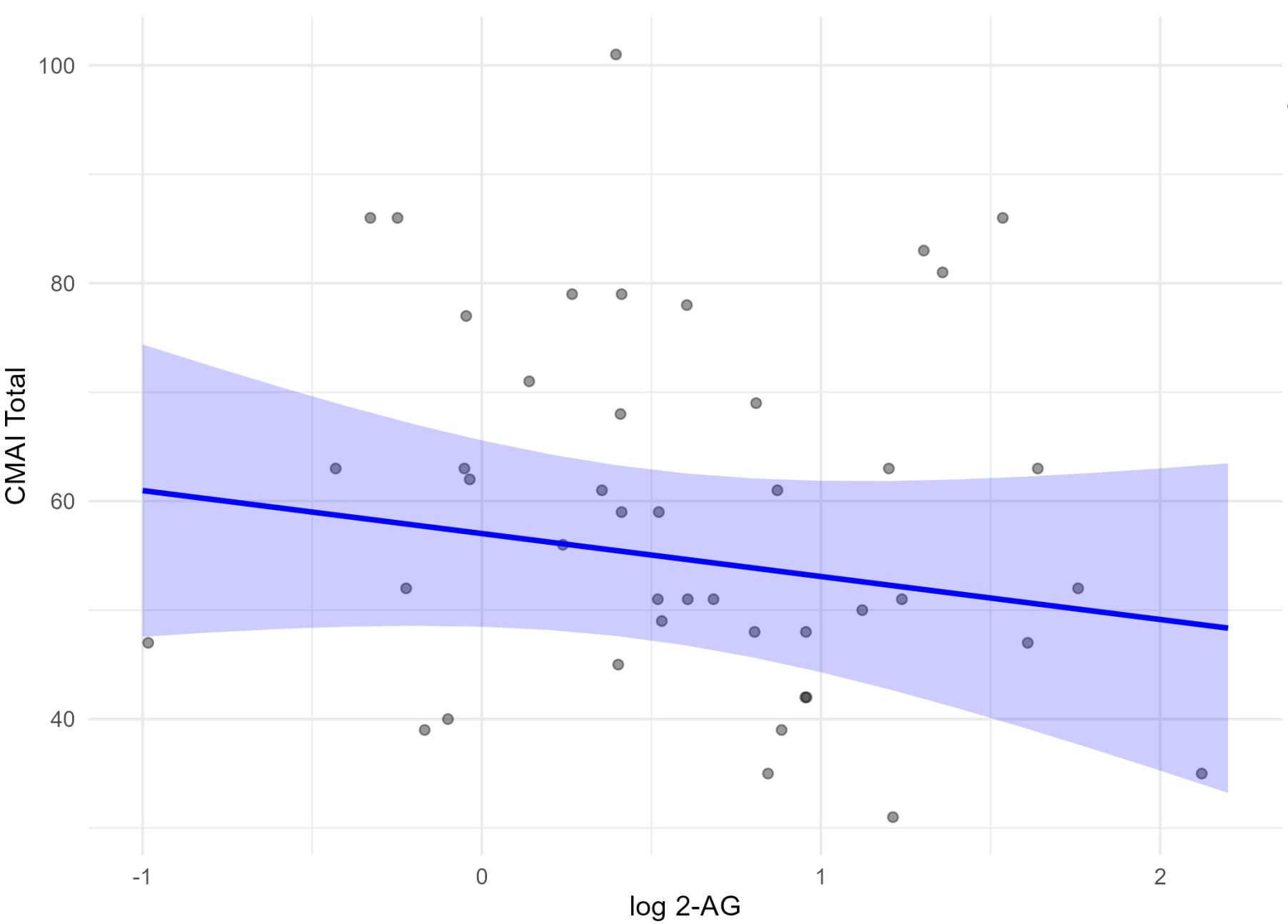
	Overall (N=44)
Age (mean $\pm$ SD)	78.3 $\pm$ 9.1
Sex (n, % female)	28 (64%)
Medical History	
Number of conditions in medical history (mean $\pm$ SD)	6.8 $\pm$ 3.4
Number of concomitant medications (mean $\pm$ SD)	15.4 $\pm$ 7.5
Psychotropic medication use (n, % yes)	44 (100%)
Antipsychotic medication use (n, % yes)	27 (61%)
Serotonergic medication use (n, % yes)	30 (68%)
Behavioural and cognitive assessments	
sMMSE (mean $\pm$ SD)	5.9 $\pm$ 6.4
CMAI total (mean $\pm$ SD)	59 $\pm$ 17
CMAI physical non-aggression (mean $\pm$ SD)	21.1 $\pm$ 8.0
CMAI physical aggression (mean $\pm$ SD)	16.8 $\pm$ 6.7
CMAI verbal aggression (mean $\pm$ SD)	7.4 $\pm$ 3.5
2-AG measurements, ng/mL (mean $\pm$ SD)	2.3 $\pm$ 1.6

