



Peripheral bile acid dysmetabolism impairs choroid plexus function and exacerbates WMHs-related cognitive decline via the GDCA–VDR–TTR axis

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Bile acid dysregulation impairs choroid plexus function and aggravates cognitive decline, positioning the GDCA-VDR-TTR axis as a new therapeutic target for WMHs.

INTRODUCTION

White matter hyperintensities (WMHs) are significant cerebrovascular factors contributing to cognitive impairment in the aging population¹. Bile acids (BAs) have increasingly been linked to neurological disorders²; however, the specific alterations in BA metabolites among patients with WMHs and their impact on WMH-related cognitive impairment remain unclear.

METHODS

This study integrated data from three independent population cohorts (Cohort I, n=375; Cohort II, n=711; Cohort III, n=92) to perform comprehensive analyses of targeted BA metabolomics, plasma proteomics, and multimodal neuroimaging, complemented by cellular experiments to elucidate underlying molecular mechanisms.

CONCLUSIONS

This study identifies distinct alterations in the peripheral BA profile of patients with WMHs and reveals the GDCA-VDR-TTR axis that links BA dysmetabolism to choroid plexus dysfunction, impaired A β clearance, and cognitive decline, thereby presenting potential therapeutic targets for WMH-related cognitive impairment.

REFERENCES

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2. S.L. Collins, J.G. Stine, J.E. Bisanz.et. al. Bile acids and the gut microbiota: metabolic interactions and impacts on disease, Nat Rev Microbiol 21(4) (2023) 236-247.

