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THE JOURNAL OF PREVENTION OF ALZHEIMER'S DISEASE

The CTAD Advanced Workshop and Course in AD Clinical Trials

**Shanghai, China
September 6-7, 2025**

**THE CHINA
CTAD ADVANCED
WORKSHOP
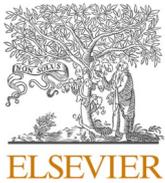AND COURSE IN AD CLINICAL TRIALS**

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The CTAD Advanced Workshop and Course in AD Clinical Trials, September 6-7, 2025, Shanghai, China

CTAD China advanced workshop and course in AD clinical trials – Shanghai, September 6–7, 2025

The **2025 CTAD China Advanced Workshop and Course in AD Clinical Trials** represented a pivotal milestone in advancing clinical research capacity for Alzheimer's disease (AD) across China. Co- organized by the Clinical Trials on Alzheimer's Disease (CTAD) organization and the China Brain Health Initiative Expert Committee, this event brought together leading investigators from throughout China, alongside distinguished experts from Europe, the United States, and the industry sector. Its core objective was to deliver a high-level platform for exchanging insights on the latest breakthroughs in AD clinical research, cutting-edge biomarkers, innovative therapeutic strategies, and the best practices for multicenter collaboration.

Globally, the scientific and clinical challenges posed by AD continues to escalate. Projections indicate that the worldwide prevalence of dementia will surge to 139 million by 2050, and China shoulders a considerable portion of this global burden. The far-reaching impacts of this trend, spanning medical system, societal well-being, and economic stability, underscore an urgent need for innovative solutions in prevention, early detection, and disease-modifying treatments. The CTAD China initiative directly addresses these pressing challenges by integrating rigorous scientific standards, global collaborative networks, and a strategic focus on building sustainable clinical trial infrastructure.

Highlights from the 2025 Program

The abstracts presented in this special section of *The Journal of Prevention of Alzheimer's Disease (JPAD)* reflect a field that is advancing rapidly on multiple fronts.

- **Advances in disease-modifying therapies**: Phase 3 trials, including TRAILBLAZER-ALZ 3 (donanemab) and TRAILRUNNER-ALZ 3 (remternetug), provide compelling evidence that intervening in the preclinical and prodromal stages of AD can meaningfully slow clinical progression. Moreover, data from long-term extension studies of these therapies further support the sustained clinical benefit of amyloid-targeted therapies.
- **Real-world implementation**: The first multicenter Chinese experience with lecanemab demonstrates that integration of multidisciplinary teams, confirming via amyloid/tau PET imaging, and structured monitoring for Amyloid-Related Imaging Abnormalities (ARIA) is feasible and safe, laying a critical foundation for the broader adoption of disease-modifying treatments in real-world clinical practice.
- **Emerging therapeutic approaches**: Early-phase studies highlight the promising potential of innovative therapeutic strategies for AD, including bispecific antibodies engineered for enhanced blood–brain barrier penetration (trontinemab, Brainshuttle™ platform) and

small-molecule modulators targeting synaptic plasticity (e.g., Rac1 inhibitors). These novel approaches represent a meaningful expansion of the AD therapeutic armamentarium, moving beyond the traditional focus on amyloid pathways.
- **Precision medicine through biomarkers**: Plasma biomarkers (e.g. p-tau217, GFAP, NfL), when compared with amyloid and tau imaging, are enabling earlier and less invasive diagnosis of AD, as well as more precise stratification of clinical trial participants. Notably, several studies presented at this event (e.g. Clear-AD) demonstrate the potential of these integrated biomarkers to serve as surrogate endpoints, ultimately paving the way for more efficient, targeted and cost-effective AD clinical trials.
- **Novel insights into disease mechanisms**: Investigations into glymphatic system dysfunction, neuroinflammation, and microglial activation are shedding new light on the pathophysiological mechanisms of AD and providing fresh perspectives on treatment response variability. By integrating these mechanistic insights with real-world and clinical trial data, researchers can better guide the development of next-generation AD therapeutics, ones that target these understudied pathways to address unmet clinical needs.

Building Clinical Trial Infrastructure in China

A core objective of this workshop was to advance the **CTAD China Clinical Trial Center Initiative**, an effort designed to establish a nationally coordinated network of research sites. These sites would be equipped to conduct high-quality, biomarker-driven AD clinical trials that meet rigorous international standards.

To achieve this goal, the initiative encompasses key actions: harmonizing clinical trial protocols to ensure consistency across sites, developing Standard Operating Procedure to standardize biomarker testing and data analysis, providing targeted training for investigators to enhance expertise in AD research, and facilitating proactive dialogue with regulatory authorities. Together, these measures aim to accelerate the approval of novel AD therapies in China and expand patient access to these treatments.

Outlook

As the field moves toward an era of precision medicine, the integration of disease-modifying therapies with biomarker-guided prevention and early detection strategies will be essential to alleviating the individual, familial and societal burden of AD. The success of the 2025 CTAD China Workshop underscores the importance of sustained collaboration across academia, industry, government agencies, and patient advocacy organizations, partnerships that are foundational to achieving this goal.

On behalf of the organizing committee, I am pleased to present this special collection of abstracts, which showcase state-of-the-art research and clinical innovation in AD. These contributions not only reflect the rigor of global AD research but also embody the shared commitment of the international research community to advancing scientific discovery and, ultimately, improving outcomes for patients and families affected by this devastating disease.

We look forward to welcoming you back to Shanghai in September 2026, as we continue to build a robust and inclusive international platform for collaboration. Together, we will accelerate progress toward our shared vision: a world of healthy aging, free from the burden of Alzheimer's disease.

CRediT authorship contribution statement

Yong Shen: Writing – review & editing. **Xiaochun Chen:** Writing – review & editing. **Jiong Shi:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Yong Shen[a], Xiaochun Chen[b], Jiong Shi[c,*] (iD)

[a] *Neurodegenerative Disorder Research Center, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, 230001, China*

[b] *Department of Neurology, Fujian Medical University Union Hospital, Fuzhou 350001, Fujian Province, China*

[c] *Department of Neurology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, 230001, Anhui Province, China*

[*] Corresponding author.
E-mail address: Jshi2022@ustc.edu.cn (J. Shi).

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ABSTRACTS

ORAL COMMUNICATIONS

CLINICAL TRIALS: METHODOLOGY

OC02- SCREENING AND BASELINE RESULTS FROM THE DONANEMAB PHASE 3 STUDY IN PRECLINICAL ALZHEIMER'S DISEASE. N. Hatakeyama[1], K.C. Holdridge[2], R. Yaari[2], M. Williamson[2], A.M. Wessels[2], S. Shcherbinin[2], V. Kotari[2], P.N. Tariot[3], E.M. Reiman[3], J.B. Langbaum[3], J. Sims[2], S. Cai[4] *(1. Eli Lilly and Company - Kobe (Japan), 2. Eli Lilly and Company - Indianapolis (United States), 3. Banner Alzheimer's Institute - Tucson (United States), 4. Eli Lilly and Company - Shanghai (China))*

Background: We are conducting a multicenter, randomized, double-blind, placebo-controlled event-driven Phase 3 trial (TRAILBLAZER-ALZ 3) using a decentralized clinical trial (DCT) approach to evaluate the efficacy of donanemab in preclinical AD (with evidence of AD pathology but without cognitive impairment). We present the screening/baseline characteristics at enrollment completion. **Methods:** Inclusion criteria are age 55-80, Modified Telephone Interview for Cognitive Status (TICS-m) score ≥35, and plasma P-tau217 results consistent with the presence of amyloid and early tau pathology. **Results:** We screened 63,124 participants using plasma P-tau217, enabling randomization of 2,196 participants: US (n=2,137)/Japan (n=59). The mean age was 70.2 years. Plasma P-tau217 (81.2%) and TICS-m (5.4%) were the main drivers of screen failure. P-tau eligibility increased with age. The median baseline TICS-m and Montreal Cognitive Assessment (MoCA) scores for a subgroup of participants with a baseline Clinical Dementia Rating-global score (CDR-GS) of 0 (CDR0) were 40 and 25, respectively, and 39 and 23 for participants with a baseline CDR-GS of 0.5 (CDR0.5). **Conclusion:** Enrolling participants in a preclinical AD study using a blood-based biomarker and a DCT approach is feasible. This cohort represents an earlier clinical and pathological stage compared with prior studies on early symptomatic AD, despite enrolling CDR0.5 participants. The outcome study is ongoing to assess donanemab treatment for slowing of progression to symptomatic AD. **Disclosures:** Karen C Holdridge, Roy Yaari, Melissa Williamson, Alette Wessels, Sergey Shcherbinin, Vikas Kotari, Naohisa Hatakeyama, John Sims and Shuang Cai (non-author presenter) are full-time employees and minor shareholders of Eli Lilly and Company. Pierre Tariot, Jessica Langbaum, Robert Alexander, and Eric Reiman are employees of Banner Health. Banner Alzheimer's Institute's receives funding from Eli Lilly and Company for its collaborative partnership on TRAILBLAZER-ALZ 3. Robert Alexander reports consulting income from Alkermes, Boehringer- Ingelheim, Biohaven, Cardiff University Medicines Discovery Unit, Immunobrain, Lundbeck, Novartis, Novo Nordisk, Reunion Neuro, T3D Therapeutics, and Vigil Neuro. Jessica Langbaum reports consulting in income from Biogen and Denovo Biopharma. Eric Reiman is a co-founder and advisor of ALZpath and a compensated scientific advisor to Alzheon, Denali, Cognition Therapeutics, Enigma, Retromer Therapeutics, and Vaxxinity. Pierre Tariot reports consulting income from AC Immune, Acadia, Athira, Biogen, BioXcel, Bristol Myers Squibb, Cognition Therapeutics, Corium, Cortexyme, CuraSen, Eisai, Genentech, Immunobrain, Janssen, Lundbeck, MapLight, Merck & Co., Novartis, Novo Nordisk, Otsuka & Astex, Roche, Syneos, and T3D Therapeutics.

OC05- TRAILRUNNER-ALZ 3: A DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 CLINICAL TRIAL OF SUBCUTANEOUS REMTERNETUG IN ALZHEIMER'S DISEASE STAGE 1-3. K. Biglan[1], E. Rizvi[1], T. Wang[1], M. Hufford[1], M. Lidogoster[1], C. Dickson[1], S. Warner[1], I. Gueorguieva[1], Y. Vandenburg[1], M. Dabora[1], L.L.S. Sun[2] *(1. Eli Lilly and Company - Indianapolis (United States), 2. Eli Lilly and Company - Shanghai (China))*

Aims/Objectives: Emerging data suggest treatment with amyloid-targeting therapies in the earliest stages of Alzheimer's disease (AD) results in greater clinical benefit. Treatment with remternetug, an IgG1 monoclonal antibody directed at deposited brain amyloid plaques, demonstrated robust dose-dependent amyloid plaque removal in individuals with AD. TRAILRUNNER-ALZ 3 (NCT06653153) tests the hypothesis that remternetug treatment will delay clinical progression of AD compared to placebo in individuals with AD Stages 1-3, the earliest stages of the pathological cascade, which precede dementia. **Methods:** TRAILRUNNER-ALZ 3 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, event-driven trial evaluating efficacy and safety of subcutaneous remternetug treatment compared to placebo in participants at AD Stages 1-3. The primary endpoint is time to clinical progression, defined as an increase in Clinical Dementia Rating (CDR) score. Participants will have evidence of amyloid pathology by plasma P-tau, Mini-Mental State Examination (MMSE) score ≥27, and Functional Activities Questionnaire (FAQ) score <6. **Results:** Applying TRAILRUNNER-ALZ 3 criteria to publicly available data suggests TRAILRUNNER-ALZ 3 will enroll a population consistent with AD Stages 1-3. Internal trial cohort analyses suggest the study population will have a relatively low tau burden (>50% with very low/no tau assessed by tau positron emission tomography). TRAILRUNNER-ALZ 3, sponsored by Eli Lilly and Company, is being conducted at multiple sites globally. Enrollment opened in Q4, 2024. **Conclusions:** The TRAILRUNNER-ALZ 3 study entry criteria are anticipated to facilitate enrollment of the appropriate population to test the hypothesis that remternetug meaningfully slows clinical progression in individuals with AD Stages 1-3. **Disclosures:** K. Biglan, E. Rizvi, T. Wang, M. Hufford, M. Lidogoster, C. Dickson, S. Warner, I. Gueorguieva, Y. Vandenburg, and M. Dabora are employees and shareholders of: Eli Lilly and Company. This study is sponsored by Eli Lilly and Company. This study was initially presented at International Conference on Alzheimer's and Parkinson's Diseases; Vienna, Austria, and Online ; April 1-5, 2025.

OC08- DONANEMAB IN EARLY SYMPTOMATIC ALZHEIMER'S DISEASE: EFFICACY AND SAFETY FROM THE TRAILBLAZER-ALZ 2 LONG-TERM EXTENSION. J.R. Sims[1], J.A. Zimmer[1], C.D. Evans[1], E.S.M. Nery[1], H. Wang[1], A.M. Wessels[1], L.L. Raket[1], S.W. Andersen[1], C. Sapin[1], I. Gueorguieva[1], P. Ardayfio[1], R. Khanna[1], D.A. Brooks[1], M.A. Mintun[1], S. Epelbaum[1] *(1. Eli Lilly and Company - Indianapolis (United States))*

Objective: Describe the clinical efficacy and safety of donanemab in early and delayed start participants treated during the TRAILBLAZER-ALZ 2 placebo-controlled trial and long-term extension. **Background:** TRAILBLAZER-ALZ

2 (NCT04437511) is a multicenter, randomized, double-blind, placebo-controlled (PC) Phase 3 trial designed to assess the efficacy and safety of donanemab in participants with early symptomatic Alzheimer's disease. Donanemab treatment significantly slowed clinical progression in the PC period. Participants who completed the PC period were eligible to continue into the participant- and investigator-blinded long-term extension (LTE) period, lasting an additional 78 weeks. **Method:** Early start participants (those initially randomized to donanemab in the PC period) were switched to placebo if treatment completion criteria were met based on amyloid level during any treatment period. Delayed start participants (those initially randomized to placebo in the PC period) started treatment with donanemab in the LTE. Matched participants from the Alzheimer's Disease Neuroimaging Initiative served as external control groups. All analyses are exploratory and not controlled for multiplicity. **Result:** The results are expected to include efficacy analyses, biomarker analyses, and a safety overview. Data will be presented by the time of the conference. **Conclusions:** Conclusions are pending completion of the final analysis. **Disclosure:** All authors and Stephane Epelbaum (Non-author Presenter) are employees and minor shareholders at Eli Lilly and Company. This study is initially submitted and will be presented at Alzheimer's Association International Conference® July 27-31, 2025; Toronto, Canada, and Online.