CMAI subsection scores range from:

- 11–77 for physical aggression
- 10–70 for physical non-aggression
- 3–21 for verbal aggression

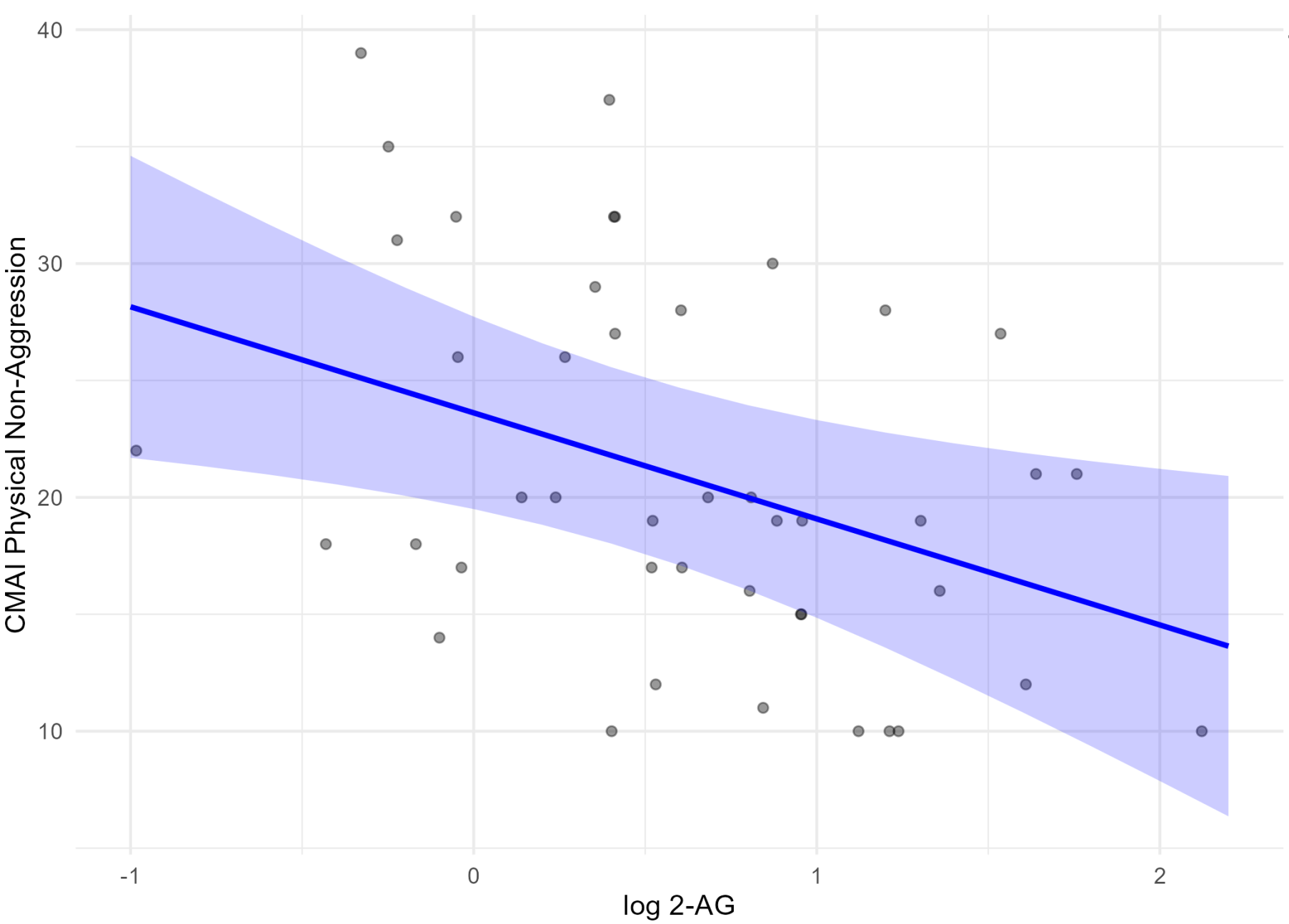
*Abbreviations: SD, Standard Deviation; CMAI, Cohen-Mansfield Agitation Inventory; CGI, Clinician's Global Impression; PAINAD, Pain Assessment in Advanced Dementia; MMSE, Standardized Mini-Mental State Examination; NPI-NH, Neuropsychiatric Inventory Nursing Home Version