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RESULTS

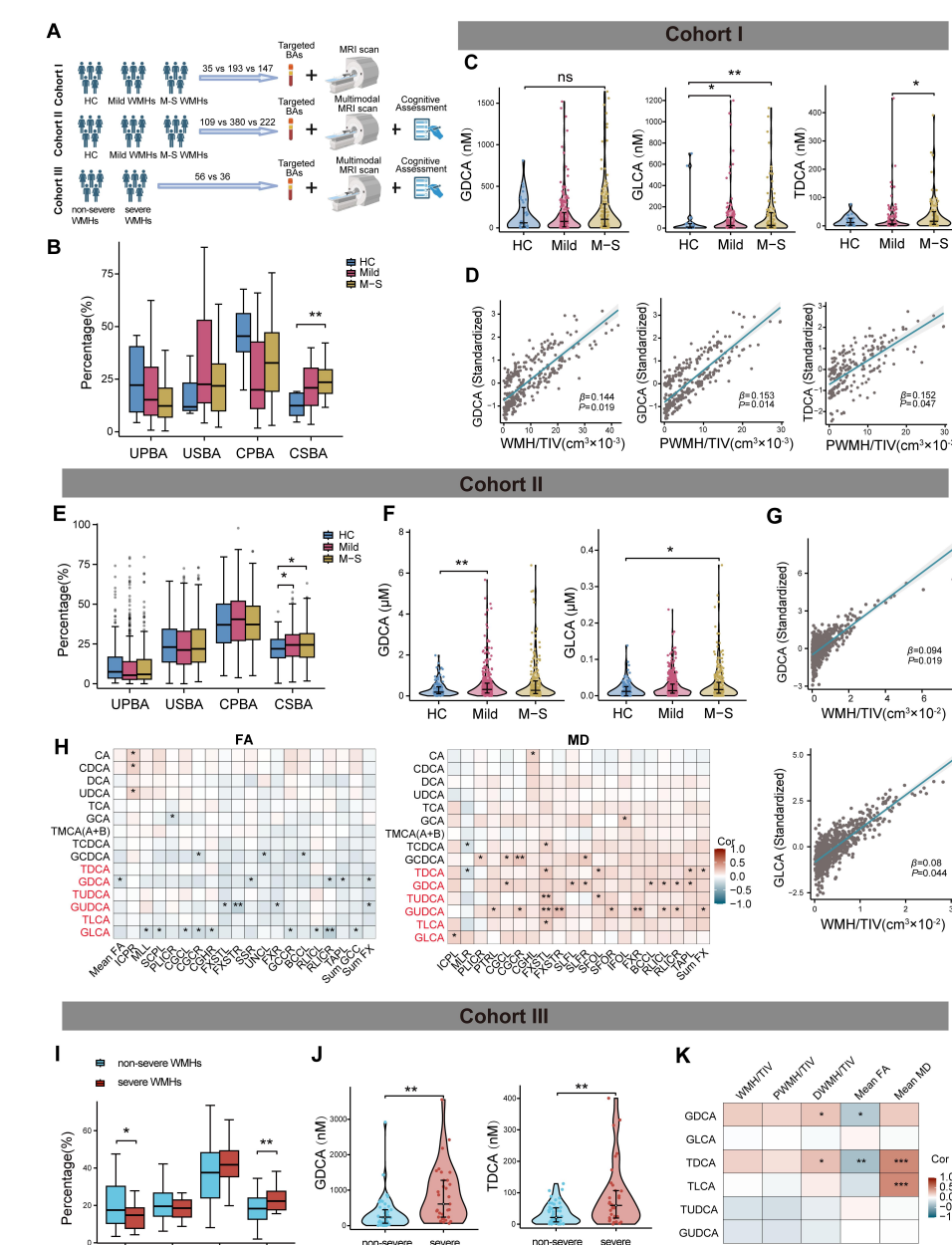


Figure 1 Elevated serum conjugated secondary BAs are associated with white matter hyperintensity burden and WM microstructural damage