OC21- MULTIMODAL INTEGRATION OF GAIT DYSFUNCTION, AMYLOID PET, AND PLASMA BIOMARKERS FOR DIFFERENTIATING ETIOLOGICAL SUBTYPES IN MILD COGNITIVE IMPAIRMENT.

J. Wu[1], F. Tang[1], X. Lv[1], Z. Cheng[1], J. Shi[2] *(1. Department of Neurology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui (China), 2. Institute on Aging and Brain Disorders, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China - Hefei, Anhui (China))*

Objective: To investigate gait characteristics and plasma biomarkers in individuals with mild cognitive impairment (MCI) stratified by amyloid-β (Aβ) positivity on positron emission tomography (PET), and to evaluate the predictive value for Alzheimer's disease (AD)-related MCI. **Methods:** It is a cross-sectional study based on the China Aging and Neuro-degenerative Initiative (CANDI) cohort [1], which is a longitudinal study initiated in 2018. This study included 35 amyloid PET-negative MCI (MCI-), 51 amyloid PET-positive MCI (MCI+), and 61 cognitively normal (CN) individuals. Gait assessments [2, 3] and plasma samples such as glial fibrillary acidic protein (GFAP) [4] and phosphorylated tau at threonine 217 (p-tau217) [5] were conducted and analyzed. **Results:** Gait analyses identified 125 features, with 69 distinguishing MCI+ from CN and 36 differentiating MCI+ from MCI-. Receiver operating characteristic (ROC) curve for distinguishing MCI+ from CN were GCD&GAN (AUC=0.850), integration GFAP or p-tau 217 (AUC=0.919 and 0.951, respectively). Similarly, GCD&GAN features demonstrated an AUC of 0.862 for distinguishing MCI+ from MCI−, with GFAP (AUC=0.933) and p-tau217 (AUC=0.986) enhancing predictive performance. **Conclusions:** This study indicated that integrating dual-task gait assessments with plasma biomarkers improve discriminatory power for identifying MCI+. **Keywords:** mild cognitive impairment; amyloid PET; plasma biomarkers; gait analysis; dual-task gait. **Disclosures:** The authors declare that they have no conflict of interest. **References:** 1. Gao F, Lv X, Dai L, et al. A combination model of AD biomarkers revealed by machine learning precisely predicts Alzheimer's dementia: China Aging and Neurodegenerative Initiative (CANDI) study[J]. Alzheimers Dement, 2023,19(3):749-760. 2. Allali G, Launay C P, Blumen H M, et al. Falls, Cognitive Impairment, and Gait Performance: Results, From the GOOD Initiative[J]. J Am Med Dir Assoc, 2017,18(4):335-340. 3. Montero-Odasso M, Sarquis-Adamson Y, Song H Y, et al. Polypharmacy, Gait Performance, and Falls in Community-Dwelling Older Adults. Results from the Gait and Brain Study[J]. J Am Geriatr Soc, 2019,67(6):1182-1188. 4. Groot C, Cicognola C, Bali D, et al. Diagnostic and prognostic performance to detect Alzheimer's disease and clinical progression of a novel assay for plasma p-tau217[J]. Alzheimers Res Ther, 2022,14(1):67. 5. Escartin C, Galea E, Lakatos A, et al. Reactive astrocyte nomenclature, definitions, and future directions[J]. Nat Neurosci, 2021,24(3):312-325.

CLINICAL TRIALS: RESULTS

LB02- ANTI-AMYLOID THERAPY IN ALZHEIMER'S DISEASE: REAL-WORLD EXPERIENCE WITH LECANEMAB IN A CHINESE TERTIARY COGNITIVE CENTER.

R. Wang[1], H. Gao[1], N. Hu[2], L. Li[3], X. Yang[2], N. Zhang[4], Y. Tang[1], N. Li[1], Y. Li[5], W. Kuang[4], Z. Jia[3], Q. Yuan[1], R. Tian[3], S. Lui[2], Q. Chen[1] *(1. Department of Neurology, West China Hospital of Sichuan University - Chengdu (China), 2. Department of Radiology, West China Hospital of Sichuan University - Chengdu (China), 3. Department of Nuclear Medicine, West China Hospital of Sichuan University - Chengdu (China), 4. Mental Health Center, West China Hospital of Sichuan University - Chengdu (China), 5. The Center of Gerontology and Geriatrics, National Clinical Research Center for Geriatrics, West China Hospital of Sichuan University - Chengdu (China))*

Background: Lecanemab, an anti-amyloid monoclonal antibody, has recently been approved for clinical use in early Alzheimer's disease (AD). This study aimed to characterize the real-world implementation of Lecanemab at a Chinese tertiary cognitive center, and to evaluate the clinical profiles and safety outcomes of treated patients, with a particular focus on amyloid-related imaging abnormalities (ARIA). **Methods:** This retrospective observational study included patients with mild cognitive impairment or mild dementia due to AD who initiated Lecanemab treatment at West China Hospital between June 2024 and April 2025. Patients were evaluated through a standardized clinical pathway including neuropsychological testing, amyloid and tau PET imaging, APOE genotyping, and multidisciplinary team (MDT) review. Safety monitoring involved serial MRI scans with consistent imaging protocols and structured ARIA-specific reporting, interpreted by the same neuroradiologist for each patient to ensure longitudinal consistency. Urgent MRI evaluations were conducted in case of suspected adverse reaction. The primary outcome was the incidence and severity of ARIA. **Results:** Among 111 patients (mean age 66.6 ± 10.6 years; 33.3% male), all were amyloid PET-positive and 45.0% underwent tau PET. APOE ε4 carriers comprised 63.1%. Infusion-related reactions were observed in 12 patients (10.81%) and were generally mild. Among 105 patients who received ≥4 infusions with MRI monitoring, asymptomatic ARIA was detected in 11 patients (10.48%). Specifically, ARIA-H was observed in 10 patients (9.52%), with 6 exhibiting only a single new microhemorrhage, and ARIA-E in 2 patient (1.90%). Mild ARIA accounted for the majority of cases (n = 8), while 3 presented with moderate to severe findings. **Conclusions:** This

study demonstrates the feasibility and safety of Lecanemab administration in a real-world Chinese clinical setting. The integration of MDT-based recruitment, PET-based diagnostic confirmation, standardized ARIA monitoring, and efficient patient communication may contribute to a comparatively lower incidence and milder presentation of ARIA.

OC01- TRONTINEMAB: UPDATE ON THE BRAINSHUTTLE™ AD STUDY AND PLANS FOR THE PIVOTAL PHASE III.

L. Kulic[1], G. Klein[1], J. Smith[2], B. Shi[1], C. Lane[2], J. Wojtowicz[1], C. Hofmann[1], S. Ahlers[3], S. Salloway[4], G. Rabinovici[5], C. Mummery[6], S. Hanno[1] (1. F. Hoffmann-La Roche Ltd - Basel (Switzerland), 2. Roche Products Ltd - Welwyn Garden City (United Kingdom), 3. Excelya Germany GmbH - Mannheim (Germany), 4. Butler Hospital and Warren Alpert Medical School, Brown University - Providence, Ri (United States), 5. Weill Institute for Neurosciences, and Department of Radiology and Biomedical Imaging, University of California San Francisco - San Francisco, Ca (United States), 6. Queen Square Institute of Neurology, University College London - London (United Kingdom))

Background: Trontinemab is a novel amyloid-targeting Brainshuttle™ bispecific 2+1 monoclonal antibody specifically engineered for efficient transferrin receptor 1-mediated transport across the blood–brain barrier. It is currently under evaluation in the Phase Ib/IIa Brainshuttle™ Alzheimer's disease (AD) study (NCT04639050) in participants with mild cognitive impairment due to AD or mild-to-moderate AD. **Methods:** The Brainshuttle™ AD study is a randomized, double-blind, placebo-controlled, multiple ascending dose study designed to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of trontinemab following intravenous (IV) infusion. Part 1 (dose-escalation) enrolled at least 10 participants to four initial dose cohorts: 0.2 (Cohort 1), 0.6 (Cohort 2), 1.8 (Cohort 3), and 3.6 mg/kg (Cohort 4). Part 2 (dose-expansion) enrolled an additional 60 participants each in Cohorts 3 and 4. Participants in both Part 1 and Part 2 were randomized 4:1 within each cohort to trontinemab or placebo IV every four weeks for a total of seven doses. Biomarker results, including amyloid positron emission tomography (PET), cerebrospinal fluid (CSF), and plasma biomarkers will be presented. Plasma and CSF samples are analyzed using the Roche Elecsys® NeuroToolKit. **Results:** An interim analysis (data cut-off: Nov 14, 2024) revealed dose-dependent amyloid plaque lowering and downstream effects on biomarkers across all active dose levels. In Part 1 + Part 2, participants on 3.6 mg/kg who had the opportunity to complete the double-blind treatment period exhibited rapid mean amyloid depletion: -61 CL (n=6) at the Day 50 scan, -89 CL (n=19) at the Day 78 scan, -101 CL (n=4) at the Day 106 scan, -99 CL (n=26) at the Day 196 scan. Those participants had a median % change in CSF total tau, ptau 181 and neurogranin of -22%, -29% and -21%. Amyloid-related imaging abnormalities-edema/effusion (ARIA E) were observed in <5% of participants (blinded data). Updated results from the most recent data snapshot will include 28-week PET data, as well as CSF and plasma biomarker results from Part 2. **Conclusions:** Preliminary results from the ongoing Brainshuttle™ AD study suggest that rapid and deep amyloid reduction can be achieved in most participants at 1.8 and 3.6 mg/kg doses within ≤28 weeks, with a low incidence of ARIA. Combined with the favorable safety and interim biomarker findings to date, these results support the rationale for initiating the pivotal Phase III studies. TRONTIER 1 and 2 are two identically designed global, randomized, double-blind, placebo-controlled, parallel-group Phase III studies designed to investigate the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of trontinemab following intravenous infusion in participants with biomarker confirmed early symptomatic AD. These studies will provide the opportunity to assess whether treatment with trontinemab slows disease progression in people living with early symptomatic AD.

OC09- A REAL-WORLD SURVEY OF THE DIAGNOSTIC JOURNEY, CURRENT TREATMENT, AND BURDEN OF MILD COGNITIVE IMPAIRMENT OR DEMENTIA DUE TO ALZHEIMER'S DISEASE IN CHINA.

J. Xin[1,2], H. Zhang[3], S. Cai[3], J. Li[3], G. Dou[3], B.B. Estrada[4], C. Walker[5], X. Chen[1,2] (1. Department of Neurology, Fujian Medical University Union Hospital, Fuzhou, China - Fuzhou (China), 2. Fujian Medical University - Fuzhou (China), 3. Eli Lilly and Company, Shanghai, China - Shanghai (China), 4. Eli Lilly and Company, Bracknell, United Kingdom - Bracknell (United Kingdom), 5. Adelphi Real World, Bollington, United Kingdom - Bollington (United Kingdom))

Background: We aimed to describe the diagnostic journey, current treatment, caregiving needs, and burden of patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia in China. **Method:** Data were drawn from the Adelphi Real World AD Disease Specific Programme™, a cross-sectional survey of neurologists and their patients with MCI/AD across China, between 2024/02–2024/05. Neurologists completed patient record forms for their next (up to) nine consecutively consulting MCI/AD patients, capturing the diagnostic journey, current treatment, and caregiver support. Patients were invited to provide a self-completion questionnaire, reporting on delays to first seeing a doctor and quality of life via the EQ-5D visual analogue scale. Disease severity was defined using Mini Mental State Examination (MMSE) score: MCI/mild AD (20-28) or moderate/severe AD (0-19). Analyses were descriptive. **Results:** Ninety-three neurologists reported data on 774 patients (mean±standard deviation age 69.2±8.3 years, body weight 64.2±11.4 kg, 49.1% female), of whom 192 self-completed a patient survey. Of 699 patients with an available MMSE, 52.5% were currently MCI/mild AD and 47.5% moderate/severe AD. Median (interquartile range [IQR]) time between symptom onset and first consultation was 18.1 (8.4, 40.3) weeks, with 34.7% of patients experiencing moderate/severe AD by their initial consultation. Most patients (80.0%) were not diagnosed at initial consultation, with median (IQR) time from first consultation

to diagnosis taking 4.4 (1.9, 12.9) weeks. Few patients (18.8%) had a biomarker confirmed diagnosis (mainly cerebral spinal fluid [11.2%] and amyloid positron emission tomography [7.7%]). Acetylcholinesterase Inhibitors (66.0%), N-methyl-D-aspartate antagonist (33.5%), and nootropics (26.4%) were the most common current treatments, and long-lasting effect was the top (37.1%) identified area for improvement. Among those with MCI/mild AD, 79.4% received non-professional care (NPC) and 2.7% required professional care (95.2% and 15.7% for moderate/severe AD, respectively). On average, NPC partners spent 36.7±39.5 hours/week for MCI/mild AD and 47.3±39.6 hours/week for moderate/severe AD, and spouse/partner was the most frequent NPC partner. Mean EQ-5D-VAS score was 71.9±11.1 for those with current MCI/mild AD and 63.7±16.6 for moderate/severe AD. **Conclusions:** Further improvement is needed in early detection and accurate diagnosis of MCI/AD to lessen the burden to patients, care partners, and society. **Keywords:** Mild cognitive impairment, diagnostic testing, biomarker, healthcare system. **Disclosures:** 1. Data collection was undertaken by Adelphi Real World as part of an independent survey, entitled the Adelphi Real World Dementia Disease Specific Programme. The analysis described here used data from the Adelphi Dementia DSP. The DSP is a wholly owned Adelphi product. Eli Lilly is one of multiple subscribers to the DSP. Publication of survey results was not contingent on the subscriber's approval or censorship of the publication. 2. Hanxi Zhang, Shuang Cai , Jinnan Li , Guanshen Dou are full-time employees and minor shareholders of Eli Lilly and Company; Chloe Walker is an employee of Adelphi Real World. 3. This study is initially presented at 2025 Alzheimer's Association International Conference, July 27-31, 2025, Toronto, Canada, and Online.

