

Comparison of cerebrospinal fluid biomarkers in people with mild cognitive impairment and Alzheimer's disease and the aged canine model of Alzheimer's disease

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Introduction

Mild cognitive impairment (MCI) is a disorder wherein an individual's cognitive decline is accelerated relative to their age group. MCI can progress to dementias such as Alzheimer's disease (AD). Canine ageing is associated with cognitive decline that is linked to AD-like neuropathology¹ that can be improved by BACE1 inhibitors and cholinesterase inhibitors². The current study aimed to further validate the canine AD model by assessing cerebrospinal fluid (CSF) biomarkers of AD progression, neuroinflammation and neuronal cell damage.

Aim:
I) To investigate CSF A β , neurofilament light chain (NfL) and cytokine concentrations in people with MCI, AD, and the canine model of AD.

Methods

Subjects: CSF from people with MCI, AD and age matched controls (n=15 per group) were obtained from a biobank.

Cognitive assessments: Mini Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale- Cognitive Subscale (ADAS-Cog) tests were performed prior to sample collection.

Animals: CSF was collected from three groups of Beagles (n=13-15 per group): young (under 6 years), middle-aged (between 6 and 10 years) and aged (over 10 years).

MesoScale Discovery: Protein biomarkers in CSF were quantified using a selection of MESO QuickPlex SQ 120 custom panels, following the protocol provided by the suppliers: 1) A β 42, A β 40, A β 38; 2) NfL; 3) TNF- α , IL-2, IL-6, IL-8.

Conclusion

- The CSF biomarker profile of aged canines exhibits similarities to that of patients with MCI and AD.
- Differences seen in the current study may partially reflect age stratification in dogs versus cognitive stratification in humans.
- These results further support the aged Beagle as a clinically relevant model of AD.

Cognitive testing in MCI and AD patients

MMSE & ADAS-Cog tests were used; a decreasing score defines declining cognition in the former and an increasing score defines declining cognition in the latter.

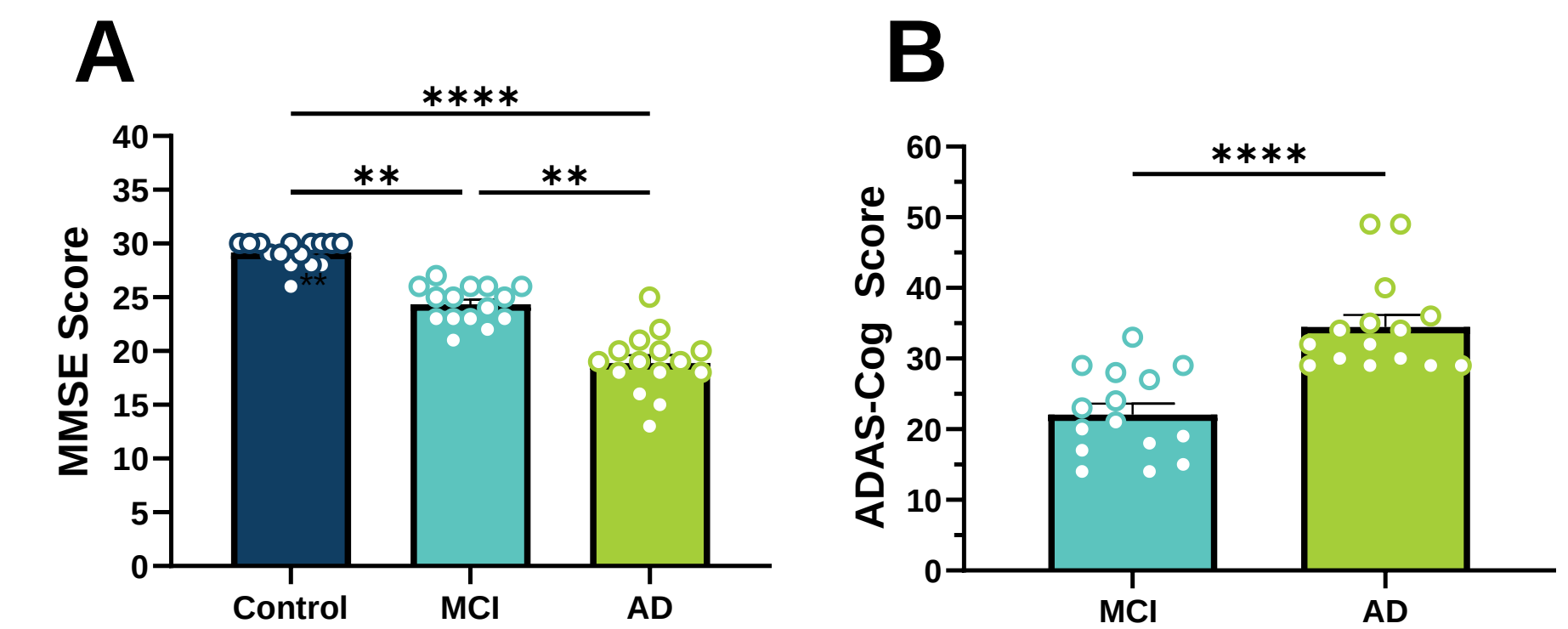


Figure 1 (A) MMSE (B) ADAS-Cog. Error bars represent SEM, n=15. (A) Kruskal-Wallis followed by uncorrected Dunn's multiple comparisons test (B) Student's t-test. ** p<0.01, **** p<0.0001.