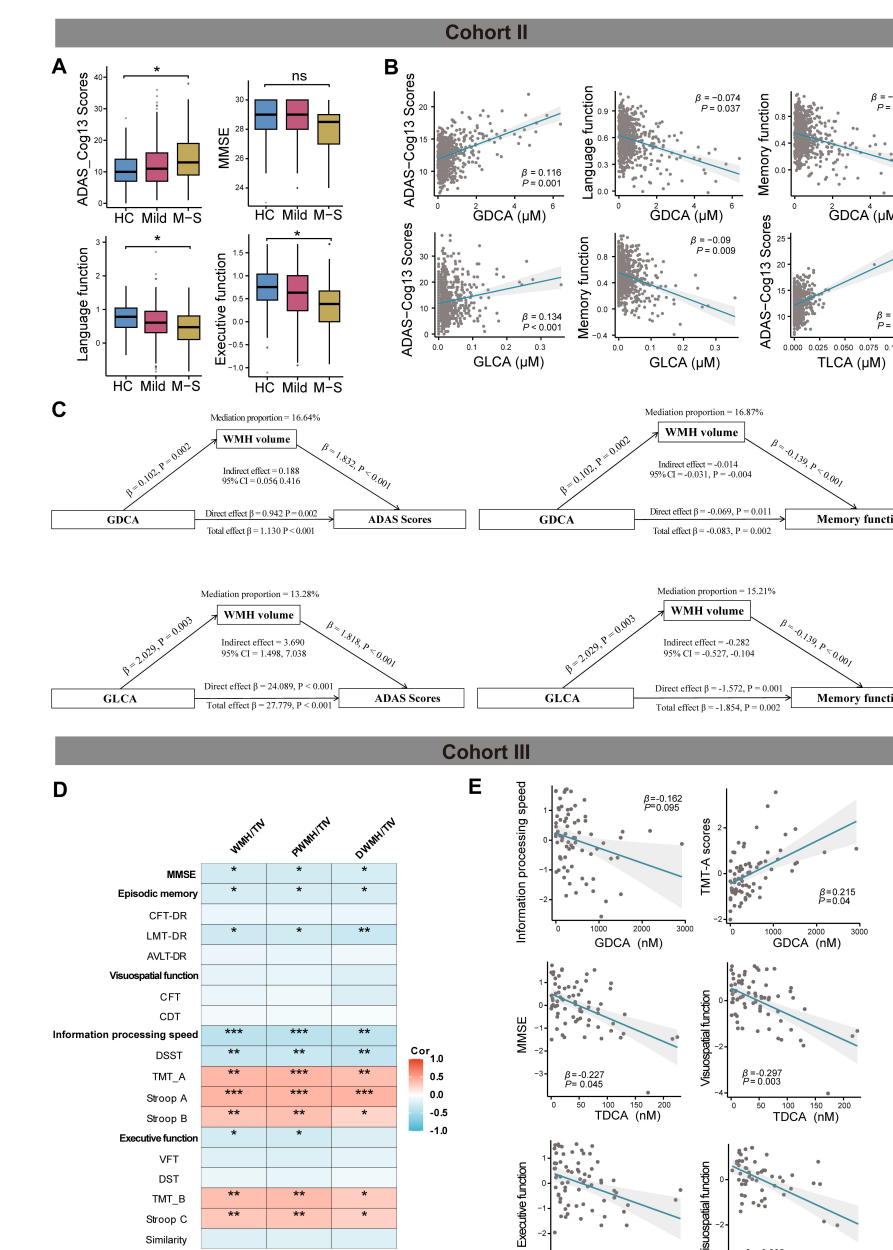


Figure 2 Serum CSBAs were associated with WMH-related cognitive impairment

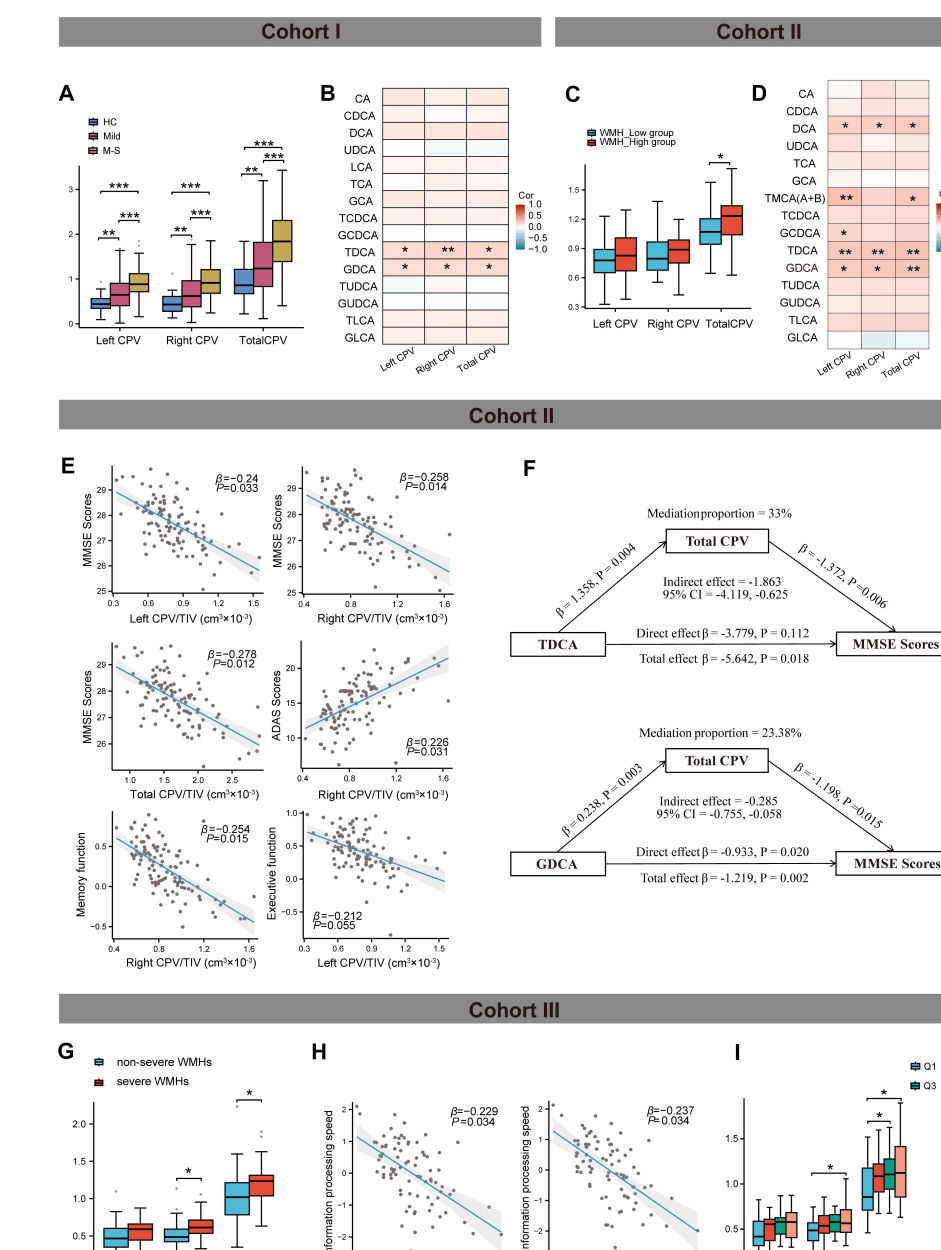


Figure 3 Choroid Plexus enlargement mediates the association between increased GDCA levels and cognitive impairment in WMHs