OC11- PHASE I SINGLE AND MULTIPLE ASCENDING DOSE STUDY OF 50561 (NOVEL ORAL RAC1 ACTIVITY INHIBITOR) IN HEALTHY VOLUNTEERS.

M. Wu[1], W. Ma[1] *(1. Beijing Joekai Biotechnology LLC, Beijing (China))*

Background: 50561 is a novel selective inhibitor of Rac1, a synaptic plasticity protein dysregulated in Alzheimer's disease (AD) and might cause accelerated forgetting. 50561 had an IC50 of 87nM in cells and reduced rac1 activity in hippocampus of AD models. It also improved memory deficits after dosing 10 mg/kg daily for 7 consecutive days. Our study aims to assess the safety, tolerability, and pharmacokinetics (PK) of oral 50561 in Chinese healthy volunteers. **Methods:** Our phase I study included two randomized, double-blind, placebo-controlled trials. The first was a single ascending dose (SAD) study with doses from 8 mg to 384 mg. The 8 mg cohort included 4 subjects, with 2 receiving 50561 and 2 receiving placebo. Subsequent cohorts included 8 subjects each, with a 3:1 randomization ratio of 50561 to placebo. The second was a multiple ascending dose (MAD) study with 64 mg, 128 mg, and 256 mg administered once daily (QD) for 7 days. Each cohort included 8 subjects, with the same 3:1 randomization. An independent Safety Review Committee (SRC) reviewed safety, tolerability, and PK before dose escalation. **Results:** In the SAD study, 52 subjects were enrolled and received the investigational drug, with 38 receiving 50561. In the MAD study, 24 subjects were enrolled, with 18 receiving 50561. No grade 3 or higher adverse events (AEs) or serious adverse events (SAEs) were reported in neither study. No AEs led to early withdrawal nor death. The incidence and types of AEs showed no significant dose dependency. The in vivo exposure levels of 50561 demonstrated a generally proportional increase with escalating doses. **Conclusions:** 50561

demonstrated favorable safety and tolerability in Phase I clinical studies, supporting its further evaluation in Alzheimer's disease patients. **Keywords:** Alzheimer's disease, Rac1 activity, phase I clinical trail. **Disclosures:** The authors declared no competing interests. **References:** 1. Wu W, Du S, Shi W, Liu Y, Hu Y, Xie Z, et al. Inhibition of Rac1-dependent forgetting alleviates memory deficits in animal models of Alzheimer's disease. Protein Cell. 2019;10(10):745-59.

OC19- MENTAL HEALTH, BIOLOGICAL AGING, AND LIFESTYLE MEDIATE THE ASSOCIATIONS BETWEEN SOCIAL DETERMINANTS OF HEALTH AND DEMENTIA.

P.Y. Gao[1], J. Chang[1], Y. Tang[1] *(1. Xuanwu Hospital Capital Medical University - Beijing (China))*

Background: Social determinants of health (SDoH) represent multiple interconnected social and economic factors that have been proposed by the World Health Organization as critical non-medical influences on health outcomes. However, few studies have investigated the relationships and potential mechanisms between SDoH and dementia in large-scale population-based cohorts. **Method:** This population-based prospective study utilized data from the UK Biobank. Our study incorporated 7 factors across 4 domains—economic stability, educational attainment, social contact, and environmental factors—to assess SDoH levels. Cox proportional hazard models and linear regression models were conducted to examine the relationship between SDoH and risk of all-cause and cause-specific dementia, brain structure (focusing on hippocampal volume), and cognitive performance. Causal mediation analysis explored potential mediating factors, including mental health, biological aging, and lifestyle, linking SDoH and dementia. Survival models were applied to estimate differences in life expectancy. **Result:** Among 359,419 participants (median follow-up: 13.46 years), those with favorable SDoH levels demonstrated significantly lower risks of developing all-cause dementia (HR: 0.57, 95% CI: 0.53–0.60), Alzheimer's disease (HR: 0.62, 95% CI: 0.56–0.68), and vascular dementia (HR: 0.48, 95% CI: 0.41–0.55) compared to those with unfavorable SDoH levels. In terms of impact on dementia risk, SDoH ranked second only to age among all analyzed factors. Higher SDoH levels were positively associated with larger hippocampal volume and better performance across cognitive domains. The relationship between SDoH and dementia was mediated by multiple factors: depression (24.00%), frailty (13.60%), biological aging measured by PhenoAge (6.33%), and smoking (2.82%). At age 65, participants with dementia who had favorable SDoH levels demonstrated an average life expectancy 0.909 (95% CI 0.002–1.873) years longer than those with unfavorable SDoH levels. **Conclusions:** Higher levels of SDoH are associated with a reduced risk of dementia, and the associations are mediated by mental health, biological aging, and lifestyle. These findings highlight that prioritizing improvements in SDoH should be a key component of global efforts aimed at mitigating dementia risk and promoting cognition and longer lifespans across populations.

CLINICAL TRIALS IMAGING

LB04- HEAD-TO-HEAD COMPARISON OF THE ASSOCIATIONS BETWEEN IMAGING AND PLASMA A-T-N BIOMARKERS WITH SYNAPTIC DENSITY IN ALZHEIMER'S DISEASE.

J. Wang[1], F. Xie[1], Q. Huang[1] *(1. Fudan Huashan Hospital - Shanghai (China))*

Objective: To compare the associations between imaging and plasma A-T-N biomarkers with synaptic density assessed by 18F-SynVesT-1 PET/MRI in Alzheimer's disease. **Methods:** This study enrolled 193 participants: 62 with Alzheimer's disease (AD), 56 with mild cognitive impairment (MCI), and 75 normal controls (NC). All underwent 18F-SynVesT-1 PET/MRI scans to assess synaptic density and T1-weighted imaging for hippocampal volume. 18F-Florbetapir PET/CT and 18F-MK6240 PET/CT scans were used to evaluate amyloid-β and tau pathology, respectively. Cognitive function was assessed using neuropsychological tests. Plasma Aβ42, Aβ40, p-Tau181, and neurofilament light chain (NfL) levels were measured. Correlations between synaptic density and "A-T-N" biomarkers from imaging and plasma were analyzed at the volume of interest (VOI)and voxel levels, with comparisons made between the strengths of these correlations. **Results:** For «A», synaptic density in the medial temporal lobe was negatively correlated with global Aβ deposition (r = -0.272, p < 0.001) and positively correlated with plasma Aβ42/40 levels (r = 0.307, p < 0.001). In the AD group, only global Aβ deposition showed a negative correlation with medial temporal synaptic density (r = -0.284, p = 0.028). For «T», tau burden was negatively associated with synaptic density in the medial temporal lobe and widespread neocortex across the whole population, as well as within the AD and MCI groups. Plasma p-Tau181 levels were also negatively correlated with synaptic density in the medial temporal lobe and widespread neocortex in both the whole population and the NC group. For «N», hippocampal volume was positively correlated with synaptic density in the medial temporal lobe and widespread neocortex in the whole population and NC group, and showed positive correlations with synaptic density in both the lateral and medial temporal lobes in the AD and MCI groups. Plasma NfL levels were negatively correlated with synaptic density in the lateral temporal lobe across the whole population, and with medial temporal synaptic density as well. Notably, the correlation between synaptic density and hippocampal volume was stronger than that between synaptic density and plasma NfL levels. **Conclusions:** Synaptic density showed varying degrees of correlation with imaging and plasma A-T-N biomarkers, with stronger associations observed for imaging biomarkers. Among the A-T-N components, T-related biomarkers exhibited the strongest correlation with synaptic density. Given their accessibility, plasma biomarkers may serve as convenient surrogate indicators of synaptic density changes throughout the course of Alzheimer's disease in the future.

LB07- INCREASED IRON DEPOSITION IN THE PCC OF OLDER WOMEN WITH AMCI.

T. Gong[1], L. Song[1] *(1. Shandong Provincial Hospital - Jinan (China))*

Introduction: Brain iron deposition is linked to the pathophysiology of Alzheimer's disease (AD), other neurodegenerative disorders, and cognitive dysfunction, particularly in the posterior cingulate cortex (PCC)—a key region for memory and cognitive processing. However, the role of brain-wide iron accumulation in the pre-dementia stage, specifically amnestic mild cognitive impairment (aMCI), and potential sex differences remain underexplored. This study investigates whether brain iron deposition increases in aMCI, its sex dependence, and its correlation with cognitive performance in older adults. **Methods:** A cross-sectional analysis was conducted on 146 elderly participants (60 aMCI patients and 86 age-matched healthy controls). Iron deposition was measured using quantitative susceptibility mapping (QSM) based on strategically acquired gradient echo (STAGE) imaging, and cognitive function was assessed via the Mini-Mental State Examination (MMSE). Statistical analyses compared iron levels between groups, with subgroup analyses for sex, and correlations between iron deposition and cognition were evaluated using Pearson's coefficients and multiple regression, controlling for confounders like age, education, and comorbidities. **Results:** Results showed significantly higher PCC iron deposition in aMCI patients than controls (p < 0.001), with a stronger effect in females: female aMCI patients had higher PCC iron levels than male aMCI patients and controls (p < 0.01), whereas male aMCI patients showed no significant difference from male controls (p = 0.3). PCC volume remained unaltered. Additionally, PCC iron levels negatively correlated with cognitive decline (MMSE and Memory_z scores, all p < 0.05), with a stronger correlation in females (r = -0.65, p < 0.001) than males (r = -0.34, p = 0.05), indicating female-driven PCC iron accumulation linked to cognitive changes. **Discussion:** These findings suggest PCC iron accumulation as an early biomarker for aMCI cognitive impairment, preceding structural atrophy, with marked sex differences. The female-specific iron increase highlights the need to consider sex in neurodegenerative research, potentially due to hormonal (e.g., estrogen-modulated iron metabolism [1]) and genetic factors affecting brain iron homeostasis. The significant correlation between PCC iron levels and cognitive decline is consistent with previous studies linking iron accumulation to neurodegenerative diseases like Alzheimer's [2] and Parkinson's [3] Iron may promote the production of reactive oxygen species, contributing to oxidative stress and neuronal damage, which could explain the observed cognitive impairments. Our study adds to the growing body of evidence suggesting that iron deposition in the PCC may be an early marker of cognitive decline, particularly in the pre-dementia stage of Alzheimer's disease. Importantly, our findings underscore the need for gender-specific approaches in the study of neurodegenerative diseases. Understanding the differential role of iron in male and female brains may lead to more personalized diagnostic tools and therapeutic interventions. Furthermore, this research opens avenues for exploring interventions aimed at regulating brain iron levels, such as iron chelation therapy, in preventing or slowing cognitive decline, particularly in women who may be at greater risk due to hormonal or genetic factors. **Conclusions:** In conclusion, PCC iron deposition is significantly elevated in aMCI patients versus controls, with pronounced sex differences, and correlates with cognitive decline, especially in women. This supports PCC iron as a potential early biomarker for aMCI cognitive impairment, emphasizing gender-specific approaches in diagnosis and intervention. **Keywords:** Iron deposition, posterior cingulate cortex, amnestic mild cognitive impairment, sex differences. **Disclosures:** The authors declare no conflicts of interest. **References:** 1. Sciarra F, Campolo F, Franceschini E, Carlomagno F, Venneri MA. Gender-Specific Impact of Sex Hormones on the Immune System. Int J Mol Sci. 2023 Mar 27;24(7):6302. doi: 10.3390/ijms24076302. 2. Spence H, McNeil CJ, Waiter GD. The impact of brain iron accumulation on cognition: A systematic review. PLoS One. 2020 Oct

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LB08- LONGITUDINAL ALTERATIONS OF WHITE MATTER MICROSTRUCTURE IN LECANEMAB-TREATED PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND EARLY ALZHEIMER'S DISEASE.

Y. Wang[1], A.C. Yang[2], Y.X. Li[2], T. Gong[2], L. Song[3] (1. Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University - Jinan (China), 2. Department of Radiology, Shandong Provincial Hospital Affiliated to Shandong First Medical University - Jinan (China), 3. Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University - Jinan (China))

Background: Alzheimer's disease (AD) is characterized by progressive neurodegeneration, including reduced white matter (WM) integrity [1, 2]. Its hallmark amyloid β (Aβ) deposits and tau pathology induce axonal degeneration, myelin destruction, and neuroinflammation, leading to abnormal diffusion indices in critical fiber tracts [3]. This disrupts whole-brain network connectivity and accelerates cognitive decline. Lecanemab, a monoclonal antibody targeting Aβ, has demonstrated clinical efficacy [4, 5], but its effects on WM microstructure remain poorly understood. This study is aim to investigate the effects of lecanemab treatment on white matter microstructural integrity in patients with mild cognitive impairment (MCI) and early AD using diffusion tensor imaging (DTI) tractography with automated fiber tract segmentation. **Methods:** This study included 11 patients diagnosed with MCI or early AD who received intravenous infusions of lecanemab every two weeks. Additionally, the study also included 18 patients with MCI or early AD who were matched for age and education level with the treatment group but didn't receive any anti-Aβ therapy, as the control group. All participants underwent at least two magnetic resonance imaging (MRI) scans in 0 to 10 months period. All imaging was performed using a 3T MRI scanner according to standardized protocols. The analysis of DTI data was conducted as follow: DTI data preprocess (MRtrix), reconstruction and automated 72 fiber bundle segmentation (https://github.com/MIC-DKFZ/TractSeg). Ultimately, quantitative diffusion metrics include were extracted including fractional anisotropy (FA), mean diffusivity (MD), axial (AxD)and radial (RD) diffusivity along the segmented tracts. Longitudinal changes were analyzed using paired t-tests or non-parametric tests, depending on the distribution of the data. Then, false discovery rate (FDR) correction (p<0.05) identified significant microstructural changes. **Results:** The timeline plot for the treatment group (mean age 64.90, SD 8.27) revealed a decreasing trend in FA after treatment with Lecanemab, while MD, AxD, and RD showed an increasing trend. After FDR correction, five critical fiber tracts exhibited significant (P<0.05) increases in MD, AxD, and RD: the Commissure Anterior (CA), the all and posterior (primary Somatosensory) Corpus Callosum (CC), the left Superior longitudinal fascicle II (SLF-II), and the left Striato-premotor. In contrast, the longitudinal quantitative diffusion metrics in the control group (mean age 64.06, SD 7.63) showed no significant changes in any fiber bundle (P > 0.05). **Conclusions:** Lecanemab can improve AD-induced damage in white matter microstructure, repair myelin damage, axonal abnormalities, and tissue oedema. The fibers spatial distribution characteristics of these changes reflect the complex interplay between AD pathology and therapeutic effects, potentially providing partial imaging-based evidence for monitoring the therapeutic efficacy of lecanemab. Further investigations integrating multi-modal neuroimaging and biomarkers are warranted to elucidate the mechanisms underlying these microstructural alterations and their clinical implications. Keywords: lecanemab; mild cognitive impairment (MCI); Alzheimer's disease (AD); Diffusion tensor imaging (DTI); white matter integrity; fractional anisotropy (FA); mean diffusivity (MD); axial diffusivity (AxD), radial diffusivity (RD).