Figure 1 Adjusted association between 2-AG and CMAI total based on predicted marginal effects



- No significant association between plasma 2-AG concentrations and CMAI total scores at baseline, adjusting for age, sex, and sMMSE (B = -3.9, 95% CI [-11.4, 3.5], p = .3)

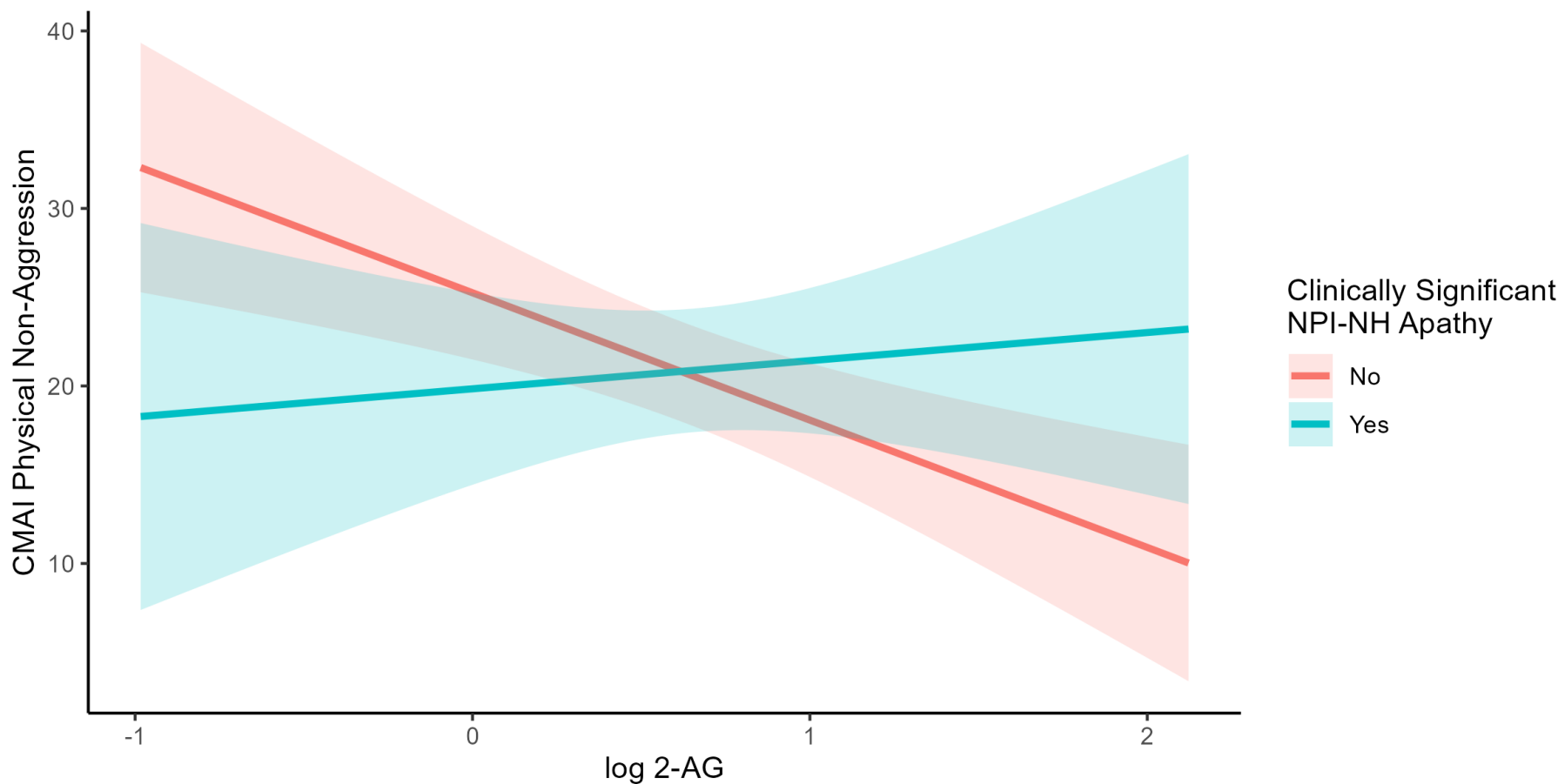
Figure 2 Adjusted association between 2-AG and CMAI physical non-aggression based on predicted marginal effects



- Significant negative association between 2-AG and CMAI physical non-aggression scores at baseline, adjusting for age, sex, and sMMSE (B = -4.5, 95% CI [-8.1, -0.9], p = .01)