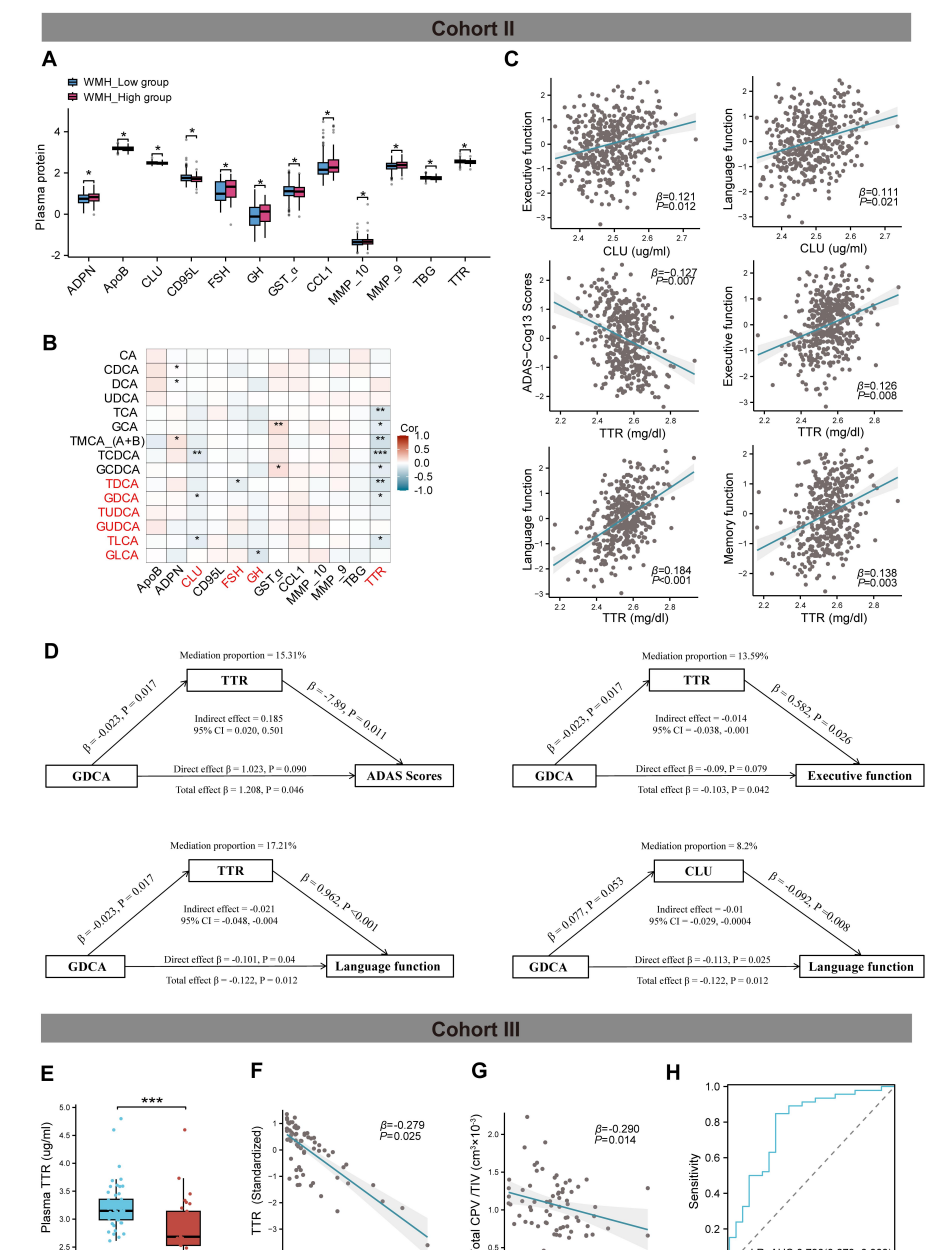


Figure 4 Transthyretin (TTR) is a key mediator of GDCA-induced WMHs and related cognitive impairment