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LB09- GLYMPHATIC SYSTEM DYSFUNCTION IS STRONGLY LINKED TO NEURODEGENERATION AND SERVES AS A BRIDGE BETWEEN ATN BIOMARKERS AND COGNITIVE DECLINE IN SEX-DEPENDENT IN ALZHEIMER'S DISEASE.

J. Wang[1], F. Xie[1] (1. Fudan Huashan Hospital - Shanghai (China))

Objective: To elucidate how glymphatic function disruption affects AD pathology and explore its relationships with ATN biomarkers, with a focus on the effects of sex and amyloid status on these relationships. **Methods:** We recruited 1,135 individuals from the Chinese Preclinical Alzheimer's Disease Study (CPAS), including 247 AD patients, 283 individuals with mild cognitive impairment (MCI), and 605 cognitively unimpaired (CU) participants. All participants underwent Aβ-PET, diffusion magnetic resonance imaging (MRI), and neuropsychological assessments; additionally, 695 participants underwent FDG-PET, 394 took part in tau-PET, and 615 provided blood samples to measure plasma ATN biomarkers. Glymphatic function was evaluated using the diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) index. A one-way analysis of variance was conducted to examine the differences among DTI-ALPS, imaging, and blood ATN biomarkers. Partial correlation and mediation models were employed to investigate the associations among glymphatic function, ATN biomarkers, and cognition. **Results:** The AD group has a lower ALPS index than the MCI group and CU, and MCIs are also lower than CUs. The Aβ-positive group had a lower ALPS index than the Aβ-negative group, and the male group had a lower ALPS index than the female group. The ALPS index was negatively associated with amyloid deposition, tau burden and plasma p-tau 181 and neurofilament light (NfL), and positively associated with glucose metabolism and hippocampal volume only in females. ALPS-index showed significant mediation effects between global amyloid deposition

and meta-temporal lobe tau burden, between global amyloid deposition and plasma p-tau 181. The ALPS index mediates the associations of Aβ pathology with neurodegeneration and tau pathology with neurodegeneration in the female or Aβ-positive groups. The ALPS index was positively associated with global cognition, memory, language and executive function. The ALPS index mediates the associations of Aβ pathology with global cognition, and tau pathology with global cognition in the female or Aβ-positive groups, and neurodegeneration with global cognition only in the female group. **Conclusions:** Compared to CU, a significant reduction in ALPS-indexes in MCI and AD patients, and males exhibit lower ALPS-indexes than females. The ALPS-index was correlated with ATN biomarkers and mediated key relationships among Aβ, tau pathology, neurodegeneration, and cognition in a sex manner. The impaired glymphatic function bridges the link between Aβ pathology, tau pathology, neurodegeneration and cognitive decline in a sex-dependent manner. These findings suggest that glymphatic dysfunction plays a critical role in the pathogenesis of AD in a sex-dependent manner.

LB11- STRUCTURAL–FUNCTIONAL COUPLING AND GLYMPHATIC FUNCTION IN DIVERGENT PROGRESSION OF MILD COGNITIVE IMPAIRMENT.

R. Chen[1], P. Wang[2], X. Han[2], C. Wei[1] (1. School of Biological Science and Medical Engineering, Beihang University - Bejing (China), 2. Innovation Center for Neurological Disorders and Department of Neurology, Xuanwu Hospital, Capital Medical University, National Clinical Research Center for Geriatric Diseases - Beijing (China))

Background: Structural–functional connectivity (SC–FC) coupling reflects the brain's capacity to integrate structural wiring with functional communication and has been linked to cognitive performance. Emerging evidence suggests that glymphatic dysfunction plays a critical role in the Alzheimer's disease (AD) continuum. Diffusion Tensor Image Analysis along the Perivascular Space (DTI-ALPS) serves as a non-invasive proxy for evaluating glymphatic activity by characterizing perivascular fluid dynamics. This study aimed to integrate SC–FC coupling metrics with DTI-ALPS indices to examine their potential interplay and implications for cognitive function and disease progression in patients with mild cognitive impairment (MCI). **Methods:** A total of 81 MCI patients (33 progressive MCI (pMCI), 48 stable MCI (sMCI)) were included from the ADNI database, each with baseline diffusion tensor imaging (DTI) and resting-state functional MRI (rs-fMRI). SC–FC coupling values were calculated from structural and functional connectivity matrices, and ALPS indices were derived from DTI data. Group comparisons of SC–FC coupling and ALPS metrics were conducted using ANCOVA with age and sex as covariates. Partial correlation analyses were performed to assess associations between altered coupling regions and cognitive scores (MMSE, MoCA, CDRSB, etc.). Structural equation modeling was used to evaluate the moderating role of DTI-ALPS in the relationship between SC–FC coupling and cognition. Statistical significance was set at $p < 0.05$ for all analyses. **Results:** Compared to pMCI patients (74.05 ± 7.14 years), sMCI patients (72.73 ± 6.95 years) exhibited increased SC–FC coupling in the left inferior frontal gyrus (pars triangularis), left inferior temporal gyrus, right inferior temporal gyrus, left inferior occipital gyrus, right middle occipital gyrus, and right calcarine cortex. Among these, only the left inferior frontal gyrus (pars triangularis) belongs to the frontoparietal network (FPN), while the remaining regions are part of the visual network (VN). After correction for multiple comparisons, significantly elevated coupling values in the left inferior frontal gyrus (pars triangularis) and right calcarine cortex in sMCI patients persisted relative to pMCI. In contrast, sMCI patients exhibited significantly reduced coupling values in the left inferior frontal gyrus (pars opercularis), left middle temporal gyrus, left fusiform gyrus, and bilateral anterior cingulate cortices. These regions are located in the frontoparietal network (FPN), visual network (VN), and default mode network (DMN), respectively. Subsequent correlation analyses focusing on these significant regions revealed that coupling values in the left inferior frontal gyrus (pars triangularis), left middle temporal gyrus, and right anterior cingulate cortex were positively associated with MMSE scores. Global SC–FC coupling was significantly negatively correlated with RAVLT forgetting scores. Moreover, regional coupling values in the left inferior frontal gyrus (pars opercularis and pars triangularis) and left inferior temporal gyrus were significantly associated with the RAVLT forgetting percentage. Additionally, global, left hemispheric, and right hemispheric DTI-ALPS indices were significantly lower in sMCI compared to pMCI. Coupling in the left inferior temporal gyrus was significantly positively correlated with both left and right ALPS indices, whereas coupling in the left fusiform gyrus was significantly negatively correlated with global and right ALPS indices. Furthermore, the left DTI-ALPS index significantly moderated the relationships between SC–FC coupling in the left inferior frontal gyrus (pars opercularis; $\beta = -0.30$, $p = 0.0093$) and left inferior frontal gyrus (pars triangularis; $\beta = 0.49$, $p = 1.72 \times 10^{-7}$) and the RAVLT forgetting percentage. Both the left ($\beta = 0.47$, $p = 4.71 \times 10^{-6}$) and right ($\beta = 0.51$, $p = 1.87 \times 10^{-6}$) DTI-ALPS indices also significantly moderated the relationship between global SC–FC coupling and RAVLT forgetting scores. **Conclusions:** This study identified significant differences between sMCI and pMCI in structural-functional coupling and DTI-ALPS metrics involving language, visual, and default mode network regions. DTI-ALPS not only correlated with cognitive performance but also significantly moderated the relationship between structural-functional coupling and cognition, suggesting its bridging role in cognitive decline. These findings highlight structural-functional coupling and DTI-ALPS as key neuroimaging biomarkers for MCI with potential diagnostic and prognostic value. **Keywords:** SC–FC coupling, DTI-ALPS index, mild cognitive impairment, glymphatic system, functional–structural integration. **Disclosures:** This study was supported by the National Key R&D Program of China (No. 2017YFC1310103), STI2030-Major Projects (No. 2021ZD0201802), and the General Program of the National Natural Science Foundation of China (No. 82471450). The authors declared no competing interests.

LB12- MICROGLIAL ACTIVATION CORRELATES WITH AMYLOID CLEARANCE AND COGNITIVE BENEFIT IN LECANEMAB-TREATED EARLY AD PATIENTS.

X.H. Qian[1], S.Y. Chen[1], M. Zhang[2], H.D. Tang[3] (1. Department of Geriatrics, Medical Center on Aging of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai (China), 2. Department of Nuclear Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai (China), 3. Department of Geriatrics, Medical Center on Aging of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai (China))

Background: Anti-Amyloid β (Aβ) immunotherapy has been shown to clear Aβ and delay cognitive decline in Alzheimer's disease (AD) [1]. Recent studies suggest that the efficacy of

this treatment is linked to microglial activation [2]. However, direct evidence from cohort studies is lacking. The 18-kDa translocator protein (TSPO)-positron emission tomography (PET) imaging allows for in vivo assessment of microglial activation [3]. **Methods:** The study included 10 early AD patients treated with Lecanemab monoclonal antibody (10 mg/kg, biweekly) for 12 months, and 7 untreated early AD patients as controls. All participants underwent Aβ (AV45) and TSPO (DPA714) PET scans and cognitive tests at baseline and after 12 months. **Results:** No significant demographic differences were found between the Lecanemab and control groups. Both groups had similar proportions of APOE4-positive individuals, cognitive levels, Aβ load, and microglial activation. At 12 months, the Lecanemab group showed a -0.34 SUVR for AV45/PET and a +0.05 SUVR for DPA714/PET. Correlation analysis revealed a positive correlation between increased frontal (r=-0.59, p=0.023) and temporal (r=-0.59, p=0.023) DPA714 SUVR levels and decreased AV45 SUVR levels. Additionally, an increase in parietal DPA714 SUVR was negatively correlated with MMSE score reduction (r=-0.53, p=0.04). **Conclusions:** Microglial activation plays a crucial role in the efficacy of Anti-Aβ immunotherapy, promoting Aβ clearance and delaying cognitive decline. **Keywords:** Alzheimer's disease, anti-Amyloid β immunotherapy, microglia, TSPO PET. **Disclosures:** The author declares no potential conflict of interest, including no financial or professional relationship with Eisai Co., Ltd or any other relevant entity.

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LB15- SYNAPTIC LOSS ON EARLY-ONSET ALZHEIMER'S DISEASE ASSESSED BY [18F]SYNVEST-1. K. He[1], J. Wang[1], T. Hu[1], W. Wang[1], Q. Huang[1], J. Zhao[2], Y. Guan[1], Q.H. Guo[3], F. Xie[1] (1. Huashan Hospital Fudan University - Shanghai (China), 2. East Hospital Affiliated To Tongji University - Shanghai (China), 3. Shanghai Sixth People's Hospital - Shanghai (China))

Introduction: This study aimed to investigate the synaptic loss on early-onset and late-onset Alzheimer's Disease and explore the underlying pathologic mechanisms. **Methods:** We enrolled 193 participants who underwent synaptic vesicle protein 2A(SV2A) and amyloid-beta (Aβ) PET imaging with [18F]SynVesT-1 and [18F]florbetapir respectively. The study comprised 24 participants with early-onset Alzheimer's Disease (EOAD), 67 with late-onset Alzheimer's Disease (LOAD), 17 with early-onset non-Alzheimer's Disease (EOnonAD), 25 with late-onset non-Alzheimer's Disease (LOnonAD), and 60 cognitively unimpaired participants. Plasma levels of glial fibrillary acidic protein (GFAP) and phosphorylated tau 181 (pTau181) were measured. The associations between age and synaptic loss were evaluated across different groups. Additionally, we assessed the relationships between GFAP, pTau181, and synaptic loss in distinct groups. Mediation effects were employed to determine whether GFAP, pTau181, and Aβ influence the relationship between age and synaptic density. **Results:** Both EOAD and LOAD groups exhibited significantly synaptic loss compared with cognitively unimpaired (CU) participants. EOAD also exhibited more pronounced synaptic loss than LOAD. Notably, younger age was significantly associated with greater synaptic loss in the precuneus in EOAD. Elevated GFAP levels correlated with greater synaptic loss in the precuneus and hippocampus in early-onset cognitive decline. Furthermore, higher pTau181 levels were associated with greater synaptic density in the precuneus in early-onset cognitive decline. Mediation analyses identified GFAP and Aβ as mediators in the relationship between age and hippocampal synaptic density. **Discussion:** Our findings suggest that the patterns of synaptic loss differ between EOAD and LOAD, indicating potentially distinct pathological mechanisms underlying these two forms of Alzheimer's Disease, These observations underscore the rationale for developing age-specific diagnostic and therapeutic approaches for individuals with Alzheimer's disease.