A β : MCI, AD and aged canines

Development of amyloid plaques in the brain is a known feature of AD pathology. The ratio of A β 42/38 and A β 42/40 in CSF gives an accurate and disease specific representation of amyloid burden in the brain where a decreasing value indicates a heavier plaque burden.

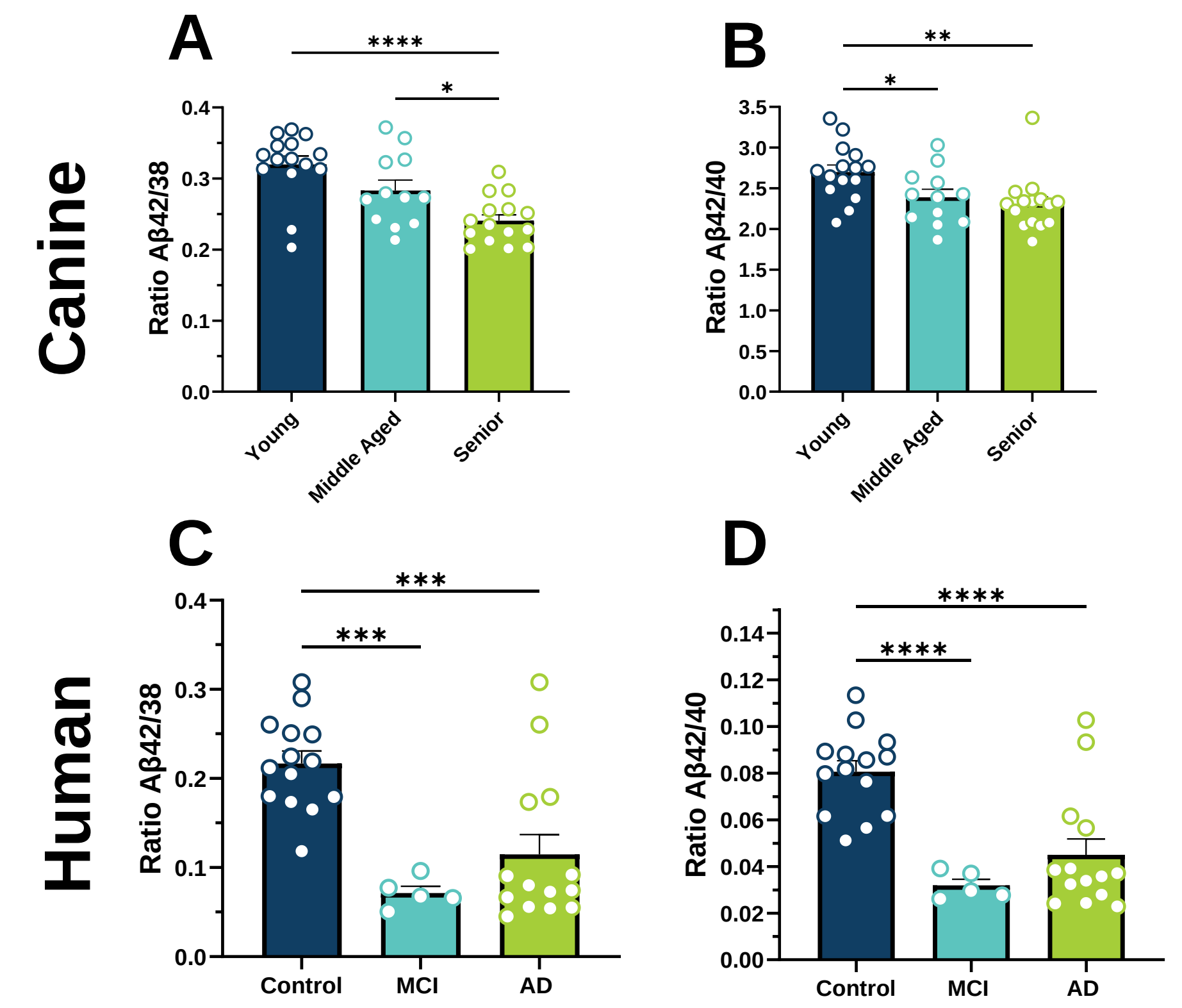


Figure 2 (A-B) Canine A β 42/38 and A β 42/40 ratios (C-D) Human A β 42/38 and A β 42/40 ratios. Error bars represent SEM, n=5-15. Statistical significance was determined by one-way ANOVA with uncorrected Fisher's LSD multiple comparisons test or Kruskal Wallis with Uncorrected Dunn's as appropriate. * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001.