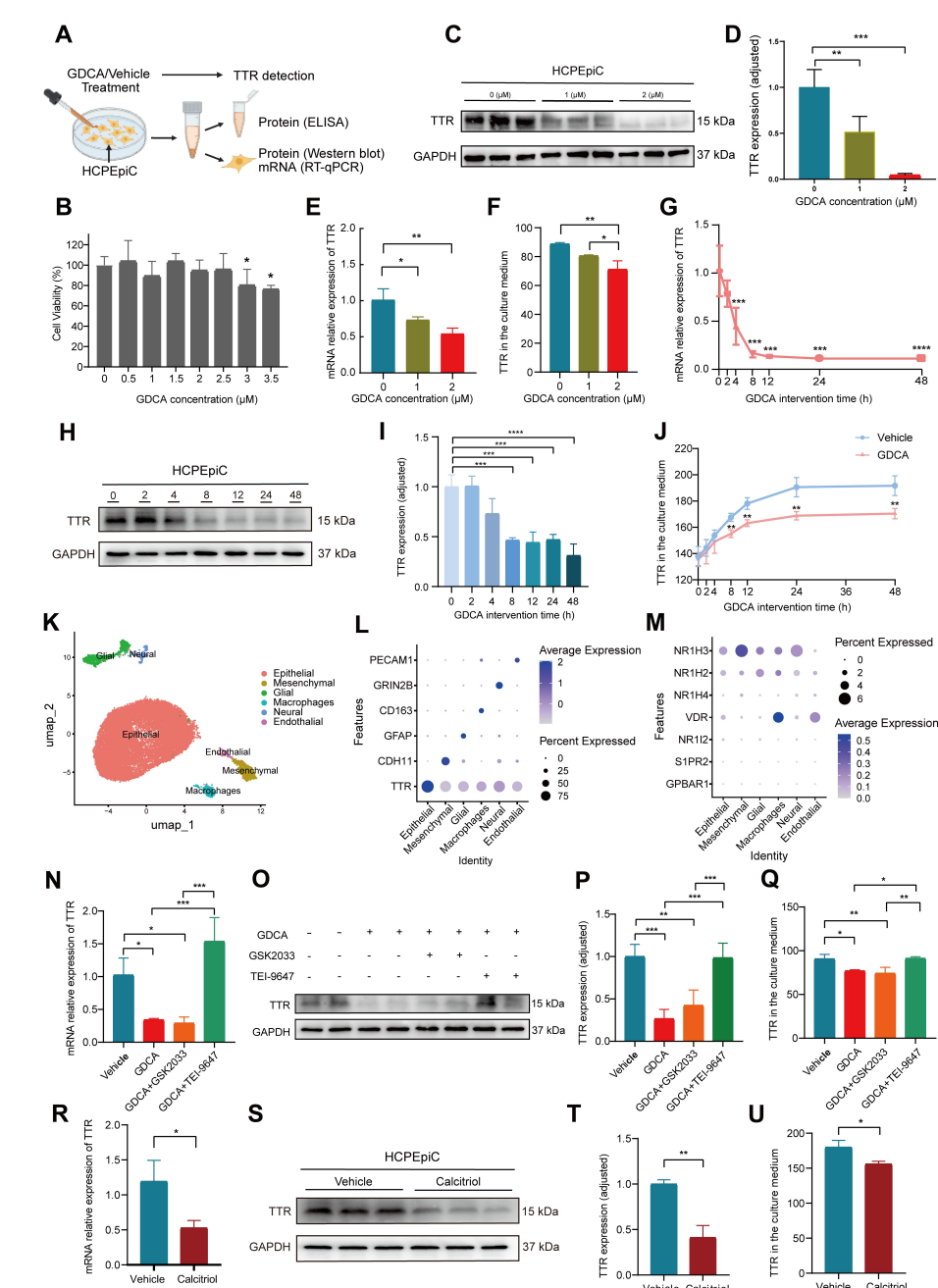


Figure 5 GDCA inhibits TTR expression in CPEpiC via VDR

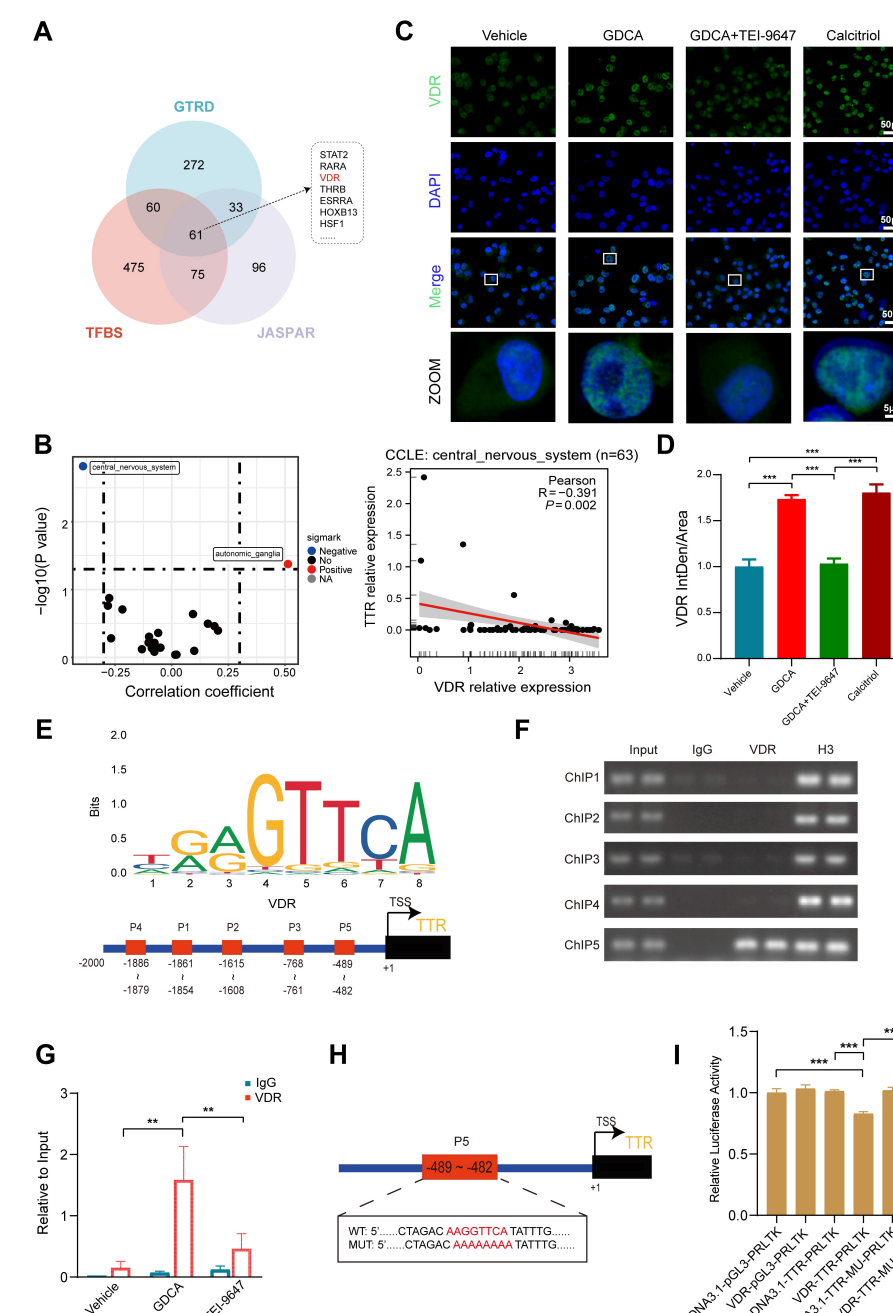


Figure 6 Vitamin D receptor functions as a transcriptional repressor of TTR in HCPEpiC upon GDCA stimulation.