OC04- 6-MONTHS FOLLOW-UP OF ARIA-H IN LECANEMAB THERAPY FOR ALZHEIMER'S DISEASE: A COMPARISON STUDY OF DIAGNOSTIC PERFORMANCE OF 3T VERSUS 7T MRI. W. Zhang[1], H.Liu[2], B. Jiao[2,3,4,5,6], K.Fang[2], Y. Zhou[3,4,5,6,7], Y. Luo[8], L. Weng[2,3,4,5,6], L. Fang[2], L. Zhou[7], L. Shen[2,3,4,5,6,7] (1. Department of Radiology, Xiangya Hospital, Central South University, Changsha (China), 2. Department of Neurology, Xiangya Hospital, Central South University, Changsha (China), 3. National Clinical Research Center for Geriatric Disorders, Central South University, Changsha (China), 4. Engineering Research Center of Hunan Province in Cognitive Impairment Disorders, Central South University, Changsha (China), 5. Hunan International Scientific and Technological Cooperation Base of Neurodegenerative and Neurogenetic Diseases, Changsha (China), 6. Key Laboratory of Hunan Province in Neurodegenerative Disorders, Central South University, Changsha (China), 7. Department of Geriatric Neurology, Xiangya Hospital, Central South University, Changsha (China), 8. Department of Neurology, The Second Xiangya Hospital, Central South University, Changsha (China), 9. FuRong Laboratory, Central South University, Changsha (China))

Background: Amyloid related imaging abnormality (ARIA) is a common side effect of anti-amyloid immunotherapy for AD, occurring in 10–30% of patients [1, 2]. There are two types of ARIA, ARIA-E (edema) and ARIA-H (hemorrhage), typically evaluated using FLAIR and susceptibility-weighted imaging (SWI), respectively [3]. The current ARIA severity grade is based on imaging obtained with 1.5T or 3T MRI scanner [4]. The imaging features and severity assessment of ARIA on ultra-high-field MRI scanner remains largely unknown. The purpose of this study was to compare 3T and 7T MRI as platforms for detecting cerebral microbleeds (CMBs) and prediction of ARIA-H in patients treated with lecanemab. **Methods:** SWI was performed with both 3T and 7T MR scanners on 42 patients who receiving lecanemab therapy at baseline and during follow-up. The number and location of CMBs were counted and compared across visits by two neuroradiologists. **Results:** We included 42 patients receiving lecanemab treatment from June 2024 to May 2025. 13 patients presented with multiple CMBs at baseline, 4 of them developed into ARIA-H (9.8%) by 6 months, including 1 case of severe ARIA-H and 3 cases of mild ARIA-H. All ARIA-H events were asymptomatic and occurred as early as the first

2 months after treatment initiation. CMBs were significantly more conspicuous on 7 T MRI than on 3 T MRI, with subtle microbleedings (typically less than 1.5 mm in diameter) being less detectable in lower fields. 7T MRI enabled earlier prediction of ARIA-H occurrence by 4 months. Using high-resolution 7T SWI, we firstly described the CMBs with high-risk of ARIA-H, which were lobar CMBs in clusters that distribute mainly in cortical region of occipital lobe, indicative of cerebral amyloid angiopathy (CAA). In contrast, deep CMBs scattered primarily within the white matter and accompanied by white matter hyperintensity (WMH) were considered low risk for ARIA-H conversion. **Conclusions:** Compared with 3T MRI, 7T MRI offers superior sensitivity for detecting cerebral microbleeds and facilitates earlier prediction of ARIA-H. Moreover, 7T MRI reveals distinct imaging features of high-risk ARIA-H that may be indicative of underlying CAA pathology. **Keywords:** Amyloid-related imaging abnormalities, cerebral microbleeds, 7 Tesla MRI, susceptibility weighted imaging. **Disclosures:** The authors declared no competing interests. **References**:
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NEW AD BIOMARKERS IN CLINICAL TRIALS

LB01- SPATIAL TRANSCRIPTOMIC SIGNATURES OF SYNAPTIC DENSITY LOSS IN ALZHEIMER'S DISEASE.
B. Li[1], L. Sun[2] (*1. Department of Neurology and Institute of Neurology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine - Shanghai (China), 2. Department of Neurology and Institute of Neurology, Ruijin Hospital affiliated with Shanghai Jiao Tong University School of Medicine - Shanghai (China)*)

Background: Synaptic loss is a core pathological hallmark and a major cause of cognitive impairment in Alzheimer's disease (AD). However, the transcriptional programs underlying regional synaptic vulnerability remain poorly understood. **Methods:** We integrated 18F-SynVesT-1 SV2A PET imaging from a prospective AD cohort—including 111 individuals with Alzheimer's disease and 54 cognitively unimpaired controls—with whole-brain transcriptomic data from the Allen Human Brain Atlas [1]. Partial least squares (PLS) regression was applied to identify genes whose spatial expression patterns were associated with SV2A-PET standardized uptake value ratio (SUVR) alterations in AD [2]. Functional enrichment analyses were performed using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases [3], while cell-type and tissue-specific enrichment was assessed using reference gene sets from neural cell type and brain tissue partitions [4-6]. To explore the transcriptional mechanisms across clinical feature, additional PLS models were constructed based on APOE ε4 carrier status, Braak stage, and MMSE scores. **Results:** SV2A SUVR was significantly reduced in AD, particularly in the hippocampus and temporoparietal cortex. Transcriptomic analysis revealed

1,233 genes significantly associated with regional SV2A-PET reduction. These genes were enriched for pathways related to synaptic organization, tau phosphorylation, cytoskeletal structure, and ubiquitin-mediated protein degradation. Enrichment was cell-type specific, with downregulated genes predominantly expressed in neurons, while upregulated genes mapped to oligodendrocytes and endothelial cells. Stratified PLS models across APOE ε4 status, Braak stages, and MMSE scores revealed both shared and divergent molecular signatures. Longitudinal analysis confirmed that progressive SV2A SUVR decline was accompanied by activation of stress- and mitochondria-related transcriptional pathways. Findings were robustly replicated in a retest cohort. **Conclusions:** SV2A PET imaging reflects a complex interplay of synaptic, glial, and metabolic transcriptional signatures in AD. These results highlight the molecular underpinnings of synaptic vulnerability and suggest candidate pathways for therapeutic intervention. **Keywords:** Synaptic loss, synaptic vesicle glycoprotein 2A positron emission tomography, image-transcriptomics, Alzheimer's disease, cellspecific analysis, tissuespecific analysis. **Clinical Trial Registry:** NCT05623124; https://clinicaltrials.gov. **Disclosures:** The authors declared no competing interests. **References:**
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LB03- PREDICTING ARIA RISK AND TREATMENT OUTCOMES IN ANTI-Aβ THERAPY USING MULTIMODAL BIOMARKERS AND AI MODELS. M. Fang[1] (*1. Shanghai Tongren Hospital - Shanghai (China)*)

Background: Anti-amyloid beta (Aβ) monoclonal antibodies offer disease-modifying potential for Alzheimer's disease (AD) [1]. However, their clinical use is limited by amyloid-related imaging abnormalities (ARIA) and variable treatment responses [2–4]. Current tools are insufficient to identify individuals at risk for ARIA or those most likely to benefit. Predictive strategies that integrate peripheral and central biomarkers are critically needed to inform treatment selection and enhance safety. **Methods:** This study consisted of three phases. First, we analyzed plasma tRNA-derived fragments (tRFs), selected for their stability and relevance to glial and vascular mechanisms implicated in ARIA. Small RNA sequencing of

ARIA and non-ARIA patients identified 1128 differentially expressed tRFs. Five were prioritized based on fold change and subtype. One fragment, 5'tiRNA-1-34-Glu-TTC-1 (TTC-1), was validated by qRT-PCR and assessed via functional annotation and in vitro assays. Second, to evaluate central fluid clearance, we performed multimodal neuroimaging in the same cohort, including diffusion tensor imaging (ALPS index), resting-state fMRI (BOLD-CSF coupling), and structural MRI. These noninvasive features served as imaging correlates of ARIA-related clearance impairment. Third, leveraging the complementary nature of plasma and imaging features, we developed a transformer-based AI model integrating tRF profiles, MRI metrics, and Aβ-PET data to predict cognitive outcomes (MMSE, MoCA) following anti-Aβ therapy. **Results:** 1. TTC-1 was significantly elevated in ARIA plasma (P < 0.01). Its predicted targets were enriched in junctional and vascular regulatory pathways. In vitro experiments demonstrated that TTC-1 binds Connexin 43, promoting its degradation via ubiquitination without affecting mRNA levels, suggesting post-transcriptional endothelial disruption. 2. Imaging revealed that ARIA patients had significantly reduced ALPS index values (P = 0.034), indicating impaired perivascular clearance. BOLD-CSF coupling was also diminished (P = 0.002), reflecting disrupted CSF-brain signal synchrony. 3. The transformer-based AI model, combining plasma and imaging inputs, accurately predicted cognitive improvement post-treatment (P < 0.05 vs. observed MMSE/MoCA), supporting its utility in outcome stratification. **Conclusions:** We identified TTC-1 as a novel plasma biomarker linked to endothelial dysfunction in ARIA through Connexin 43 degradation. Neuroimaging findings revealed fluid clearance impairments in affected patients. The integration of peripheral and neuroimaging biomarkers in an AI model enabled accurate prediction of cognitive response to anti-Aβ therapy. This multimodal approach may support individualized risk stratification and optimize clinical decision-making in AD treatment. **Keywords:** Anti-amyloid therapy, ARIA, tRNA-derived fragments, multimodal imaging, transformer model. **Disclosures:** This work was supported by the National Health Commission Brain Health Project. The authors declare no other conflicts of interest. **References:** 1. Jucker, M.; Walker, L. C. Alzheimer's Disease: From Immunotherapy to Immunoprevention. Cell 2023, 186 (20), 4260–4270. https://doi.org/10.1016/j.cell.2023.08.021. 2. van Dyck, C. H.; Swanson, C. J.; Aisen, P.; Bateman, R. J.; Chen, C.; Gee, M.; Kanekiyo, M.; Li, D.; Reyderman, L.; Cohen, S.; Froelich, L.; Katayama, S.; Sabbagh, M.; Vellas, B.; Watson, D.; Dhadda, S.; Irizarry, M.; Kramer, L. D.; Iwatsubo, T. Lecanemab in Early Alzheimer's Disease. N. Engl. J. Med. 2023, 388 (1), 9–21. https://doi.org/10.1056/NEJMoa2212948. 3. Mintun, M. A.; Lo, A. C.; Duggan Evans, C.; Wessels, A. M.; Ardayfio, P. A.; Andersen, S. W.; Shcherbinin, S.; Sparks, J.; Sims, J. R.; Brys, M.; Apostolova, L. G.; Salloway, S. P.; Skovronsky, D. M. Donanemab in Early Alzheimer's Disease. N. Engl. J. Med. 2021, 384 (18), 1691–1704. https://doi.org/10.1056/NEJMoa2100708. 4. Hampel, H.; Elhage, A.; Cho, M.; Apostolova, L. G.; Nicoll, J. A. R.; Atri, A. Amyloid-Related Imaging Abnormalities (ARIA): Radiological, Biological and Clinical Characteristics. Brain: J. Neurol. 2023, 146 (11), 4414–4424. https://doi.org/10.1093/brain/awad188.

LB05- CLINICAL EVALUATION OF BLOOD-BASED ASSAYS FOR RAPID DETECTION OF AMYLOID-B IN ALZHEIMER'S DISEASE (CLEAR-AD) — A PROSPECTIVE HEAD-TO-HEAD COMPARISON STUDY OF BLOOD BASED BIOMARKER. X. Lv[1], K. Shen[1], F. Gao[1], Q. Zhao[2], G. Peng[3], X. Pan[4], H. Liu[5], W. Chen[6], H. Zhang[7], S. Zhang[8], M. Xing[9], Q. Chen[10], Y. Pan[11], Z. Cheng[1], F. Xie[12], Y. Wang[13], S. Zeng[13], X. Chen[4], J. Shi[1] *(1. Department of Neurology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui Province (China), 2. Department of Neurology, Huashan Hospital, Fudan University, Shanghai (China), 3. Department of Neurology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province (China), 4. Department of Neurology, Fujian Medical University Union Hospital, Fuzhou, Fujian Province (China), 5. Department of Neurology, the First Hospital of China Medical University, Shenyang, Liaoning Province (China), 6. Department of Physiology and Department of Psychiatry, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province (China), 7. Department of Neurology and Neuroscience Center, The First Hospital of Jilin University, Jilin University, Changchun, Jilin Province (China), 8. Department of Neurology and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan Province (China), 9. Department of Neurology, Tianjin Neurological Institute, Tianjin Medical University General Hospital, Tianjin (China), 10. Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing (China), 11. China National Clinical Research Center for Neurological Diseases, Beijing, China, 12. Department of Nuclear Medicine & PET Center, Huashan Hospital, Fudan University, Shanghai (China), 13. Eisai China Inc., Shanghai City (China))*

Background: Blood-based biomarkers (BBM) have been shown to predict Alzheimer's disease (AD) pathology and disease progression; however, standards for detecting AD biomarkers are inconsistent. Therefore, a head-to-head comparison of the performance of commercially available biomarkers would help optimize the clinical pathway in screening and diagnosis for AD. **Objectives:** Using amyloid-beta positron emission tomography (Aβ-PET) imaging as the reference, the primary objective of this study is to explore the predictive value of BBM for cerebral amyloid pathology. **Methods:** The cohort included 431 participants from 10 tertiary medical centers, covering most regions of China. All participants underwent Aβ-PET scans, with blood samples collected within three months post-scan. Participants were in one of the five groups: cognitively normal controls, mild cognitive impairment with amyloid PET positive (Aβ+) or negative (Aβ–), and dementia with Aβ+ or Aβ–. Blood samples, either fresh or previously stored (after January 1, 2024) in compliance with project quality standards, were analyzed at a central laboratory in a blind manner to assess the sensitivity and specificity of various BBM for predicting amyloid pathology confirmed by Aβ-PET. **Results:** Median age is 68 years with 60.9% female. Cognitive scores decline progressively from CN to AD groups (MMSE: 28 to 16; MoCA: 25 to 10). Remaining baseline data are under verification and will be presented at the meeting. **Conclusions:** This multicenter study, by comparing head-to-head various BBM assays, aims to optimize early screening of AD. **Keywords:** Alzheimer's disease, blood biomarkers, cerebral amyloid pathology, Aβ-PET, cognitive impairment, Chinese population

LB06- WHITE BLOOD CELL TRPC6 MRNA AS A BIOMARKER FOR DIAGNOSING ALZHEIMER'S DISEASE: A NATIONWIDE, MULTICENTER TRIAL IN CHINA.