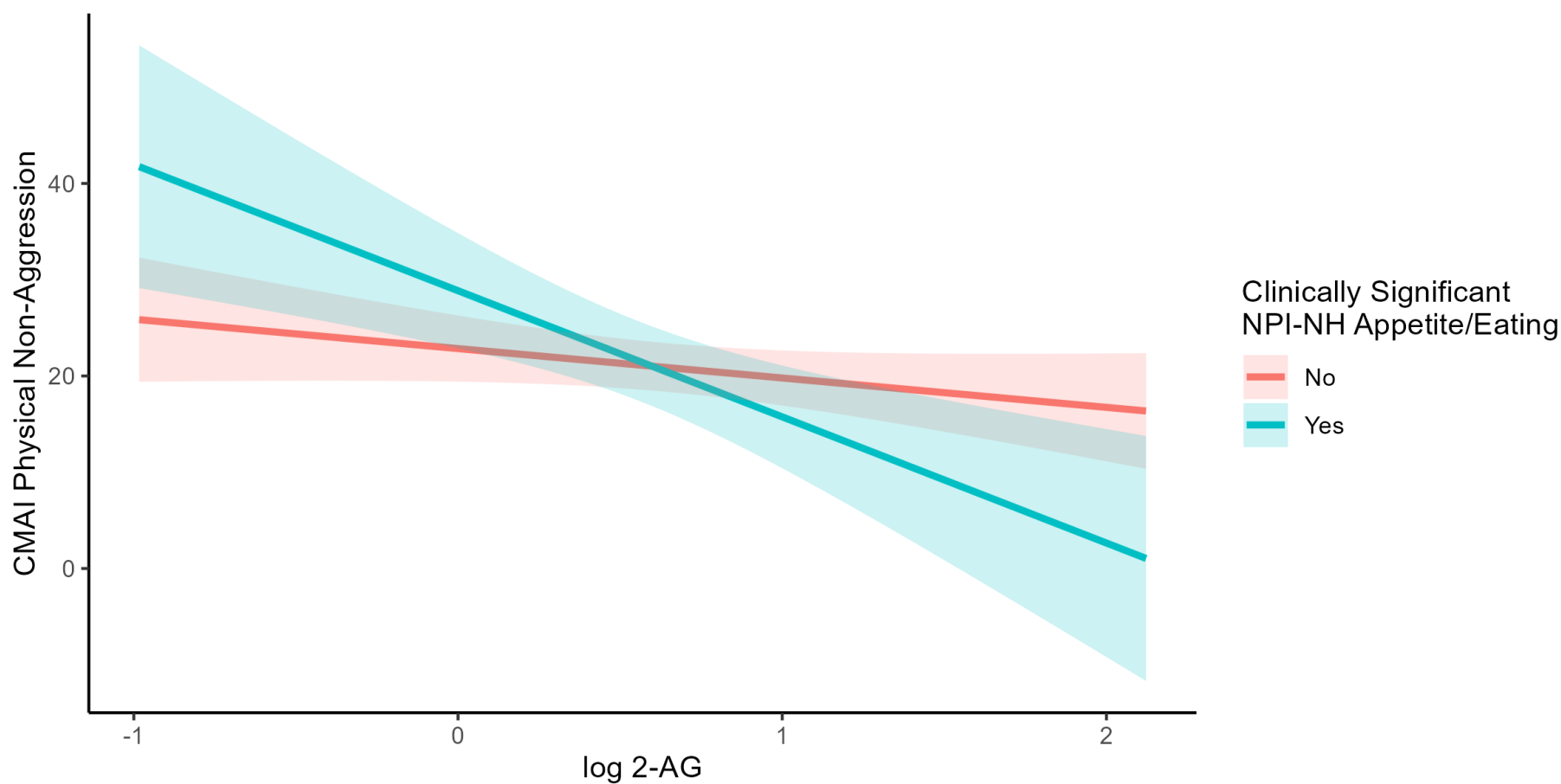
Results (cont'd)

Figure 3 Moderating effect of NPI-NH apathy on the association between 2-AG and CMAI physical non-aggression



- 2-AG*apathy interaction B = 8.8, 95% CI [1.3, 16.2], p = .02
- Lower 2-AG was associated with greater physical non-aggression in individuals without clinically significant apathy (B = -7.2, 95% CI [-11.2, -3.2]), but not in those with apathy (B = 1.6, 95% CI [-4.7, 7.9])

Figure 4 Moderating effect of NPI-NH appetite/eating on the association between 2-AG and CMAI physical non-aggression



- 2-AG*appetite interaction B = -10.1, 95% CI [-18.6, -1.5], p = .02
- Lower 2-AG was associated with greater physical non-aggression in individuals with clinically significant appetite/eating disturbances (B = -13.1, 95% CI [-20.8, -5.4]), but not in those without these symptoms (B = -3.1, 95% CI [-6.7, 0.6])

Conclusions

- 2-AG was not significantly associated with CMAI total score
- Lower 2-AG levels were associated with higher physical non-aggressive agitation; this negative association was suggested to be moderated by apathy and appetite/eating disturbances
- Findings suggest possible neurobiological differences between non-aggressive and aggressive agitation
- Longitudinal studies needed to assess the predictive and monitoring utility of 2-AG for agitation

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Contact Information: Dr. Krista L. Lanctôt; krista.lanctot@sunnybrook.ca
Sunnybrook Health Sciences Centre, 2075 Bayview Ave, Room FG21, Toronto, ON M4N 3M5, Canada