NfL: MCI, AD and aged canines

Neurodegeneration in patients with AD typically results in an increase of the neuronal cytoplasmic protein, NfL, in CSF.

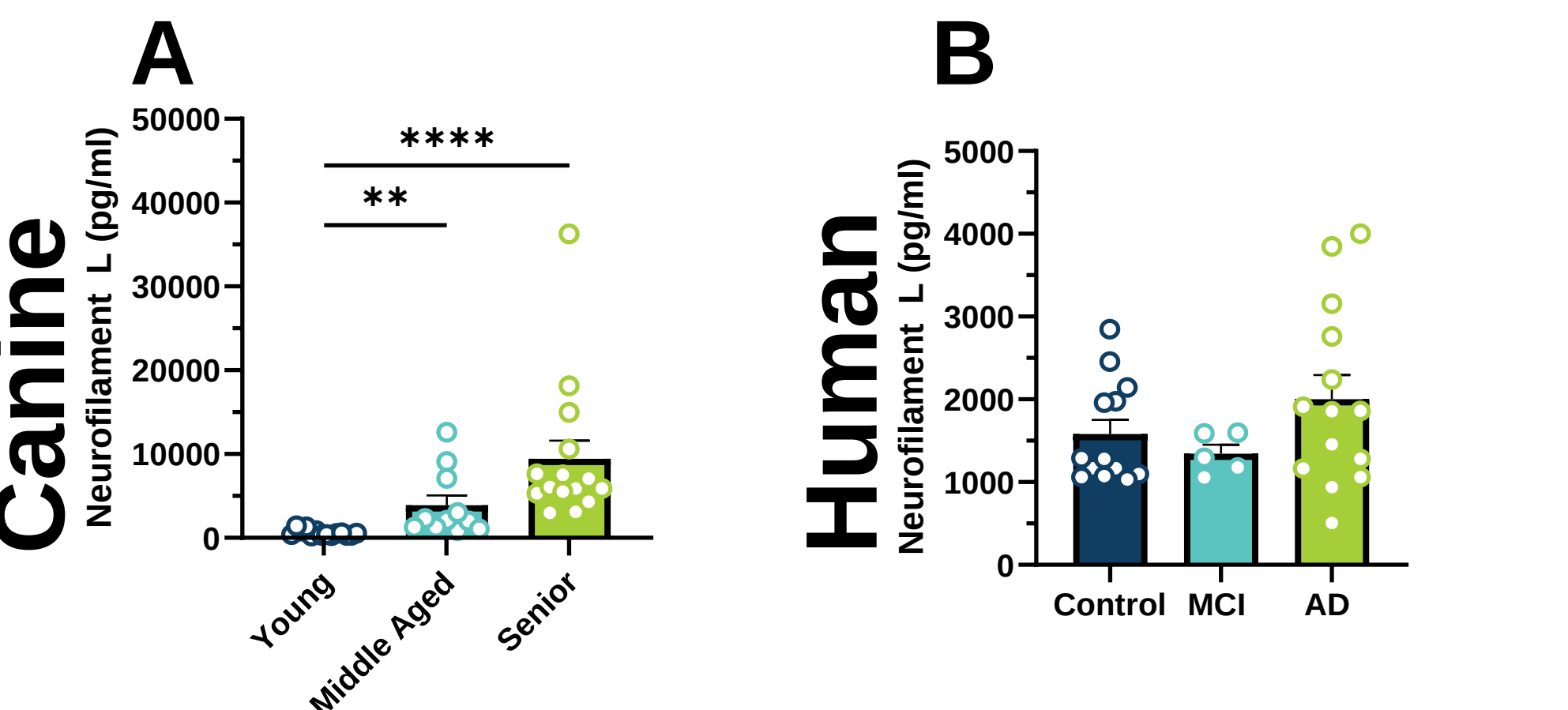


Figure 3 (A) Canine (B) Human. Error bars represent SEM, n=5-15. Statistical significance was determined by one-way ANOVA with uncorrected Fisher's LSD multiple comparisons test or Kruskal Wallis with Uncorrected Dunn's as appropriate. ** p<0.01, **** p<0.0001.

Cytokines: MCI, AD and aged canines

An increase in pro-inflammatory cytokines in CSF is a strong indicator of neuroinflammation, a key driver of neurodegeneration.