M. Mei[1], Z. Qianhua[1], W. Yizheng[1] (1. Fudan university - Shanghai (China))

Background: Diagnosis of Alzheimer's disease (AD) generally rely on either positron emission tomography (PET) imaging or cerebrospinal fluid (CSF) testing for β-amyloid (Aβ) and tau proteins, which are expensive and invasive. Finding biomarkers with better accessibility and lower cost remains a critical challenge in the screening and diagnosis of AD. We investigated whether blood transient receptor potential canonical 6 (TRPC6), a molecule essential for synaptogenesis and neuronal survival, could serve as a reliable diagnostic biomarker for AD. **Methods:** A total of 1,100 individuals (n=1,100) were enrolled, including AD (n=366) patients and cognitively unimpaired (CU) individuals (n=734). Aβ deposition was determined by 18F-AV45 PET, while brain volume was quantified via magnetic resonance imaging (MRI). All study participants underwent TRPC6 mRNA assessments. AD patients were confirmed as Aβ positive through PET imaging. A subset of participants underwent Aβ-PET imaging, 3-dimensional (3D) T1-weighted MRI, and plasma biomarkers analysis. **Results:** The median age of 1,100 participants was 68.67 years (IQR: 63.72 to 73.91) with women participants accounted for (60.18%). Among the 366 AD patients, 200 were mild AD (CDR≤1), 166 were moderate and severe AD (CDR≥2). Blood TRPC6 mRNA levels were significantly lower in AD patients compared to CU individuals (1.29 vs. 4.50, P<0.0001). ROC curve analysis demonstrated that blood TRPC6 mRNA levels accurately identified AD patients from CU individuals, with an unadjusted area under the curve (AUC) of 0.935 (95% CI 0.917–0.952), and an adjusted AUC by age and sex of 0.925 (95% CI 0.908–0.943). Voxel-wise analyses revealed a strong association between blood TRPC6 mRNA levels and both Aβ deposition and brain volume. Additionally, when comparing to other plasma AD biomarkers, TRPC6 mRNA levels demonstrated satisfactory diagnostic performance, surpassing plasma Aβ42/40, P-tau181, GFAP and NfL, while being slightly inferior to P-tau217 (TRPC6, AUC=0.935; Aβ42/40, AUC=0.879; P-tau181, AUC=0.924; GFAP, AUC=0.894; NfL, AUC=0.734; P-tau217, AUC=0.965). **Conclusions:** White Blood Cell TRPC6 mRNA levels exhibited excellent diagnostic utility in identifying patients with AD from CU individuals. As a blood biomarker, TRPC6 mRNA levels offer a feasible, scalable, and cost-effective diagnostic tool that could serve as a standalone index for AD. Given its role in synaptic function and neuronal survival, TRPC6 may also represent a potential therapeutic target in AD. These findings warrant further investigation into both the diagnostic and disease-modifying potential of TRPC6 in AD.

LB13- OLFACTOMEDIN 1: A POTENT MOLECULAR TARGET FOR AMELIORATING SYNAPTIC PLASTICITY IMPAIRMENT IN ALZHEIMER'S DISEASE.

G. Zhang[1], C. Wei[1], Y. Sun[1], L. Sun[1] (1. Department of Neurology and Neuroscience Center, The First Hospital of Jilin University - Changchun (China))

Background and Objective: The global prevalence of Alzheimer's disease (AD) is continuously rising, posing a significant threat to human health, particularly among the elderly population. Against this backdrop, this study focuses on a novel peripheral blood biomarker for AD: on one hand, aiming to validate its clinical value; on the other hand, exploring its potential as a molecular target for improving synaptic plasticity impairment in AD. **Methods:** This study included 118 AD patients and 112 healthy controls, while also obtaining transcriptomic data of brain tissues from AD patients in the GEO database. Serum Olfactomedin 1 (OLFM1) levels were detected via ELISA. An AAV injection and grouping experiment in the hippocampal CA1 region was conducted on wild - type (WT) mice and 3x - Tg AD mice, and the Morris water maze test was used to assess cognitive function in mice. Relevant indicators were detected using methods such as histopathological examination, Western blotting, real - time quantitative PCR, transmission electron microscopy analysis, and Golgi staining. Weighted gene co - expression network analysis (WGCNA) and machine learning were employed to screen for key genes, and various statistical methods and software were used for data analysis. **Results:** Through WGCNA and differential expression gene (DEGs) screening, combined with integrated machine learning (Lasso, Ridge, Elastic Net), this study identified OLFM1 as a key gene for AD from AD - related datasets. Multivariate logistic regression analysis revealed a significant negative correlation between OLFM1 and AD risk (GSE33000: OR = 0.891 - 0.918; GSE44772: OR = 0.886 - 0.911). This association remained significant after adjusting for confounding factors such as age and gender, and a dose - response relationship (linear or non - linear negative correlation) was observed. The critical values varied depending on the dataset (transcript abundance: 20.21, 15.01; serum protein: 667.15 pg/ml). Moreover, the protective effect of OLFM1 was stronger in individuals with lower educational levels. Multi - omics validation demonstrated that OLFM1 levels were significantly reduced in AD patients at both the transcriptional level (GSE33000, GSE44770) and the serum protein level. In the hippocampal tissues of 3x - Tg AD mice, the mRNA and protein levels of OLFM1 were also significantly down - regulated. Functionally, OLFM1 was correlated with cognitive function in AD patients, with higher levels associated with higher cognitive scores on the Mini - Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Mouse experiments showed that overexpression of OLFM1 could significantly improve cognitive function in AD mice, increase the levels of synaptic - related proteins (PSD95, GAP43), and alleviate hippocampal neuronal damage (such as a reduction in the number of dendritic spines and abnormal synaptic structure). In terms of mechanism, OLFM1 may improve synaptic damage in AD by regulating the disarray of extracellular matrix (ECM) proteins, and its overexpression can inhibit the upward trend of ECM - related genes in AD. **Conclusions:** This study confirms that OLFM1 is a key gene for AD. Its reduced expression is closely associated with an increased risk of AD onset, cognitive decline, and synaptic/neuronal structural damage. Overexpression of OLFM1 can improve AD - related pathology and cognitive impairment by regulating ECM disarray. OLFM1 holds promise as a potential biomarker for the diagnosis and treatment of AD and as an intervention target for improving synaptic damage. **Keywords:** Alzheimer's disease, Olfactomedin 1, synaptic plasticity, extracellular matrix. **Disclosures:** The authors declared no competing interests.

LB14- PLASMA SYNAPTIC AND NEURODEVELOPMENTAL PROTEIN BIOMARKERS FOR DIAGNOSIS AND PREDICTION OF ALZHEIMER'S CONTINUUM: A MULTI-COHORT CROSS-SECTIONAL AND LONGITUDINAL STUDY. D. Yang[1], H. Zhao[1], X. Zhu[1], Y. Xu[1] *(1. Nanjing Drum Tower Hospital, Medical School of Nanjing University - Nanjing (China))*

Background: Alzheimer's disease (AD) is a heterogeneous and progressive neurodegenerative disorder, including subjective cognitive decline (SCD), mild cognitive impairment (MCI), and dementia. Early and accurate diagnosis remains challenging due to the lack of reliable, non-invasive biomarkers capable of predicting disease onset and progression, particularly during the SCD stage. **Methods:** We integrated large-scale plasma proteomics, Plasma Custom Protein Profiling, and whole-genome sequencing across a multi cohort, including a discovery set and two independent validation sets (total n = 1,093). Participants aged 50 to 90 with clinical diagnosis of SCD, MCI and dementia were recruited. Amyloid-β (Aβ) pathology was confirmed using plasma Aβ42/Aβ40, Aβ-PET imaging, or cerebrospinal fluid Aβ42/Aβ40. Machine learning algorithms were employed to evaluate diagnostic and prognostic performance. Mendelian randomization and colocalization analyses were conducted to determine potential causal protein involved in the etiology of AD. **Results:** Cross-dataset analysis identified twelve consistently robust plasma protein, primarily enriched in neurodevelopmental and synaptic pathways. When integrated with machine learning, different combinations of these proteins achieved stage-specific diagnostic accuracy and effectively predicted longitudinal cognitive decline in individuals with SCD and MCI. Notably, the twelve-protein panel identified pre-symptomatic AD up to ten years before clinical diagnosis, demonstrating strong specificity for AD with minimal cross-reactivity to other types of dementia, as assessed by the UK Biobank database. Drug target prioritization suggested that most of these proteins are amenable to small-molecule or antibody-based therapeutic strategies and have favorable safety profiles. Mendelian randomization further implicated CD302 as a likely causal driver of AD pathology. **Conclusions:** This study presents a validated, plasma-based twelve-protein biomarker panel with significant diagnostic and prognostic utility across the full AD spectrum. These findings support its potential as a non-invasive tool for early detection, disease staging, and therapeutic targeting, particularly during the critical preclinical and prodromal phases of AD.

OC13- MYELOPEROXIDASE AS A NEW PREDICTIVE BIOMARKER OF COGNITIVE DECLINE IN MILD COGNITIVE IMPAIRMENT. W.X. Sun[1], P. Wang[1], J. Gong[1], C. Wei[1] *(1. Innovation Center for Neurological Disorders and Department of Neurology, Xuanwu Hospital, Capital Medical University - Beijing (China))*

Background: Mild cognitive impairment (MCI) offers a crucial opportunity for early dementia intervention. Myeloperoxidase (MPO), an enzyme central to inflammation regulation and immune response, has not been studied in relation to MCI progression. This study aims to explore the longitudinal changes and prognostic significance of MPO in a multicenter cohort of MCI. **Methods:** Eligible MCI patients were enrolled and followed up for 12 months. Clinical and neuropsychological assessments were conducted at the start and end of the study. AD markers in blood were identified using single molecule immunoassay, and APOE genotypes were determined via Sanger sequencing. Plasma levels of MPO, IL-1β, IL-6, and TNFα were measured using ELISA. **Results:** The study included 133 patients: 58 with cognitive decline and 75 without. The cognitive deterioration group had higher levels of MPO, IL-1β, and IL-6. MPO levels were significantly associated with ADAS-Cog and MMSE scores, the inflammatory factors IL-1β and IL-6, and the AD marker Aβ42/40. After adjusting for confounders, elevated MPO levels were identified as an independent predictor of cognitive decline in MCI patients [OR = 1.018; 95% CI (1.00–1.03); p = 0.015]. The nomogram indicated that MPO was the strongest predictor of MCI prognosis. **Conclusions:** This study is the first to comprehensively reveal the role of MPO in the prognostic progression of MCI patients. It systematically illustrates the relationship between MPO and multidimensional biomarkers in the MCI population, and verifies that elevated plasma MPO levels are an independent risk factor for cognitive decline in MCI patients.

OC14- ROLE OF PERIVASCULAR SPACES IN THE THERAPEUTIC EFFICACY OF DL-3-N-BUTYLPHTHALIDE FOR MILD COGNITIVE IMPAIRMENT. P. Wang[1], R. Chen[2], X. Han[1], B. Wen[1], C. Wei[1] *(1. Innovation Center for Neurological Disorders and Department of Neurology, Xuanwu Hospital, Capital Medical University, National Clinical Research Center for Geriatric Diseases, Beijing, China. - Beijing (China), 2. School of Biological Science and Medical Engineering, Beihang University, Beijing, China. - Beijing (China))*

Background: Mild cognitive impairment (MCI) represents a critical window for the early Alzheimer's disease (AD) intervention, yet effective treatment remain lacking. As a groundbreaking discovery in neuroscience in recent years, glymphatic system (GS) may contribute to MCI pathogenesis and is a potential therapeutic target. Due to its non-invasive nature, intuitive visualization, and regional specificity, MRI-visible perivascular space (PVS) has emerged as an important imaging marker for the clinical assessment of GS function. Preclinical studies have demonstrated that DL-3-n-butylphthalide (NBP) can modulate GS function and improve cognitive performance in AD animal models. However, the impact of dynamic PVS changes on NBP treatment efficacy in MCI remains unclear. This study aims to systematically evaluate whether the evolution of PVS affects the treatment response to NBP. **Methods:** This study included 91 patients with MCI who received NBP treatment. An improved Frangi filtering algorithm was used to automatically segment PVS in the white matter (WM), basal ganglia (BG), and hippocampus (HIP), extracting total number, total volume, and mean size. Based on whether the ADAS-Cog12 score decreased after treatment, participants were classified into responders (cognitive improvement) and non-responders. Univariate and multivariate logistic regression models were applied to investigate the impact of longitudinal changes in PVS on treatment response to NBP. In addition, baseline PVS burden was dichotomized using the upper quartile of total PVS count to define extensive versus non-extensive PVS burden. Logistic regression was then used to assess whether baseline PVS burden could serve as a stratification marker for treatment responsiveness. **Results:** An increase in the total count and total volume of PVS increased the likelihood of treatment improvement, which was limited to PVS in the white matter (WM-PVS). Specifically, each unit increase in the total count of WM-PVS was associated with a 1.3% increase in the likelihood of treatment improvement (OR = 1.013; 95% CI, 1.004-1.021; P = 0.002). Additionally, an increase in WM-PVS total volume was significantly associated

with improved treatment outcomes (OR = 1.633; 95% CI, 1.091-2.445; P = 0.017). Further stratified analysis based on baseline WM-PVS count revealed that in the non-extensive WM-PVS burden group, an increase in WM-PVS total count (OR = 1.010; 95% CI, 1.002-1.019; P = 0.009) and total volume (OR = 2.082; 95% CI, 1.135-3.819; P = 0.018) was significantly associated with NBP treatment response. However, in the extensive WM-PVS burden group, the dynamic changes in all PVS indicators did not show a significant impact on treatment efficacy (P > 0.05). **Conclusions:** This study found that longitudinal expansion of WM-PVS was closely associated with the therapeutic efficacy of NBP in patients with MCI, particularly among those with low baseline PVS burden. Quantitative PVS metrics may serve as potential biomarkers for treatment response, aiding in the identification of MCI patients more likely to benefit from NBP and supporting the development of precision intervention strategies. **Keywords:** Perivascular spaces, mild cognitive impairment, therapeutic efficacy. **Disclosures:** This study was supported by the National Key R&D Program of China (No. 2017YFC1310103), STI2030-Major Projects (No. 2021ZD0201802), and the General Program of the National Natural Science Foundation of China (No. 82471450). The authors declared no competing interests.

OC15- DIFFERENT STAGES OF ALZHEIMER'S DISEASE WITH PERIODONTITIS: CORRELATION OF ENHANCED INFLAMMATION AND COMPROMISED BLOOD-BRAIN BARRIER.