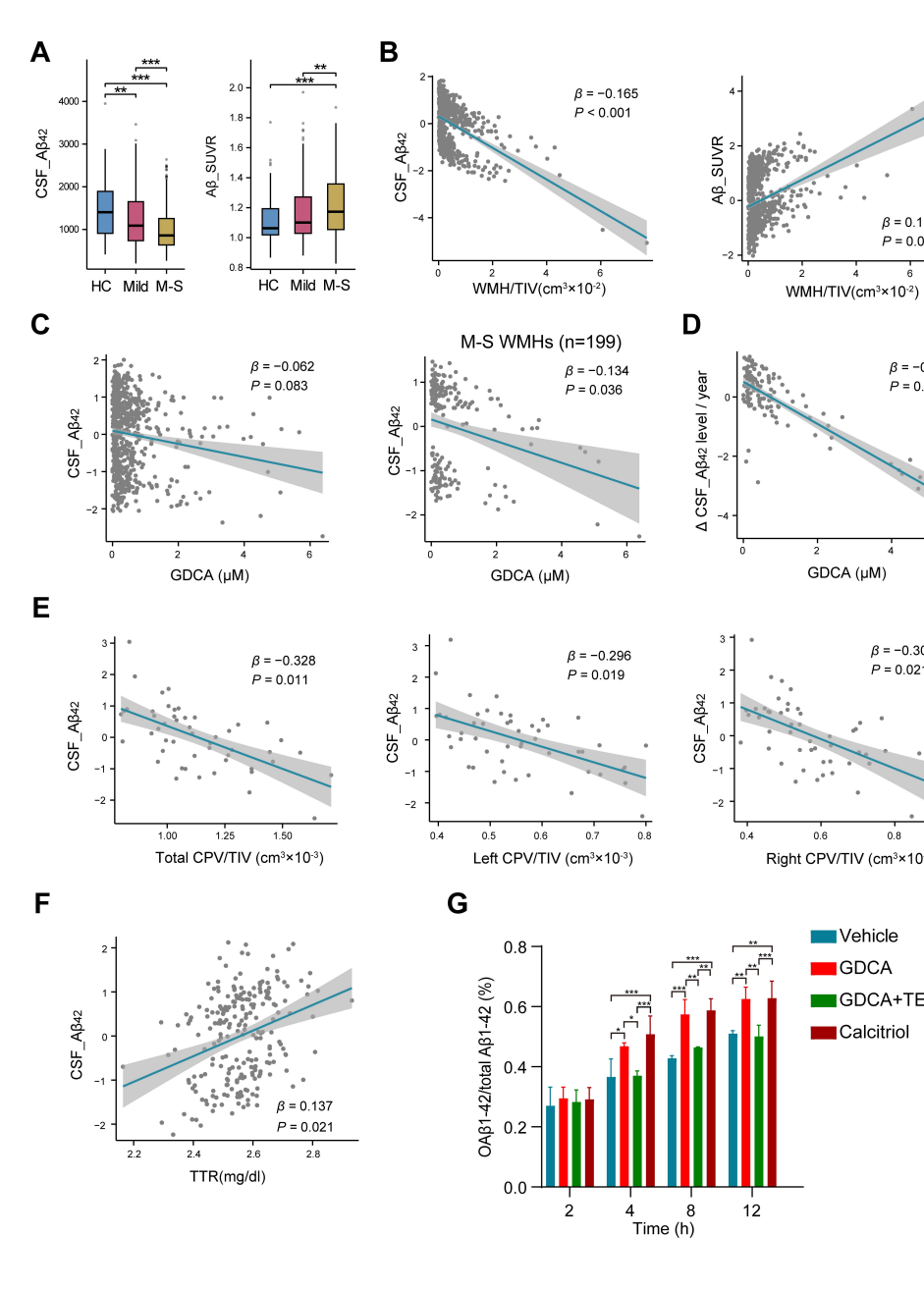


Figure 7 GDCA promotes neurotoxic A β ₁₋₄₂ oligomer formation via VDR-mediated suppression of TTR.

Serum levels of conjugated secondary BAs, particularly glycochenodeoxycholic acid (GDCA), were consistently elevated in patients with WMHs. These elevations correlated significantly with WMH burden, microstructural white matter damage, cerebral A β deposition, and cognitive decline. Longitudinal analysis indicated that baseline serum GDCA levels predicted the annual decline in cerebrospinal fluid (CSF) A β and cognitive function over a 4-year follow-up period. An increase in choroid plexus volume mediated the relationship between GDCA and cognitive impairment. Plasma proteomic profiling revealed reduced levels of transthyretin (TTR) as a key mediator connecting GDCA to cognitive deficits. A combined receiver operating characteristic model integrating GDCA, choroid plexus volume, and TTR demonstrated significant clinical diagnostic potential for distinguishing severe WMHs. Mechanistically, GDCA activated the vitamin D receptor (VDR) in choroid plexus epithelial cells, facilitating VDR nuclear translocation and subsequent binding to the TTR promoter, which transcriptionally repressed TTR expression and enhanced A β ₁₋₄₂ aggregation into neurotoxic oligomers.