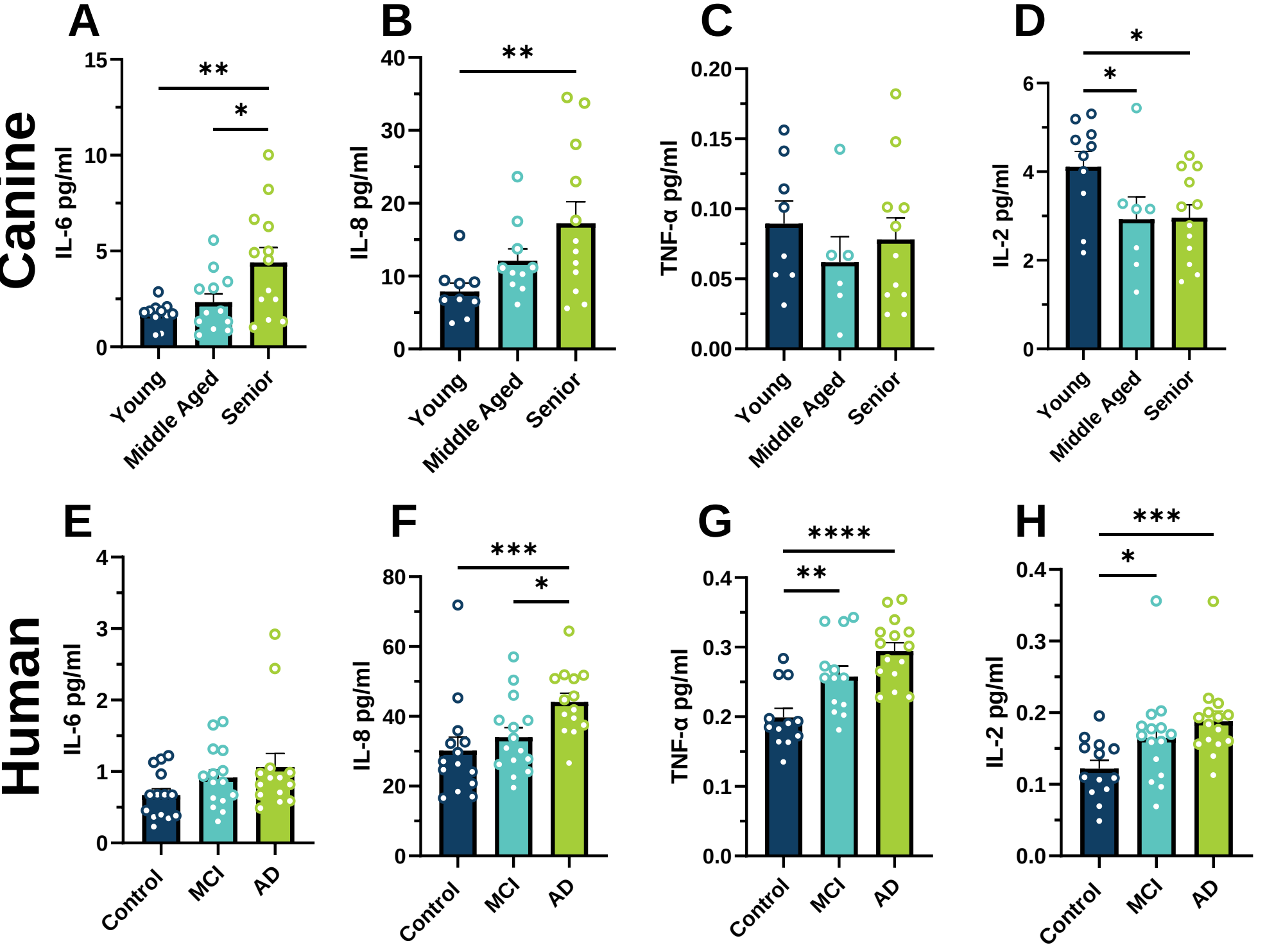


Figure 4 (A-D) Canine (E-H) Human. Error bars represent SEM, n=5-15. Statistical significance was determined by one-way ANOVA with uncorrected Fisher's LSD multiple comparisons test or Kruskal Wallis with Uncorrected Dunn's as appropriate. * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001.

¹ Dewey CW, Davies ES, Xie H, Wakshlag JJ. Canine Cognitive Dysfunction: Pathophysiology, Diagnosis, and Treatment. Vet Clin North Am Small Anim Pract. 2019 May;49(3):477-499. doi: 10.1016/j.cvsm.2019.01.013. Epub 2019 Mar 5. PMID: 30846383.
² Zakošek Pipan, M., Prpar Mihevc, S., Štrbenc, M. et al. Treatment of canine cognitive dysfunction with novel butyrylcholinesterase inhibitor. Sci Rep 11, 18098 (2021). <https://doi.org/10.1038/s41598-021-97404-2>