J.H. Li[1], T.H. Lian[1], J. Li[1], P. Guo[1], J. Qi[1], D.M. Luo[1], H. Yue[1], Z.J. Zheng[1], Z. Liu[1], F. Zhang[1], W. Zhang[1] *(1. Beijing Tiantan Hospital - Beijing (China))*

Background: Alzheimer's disease (AD) and periodontitis are prevalent among the elderly population. There is substantial evidence to suggest that inflammation plays a pivotal role in the aetiology of AD and periodontitis. Accordingly, the objective of this study was to examine the inflammatory mechanisms by which periodontitis may contribute to the development of Alzheimer's disease. **Methods:** A total of 138 AD patients were included and divided into two groups: the AD-periodontitis group (AD-P) and the AD-no periodontitis (AD-nP) group according to whether the patients were accompanied by periodontitis or not. Neuropsychological scales were used to evaluate the clinical symptoms of AD patients. Serum and cerebrospinal fluid (CSF) samples were collected and analyzed for inflammatory factors, AD biomarkers and blood-brain barrier indicators. The differences between the groups were compared and the relationship was analyzed. **Results:** Compared with the AD-nP group, the AD-P group had a higher tartar index, and the probing depth, clinical attachment loss, and number of teeth loss were more severe. The MMSE, MoCA, AVLT, and BNT scores of the AD-P group were significantly lower than AD-nP group, and the NPI, HAMA, and MAES scores were all significantly higher. There was a significant negative correlation between cognitive function and symptoms of periodontitis, while neuropsychiatric symptoms demonstrated a significant positive correlation with the number of teeth loss. In the serum, the H2O2 and TNF-α levels were significantly higher in the AD-P group compared to the AD-nP group. Furthermore, the H2O2 and NO levels were significantly positively correlated with probing depth in the AD-P group. Additionally, ·OH, TNF-α, and IL-1β were significantly positively correlated with clinical attachment loss. In the CSF, the levels of LRP1 and Aβ1-42 were found to be significantly lower in the AD-P group compared with the AD-nP group, and the levels of MMP -3, TNF-α and P-tau (T181) levels elevated. A significant positive correlation was observed between NO levels in the CSF and serum TNF-α and IL-1β levels. MMP-3 levels in the CSF of AD-P group demonstrated a significant positive correlation with serum NO and TNF-α levels, while LRP1 levels exhibited a significant negative correlation with serum IL-1β levels. Mediation analysis demonstrated that serum NO levels significantly mediated the correlation between periodontitis and MMP-3, and serum TNF-α levels also significantly mediated the correlation between periodontitis and MMP-3 (all P<0.05). **Conclusions:** AD patients with periodontitis exhibited inferior oral hygiene, more pronounced cognitive decline, and more severe neuropsychiatric symptoms with notable effects on memory, language, and apathy. AD patients with periodontitis had a more severe peripheral inflammatory response that mediated blood-brain barrier disruption and triggered an enhanced neuroinflammation, leading to increasing Aβ deposition and P-tau (T181), which exacerbated clinical symptoms in AD patients. In contrast, TNF-α levels were markedly elevated in both peripheral and central inflammatory responses, indicating that it may be a pivotal mediator in the inflammatory mechanism of periodontitis-associated Alzheimer's disease. **Keywords:** Alzheimer's disease, periodontitis, inflammatory response, blood-brain barrier. **Disclosures:** The authors declared no competing interests.

OC16- THE ASSOCIATIONS OF CEREBROSPINAL FLUID APOE AND C1Q WITH ALZHEIMER'S DISEASE BIOMARKERS.

Y. Lin[1], W. Zuoteng[1], T. Lan[1] *(1. Qingdao Municipal Hospital - Qingdao (China))*

Background: The roles of complement 1q (C1q) and Apolipoprotein E (ApoE) in driving Alzheimer's disease (AD) progression might be explained by their associations with neuroinflammation and AD pathology which were previously reported. **Objective:** We examined the associations of cerebrospinal fluid (CSF) C1q and ApoE with CSF neuroinflammatory biomarkers and AD core biomarkers, as well as explored whether C1q mediated the associations of CSF ApoE with thesebiomarkers. **Methods:** Here, we analyzed CSF proteomics data from Alzheimer's Disease Neuroimaging Initiative (ADNI) using two different ADNI proteomics datasets—SomaScan (n =579)and multiple reaction monitoring (MRM[n =207]). Linear regression analyses were conducted to explore the association of CSF ApoE and C1q. The mediation model and structural equation model (SEM) were conducted to explore the associations of ApoE and C1q with AD biomarkers. **Results:** Multiple linear regression showed that CSF ApoE was positively associated with CSF C1q in total participants and Alzheimer's continuum participants. Mediation analyses indicated that C1q mediated the associations of CSF ApoE with CSF T-tau, P-tau, sTREM2 and GFAP (mediation proportions range from 15.06 to 44.64%; all the p values < 0.05) but not with CSF amyloid-β and progranulin (PGRN). The SEM yielded similar results. **Conclusions:** Our findings suggest that C1q is linked to ApoE, and it mediates the associations of ApoE with T-tau, P-tau, sTREM2, GFAP, indicating C1q association with ApoE might be involved in AD progression.

OC22- SPATIAL DECREASE OF METABOTROPIC GLUTAMATE RECEPTOR 5 IN ALZHEIMER'S DISEASE IS ASSOCIATED WITH TAU PATHOLOGY.

Y. Wang[1], J. Wang[1], F. Xie[1], Y. Guan[1] (1. Department of Nuclear Medicine &PET Center, Huashan Hospital, Fudan University - Shanghai (China))

Objective: This longitudinal study investigates the dynamic changes in postsynaptic metabotropic glutamate receptor 5 (mGluR5) in Alzheimer's disease (AD) using 18F-PSS232 PET/MRI imaging. The primary aim is to analyze the relationship between mGluR5 and tau pathology, offering transformative insights into the fundamental mechanisms underlying synaptic dysfunction in AD. **Materials and Methods:** A cohort of 18 patients with cognitive impairment (Alzheimer's disease and mild cognitive impairment [MCI]) underwent 18F-PSS232 PET/MRI imaging at baseline and a 12-month follow-up. Among these, 10 participants also underwent 18F-MK6240 PET/CT imaging at baseline to assess tau pathology. Neuropsychological assessments included the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment-Basic (MoCA-B), Boston Naming Test (BNT), Animal Fluency Test (AFT), Symbol Trail Test (STT), Auditory Verbal Learning Test Long-Delayed Recall (AVLT LDR), and AVLT Recognition (AVLT REC). Region-of-interest (ROI) and voxel-based analyses were conducted to quantify regional mGluR5 distribution. Statistical analyses included Wilcoxon rank-sum tests, paired t-tests, and Spearman correlation analyses to evaluate longitudinal changes in mGluR5, as well as associations between mGluR5 distribution, tau pathology, and cognitive performance. **Results:** After the 12-month follow-up, a significant reduction in mGluR5 distribution was observed across multiple brain regions, including the hippocampus, frontal lobe, parietal lobe, posterior cingulate cortex (PCC), and precuneus. Baseline hippocampal tau deposition was significantly negatively correlated with changes in mGluR5 distribution in the hippocampus and medial temporal regions.Furthermore, baseline hippocampal mGluR5 levels were significantly positively correlated with changes in cognitive performance, as measured by MMSE, MoCA-B, and AFT scores. **Conclusions:** This longitudinal PET imaging study is the first to demonstrate that baseline tau protein levels can predict changes in mGluR5 distribution over time, highlighting a dynamic link between mGluR5 and tau pathology. Additionally, elevated baseline mGluR5 levels were closely associated with cognitive decline. These findings suggest that mGluR5 may serve as a promising therapeutic target in AD by modulating tau propagation, preserving synaptic function, and mitigating cognitive decline. Future studies are warranted to expand the sample size and extend the follow-up period to further elucidate the role of mGluR5 in AD progression and pathology.

OC23- DISTRIBUTION CHARACTERISTICS OF SYNAPTIC DENSITY IN DIFFERENT CLINICAL STAGES OF ALZHEIMER'S DISEASE AND ITS CORRELATION WITH COGNITION.

J. Wang[1], F. Xie[1] (1. Huashan Hospital, Fudan University - Shanghai (China))

Objective: To explore the distribution characters of synaptic density across different clinical stages of Alzheimer's Disease (AD) using 18F-SynVesT-1 Positron Emission Tomography (PET) and investigate the correlation between synaptic density and cognitive function. **Methods:** The study included 193 subjects, comprising 62 AD patients, 56 individuals with Mild Cognitive Impairment (MCI), and 75 normal controls (NC). All participants underwent 18F-SynVesT-1 PET/MRI scans to assess synaptic density, 18F-Florbetapir PET/CT scans to assess amyloid deposition, and neuropsychological tests for cognitive assessment. Group differences in synaptic density among AD, MCI, and NC groups were analyzed based on Volume of Interest (VOI) and voxel-wise analyses. The relationship between cognitive function and synaptic density was explored using partial correlation analyses at the VOI and voxel-wise levels. **Results:** Compared to the NC group, the AD group exhibited reduced synaptic density primarily in the medial temporal lobe and widespread neocortical regions. The MCI group showed decreased synaptic density localized to small portions of the medial temporal lobe, lateral temporal lobe, occipital lobe, and insula. The AD group had lower synaptic density than the MCI group, particularly in the lateral temporal lobe, small portions of the occipital lobe, medial temporal lobe, and insula. In the whole cohort and the AD group, scores from the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment-basic (MoCA-B) tests, reflecting overall cognitive status, were significantly positively correlated with synaptic density throughout the cortical regions. In the whole cohort, cognitive functions in the memory and language domains were positively correlated with synaptic density in the global cortex and all VOIs. In contrast, executive domain cognitive function showed a negative correlation with synaptic density in the global cortex and all VOIs. **Conclusions:** This study demonstrates that 18F-SynVesT-1 PET imaging can quantify changes in synaptic density across different clinical stages of AD. The reduction of synaptic density from NC to MCI to AD progresses gradually, starting from small portions of the medial temporal lobe, lateral temporal lobe, and insula and extending to widespread neocortical regions. Synaptic density is closely associated with overall cognitive status, positively correlated with cognitive functions in the memory and language domains, and negatively correlated with executive domain cognitive function.

OC24- HIGHER CSF STREM2 ATTENUATES APOE E4-RELATED RISK FOR AMYLOID PATHOLOGY IN COGNITIVELY INTACT ADULTS: THE CABLE STUDY.

Y.C. Wang[1], L. Tan[1] (1. Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China - (China))

Background: The triggering receptor expressed on myeloid cells 2 (TREM2) is a transmembrane protein found in microglia within the brain, and its soluble form (sTREM2) has been shown to reduce amyloid deposition. Whether elevated TREM2-mediated microglial activity decreases the risk of Alzheimer's disease (AD) is unclear. The aim of this study was to assess whether high cerebrospinal fluid (CSF) levels of sTREM2 attenuates the risk of APOE ε4-associated amyloid pathology. **Methods:** We included 877 cognitively intact subjects from the Chinese Alzheimer's Biomarker and LifestylE (CABLE) study, including APOE ε4 carriers (n = 136) and non-carriers (n = 741). The linear regression was used to examine the interaction effect between CSF sTREM2 levels and APOE ε4 status on CSF Aβ42 levels. Additionally, subgroup analyses stratified by sex and age were conducted. **Results:** Our main finding was that higher concentrations of CSF sTREM2 attenuated the effect of APOE ε4 carriage (i.e., the sTREM2 × APOE ε4 interaction) on amyloid deposition (β = -2.701e-05, p = 0.023). Subgroup analyses showed that the effect of interaction was still significant only in male (p = 0.041) and mid-life (p = 0.013) subgroups. **Conclusions:** Our study suggested that in cognitively intact individuals, changes in sTREM2 levels are associated with biomarkers of AD, and higher concentrations of CSF sTREM2

attenuated the risk of APOE ε4-related amyloid pathology. The identified role of the sTREM2 × APOE ε4 interaction in amyloid pathology offers new insights into potential strategies for AD prevention in APOE ε4 carriers. **Keywords:** Alzheimer's disease, amyloid deposition, APOE ε4, sTREM2, microglial activation. **Disclosures:** The authors declare no competing interests.

OC26- HIGHLY ACCURATE BLOOD TESTS FOR ALZHEIMER'S DISEASE: APPLICATIONS IN CLINICAL DIAGNOSIS, COMMUNITY SCREENING, AND CLINICAL TRIALS. S. Huang[1], J. Wang[1], Y.J. Wang[1] *(1. Daping Hospital - Chongqing (China))*

Cost-effective and accurate diagnostic tools are urgently needed to address the increasing burden of Alzheimer's disease (AD) and the recent approvals of anti-Aβ immunotherapies. Recent advancements in blood biomarker assays have demonstrated high performance in identifying Aβ and tau pathologies. In this study, we assessed the clinical utility of novel blood-based diagnostic tests implemented on the fully automated Lumipulse G platform in both a real-world clinical cohort and a community-based cohort, using Aβ and tau PET imaging as reference standards. Additionally, we evaluated the performance of these biomarkers in the early stages of AD and their potential application in clinical trials. A head-to-head comparison of these biomarkers was also conducted in a subcohort using multiple diagnostic platforms, including the Fujirebio Lumipulse G1200, Quanterix Simoa HD-X, and Vazyme Shine i2910 platforms. These biomarkers were compared against the clinically established and FDA-approved Lumipulse CSF Aβ42/40 assay. Plasma p-tau217 and p-tau217/Aβ42 demonstrated outstanding diagnostic performance, with area under the curve (AUC) values ranging from 0.940–0.960 and 0.935–0.972, respectively, for detecting abnormal Aβ and tau PET status. Their performance was clinically equivalent to that of CSF-based tests. The implementation of a two-cutoff approach further enhanced the diagnostic accuracy of plasma p-tau217 and p-tau217/Aβ42 tests, achieving an overall accuracy of approximately 95%, with both positive predictive value (PPV) and negative predictive value (NPV) exceeding 90%. The clinical application of these blood tests could significantly reduce dependence on PET imaging or CSF testing by 7%–13% in the clinical cohort and 27%–31% in the community cohort for the detection of AD pathology. This advancement would improve accessibility to accurate AD diagnosis and disease-modifying therapies, while simultaneously alleviating the global economic burden associated with the disease.

CLINICAL TRIALS: COGNITIVE AND FUNCTIONAL ENDPOINTS

OC03- EFFICACY AND SAFETY OF DL-3-N-BUTYLPHTHALIDE IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT: A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL (EBMCI STUDY). P. Wang[1], W. Sun[1], J. Gong[2], X. Han[1], C. Xu[1], H. Luan[1], S. Li[2], C. Wei[1] *(1. Innovation Center for Neurological Disorders and Department of Neurology, Xuanwu Hospital, Capital Medical University, National Clinical Research Center for Geriatric Diseases - Beijing (China), 2. College of Integrated Traditional Chinese and Western Medicine, Changchun University of Chinese Medicine - Changchun (China))*

Background: Monoclonal antibodies targeting brain Aβ plaques have shown promise in treating mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD). However, given the multiple pathogenic mechanisms involved in AD, the exploration of multi-target drugs is becoming increasingly important. The DL-3-n-butylphthalide (NBP), a multi-target neuroprotective drug, improving cognitive impairment in patient with vascular cognitive impairment has been confirmed. Since vascular cognitive impairment and AD-related cognitive impairment share many overlapping pathogenic mechanisms, the potential efficacy of NBP in patients with cognitive impairment due to AD remains unknown. This study aimed to evaluate the efficacy and safety of NBP in improving cognitive function in patients with MCI due to AD though a clinical randomized controlled trail. **Methods:** This is a 12-month, randomized, double-blind, placebo-controlled, multicentric trial. The trial included patients 50 to 85 years of age who had MCI due to AD, with a clinical dementia rating (CDR) score 0.5 and a mini-mental state examination (MMSE) score 20-26. Subjects were randomly assigned to receive either NBP soft capsule (200mg, three times a day), or equivalent dose of placebo for up to 12 months with an allocation ratio of 1:1. The primary endpoint is the change in 12-item Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog12; range, from 0 to 75, with lower scores indicating lesser severity) after 12 months. All patients were monitored for adverse events (AEs). **Results:** A total of 270 patients were enrolled, with 135 assigned to receive NBP soft capsule and 135 to receive placebo. The mean ADAS-cog score at baseline was approximately 12 in both groups. The change from baseline in the ADAS-cog score at 12 months was -1.30 with NBP and 0.73 with placebo (difference, -2.04 95% confidence interval [CI], -2.92 to -1.16; P=0.0001). Other mean differences between the two groups in the change from baseline favoring BNP were Immediate Recall score (difference, 1.53 95% CI, 0.47 to 2.59; P=0.0111). NBP-related AE were uncommon and primarily consisted of liver dysfunction and nausea symptoms. **Conclusions:** During the 12-month treatment period, NBP was effective for improving cognitive function in patients with MCI due to AD and exhibited good safety. Repurposing existing drugs and utilizing multi-target treatments show promising strategies for AD therapy. **Keywords:** Efficacy and safety, butylphthalide, mild cognitive impairment, randomized controlled trail. **Clinical Trial Registry:** ChiCTR1800018362; https://www. chictr.org.cn. **Data Deposition:** https://h6world.cn/website/login.html. **Disclosures:** This study was supported by the National Key R&D Program of China (No. 2017YFC1310103) and STI2030-Major Projects (No. 2021ZD0201802). The authors declared no competing interests.

OC06- EFFECTS AND DOSE-RESPONSE RELATIONS OF REMOTELY SUPERVISED AEROBIC TRAINING AND RESISTANCE TRAINING IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT: A THREE-ARM RANDOMISED CONTROLLED TRIAL.

X. Huang[1], S. Zhang[2], Y. Sun[3], Q. Wan[2] *(1. School of Nursing, Shanghai Jiao Tong University - Shanghai (China), 2. School of Nursing, Peking University - Beijing (China), 3. Department of Neurology, Peking University First Hospital - Beijing (China))*

Background: Although exercise is a promising approach to preventing cognitive decline, the evidence quality is low in people with mild cognitive impairment (MCI) given the inconsistent findings partly caused by the diversities of exercise types and exercise dose. Therefore, this study aims to further examine and compare the effects of remotely supervised aerobic exercise (AE) and resistance exercise (RE) interventions on cognition, as well as the potential dose-response relations in older adults with MCI. **Methods:** This study is a 6-month three-arm randomised controlled trial. Eligible participants (n=108) were recruited and randomised to the AE group, RE group or control (CON) group with a 1:1:1 ratio. Interventions were delivered at home with remote supervision. We evaluated participants' global cognition, memory, executive function, attention at baseline, 3 months (T1) and 6 months (T2) after randomisation. The average exercise dose per week for each participant was recorded. A linear mixed-effects model was adopted for data analyses after controlling for covariates. Tukey's method was used for adjusting for multiple comparisons. Linear regressions were performed to analyze the dose-effect relationships between the average exercise dose and the changes of cognitive functions within each group. We also tested the interaction effects between exercise dose and the potential moderators by multiple linear regressions. **Results:** 15 (13.89%) participants dropped out. The median compliance rates in the AE group and RE group were 67.31% and 93.27%, respectively. The median exercise doses per week were 2.76 (1.92, 3.72) (hours) for AE, and 3.00 (2.78, 3.39) (relative strength*sessions) for RE. After adjusting for covariates, the scores of the Alzheimer's Disease Assessment Scale-Cognitive subscale in the AE group decreased by 2.04 (95% confidence interval (CI) -3.41 to -0.67, t=-2.94, p=0.004) and 1.53 (95% CI -2.88 to -0.17, t=-2.22, p=0.028) points more than those in the CON group at T1 and T2, respectively. The effects of AE were still significant at T1 (estimate=-1.70, 95% CI -3.20 to -0.21, t=-2.69, p=0.021), but lost statistical significance at T2 after adjusting for multiple comparisons. As for executive function, the Stroop time interference in the RE group decreased by 11.76 s (95% CI -21.62 to -1.90, t=-2.81, p=0.015) more than that in the AE group at T2 after Tukey's adjustment. Linear regressions revealed significant or nearly significant dose-response relations between AE and global cognition (estimate=0.76, 95% CI [0.00,1.52], P=0.051), and between RE and processing speed (estimate=5.32, 95% CI [2.07,8.56], P=0.003). Age, body mass index, physical activity levels, and comorbidities at baseline were moderators of the relationship between AE dose and cognitive responses, while age, gender, body mass index, and sleep duration were moderators of the association between RE dose and cognitive responses. **Conclusions:** Both remotely supervised AE and RE programs are feasible in older adults with MCI. AE has positive effects on global cognition, and RE improves executive function. Positive dose-effect relations existed between distinct types of exercise and cognitive functions in older adults with MCI, which might be moderated by some factors, such as age, gender, body mass index, physical activity levels at baseline. **Keywords:** Mild cognitive impairment, aerobic exercise, resistance exercise, older adults.

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OC17- DISSECTING THE CLINICAL AND PATHOLOGICAL PROGNOSIS OF MCI PATIENTS WHO REVERTED TO NORMAL COGNITION: A LONGITUDINAL STUDY.

H.-H. Yu[1], L. Tan[1], W. Xu[1] *(1. Department of Neurology, Qingdao Municipal Hospital, Qingdao University, Qingdao, China)*

Background: Controversy existed in the prognosis of reversion from mild cognitive impairment (MCI) to normal cognition (NC). We aim to depict the prognostic characteristics of cognition, neuroimaging, and pathology biomarkers, as well as the risk of Alzheimer's disease (AD) dementia for MCI reverters. **Methods:** A total of 796 non-demented participants (mean age = 73.3 years, female = 54.4%, MCI = 55.7%), who were divided into MCI reverters (n = 109), stable MCI (n = 334), and stable NC (n = 353) based on two-year diagnosis changes, were subsequently followed up for six years. Cox proportional hazard regression models were applied to assess the AD dementia hazard. Linear mixed-effect models were used to evaluate the differences in changing rates of cognitive scores, brain volumes, brain metabolism, and AD biomarkers among three groups. **Results:** The 2-year MCI reversion rate was 18.17%. MCI reversion was associated with an 89.6% lower risk of AD dementia (HR = 0.104, 95% confidence interval = [0.033, 0.335], p < 0.001) than stable MCI. No significant difference in incident AD risk was found between MCI reverters and stable NC (p = 0.533). Compared to stable MCI, reverters exhibited slower decreases in cognitive performance (False Discovery Rate corrected p value [FDR-Q] < 0.050), brain volumes (FDR-Q < 0.050), brain metabolism (FDR-Q < 0.001), and levels of cerebrospinal fluid β-amyloid1–42 (FDR-Q = 0.008). The above-mentioned differences were not found between MCI reverters and stable NC (FDR-Q > 0.050). **Conclusions:** Reversion from MCI to NC predicts a favorable prognosis of pathological, neurodegenerative, and cognitive trajectory. **Keywords:** Mild cognitive impairment, reversion, dementia, prognosis, biomarker. **Disclosures:** The authors declared no competing interests.

VASCULAR CONTRIBUTION IN AD INCLUDING CEREBRAL SMALL VESSEL DISEASE (SVD)

LB18- THREE-DIMENSIONAL SPATIAL PROFILING REVEALS HETEROGENEITY OF CEREBRAL MICROVASCULATURE IN ALZHEIMER'S DISEASE AND CEREBRAL AMYLOID ANGIOPOPATHY.

P. Wang[1], D.B. Xia[2], H. Wang[2], Y.C. Zhu[1] (1. Peking Union Medical College Hospital - Beijing (China), 2. University of Science and Technology of China - Hefei (China))

Background: Emerging evidence suggests that cerebrovascular pathology may serve as a key pathological nexus linking Alzheimer's Disease (AD) and Cerebral Amyloid Angiopathy (CAA). This study aims to achieve three-dimensional reconstruction of microvascular-Aβ networks in centimeter-scale human brain tissues using triple immunofluorescence labeling and a high-throughput three-dimensional imaging system. **Methods:** A total of 10 donors were included: 3 AD cases, 4 CAA cases, and 3 non-AD/non-CAA controls [1]. A triple immunofluorescence co-labeling technique was employed to simultaneously visualize: microvascular basement membrane components (anti-Collagen IV), venous and capillary endothelial markers (anti-MCT1 [2]) and β-amyloid deposits (anti-Aβ17-42). Whole-sample scanning was performed using a high-throughput three-dimensional imaging system [3] to acquire synchronized three-dimensional colocalization data of microvascular network topology and β-amyloid pathological burden. Vascular and plaque features were extracted through segmentation and skeletonization of vessels and plaques. Key quantified parameters included: vascular metrics (average diameter, volume fraction, surface area, length density, branching point density, and tortuosity) and Aβ plaque metrics (density per unit volume, numerical density, and average diameter). Comparative analyses of microvascular and venular morphological parameters were conducted across brain regions (frontal cortex/subcortical white matter/periventricular white matter) and groups (AD/CAA/controls). Spearman rank correlation analysis was applied to evaluate pathological interactions between cortical microvascular network remodeling and Aβ plaque burden. **Results:** This study completed centimeter-level 3D reconstruction of 20 brain tissue regions from 10 human cases (10 frontal cortex specimens and 10 periventricular white matter specimens), acquiring 763 brain sections at 300 μm thickness. We observed significant spatial heterogeneity in microvascular networks across brain regions, with progressive structural changes from the cortex to white matter: vascular density gradually decreased from the cortex to deep white matter, while vessel diameter progressively increased. Cerebrovascular pathologies in AD and CAA exhibited distinct spatial heterogeneity. In the frontal cortex of AD/CAA groups, microvascular atrophy coexisted with venous degeneration. Furthermore, in the periventricular white matter, the AD group displayed a venous network remodeling pattern characterized by «high density–small diameter.» Stratified analysis of venular parameters (diameter >10 μm) revealed divergent venule-plaque interaction patterns between AD and CAA. In the AD group, Aβ plaques showed strong negative correlations with venular atrophy: plaque volume density was inversely associated with venular volume fraction (r = -0.93), length density (r = -0.83), average diameter (r = -0.78), and surface area (r = -0.87) (all q < 0.001). In contrast, the CAA group exhibited positive associations between plaque burden (volume/numerical density) and venular hyperplasia, including increased venular volume fraction, length density, diameter, surface area, and branching point density, suggesting Aβ may trigger compensatory venular proliferation. **Conclusions:** By integrating triple immunofluorescence labeling with the VISoR high-throughput 3D imaging system, this study systematically unveils the heterogeneity of cerebral microvascular networks in AD and CAA and their spatial interactions with Aβ deposits, providing three-dimensional spatial evidence for vascular pathological mechanisms in these diseases. Our findings highlight the potential role of venular remodeling in AD/CAA vascular pathology. **Keywords:** Microvascular network, venules, three-dimensional microscopic imaging, Alzheimer's disease, cerebral amyloid angiopathy. **Disclosures:** The authors declared no competing interests. **References:** 1. Qiu W Y, Zhang H L, Bao A M, et al. Standardized Operational Protocol for Human Brain Banking in China [J]. Neurosci Bull, 2019, 35(2): 270-276. 2. Cao Y, Ao D H, Ma C, et al. Immunoreactivity and a new staining method of monocarboxylate transporter 1 located in endothelial cells of cerebral vessels of human brain in distinguishing cerebral venules from arterioles [J]. Eur J Histochem, 2021, 65(s1). 3. Wang H, Zhu Q, Ding L, et al. Scalable volumetric imaging for ultrahigh-speed brain mapping at synaptic resolution [J]. Natl Sci Rev, 2019, 6(5): 982-992.

OC18- LONGITUDINAL AND CAUSAL ASSOCIATIONS BETWEEN PERIVASCULAR SPACES AND MILD COGNITIVE IMPAIRMENT.

R. Chen[1], P. Wang[2], X. Han[2], C. Wei[2] (1. School of Biological Science and Medical Engineering, Beihang University, Beijing, China. - Beijing (China), 2. Innovation Center for Neurological Disorders and Department of Neurology, Xuanwu Hospital, Capital Medical University, National Clinical Research Center for Geriatric Diseases, Beijing, China. - Beijing (China))

Background: Perivascular spaces (PVS) are fluid-filled channels involved in CSF–ISF exchange, contributing to waste clearance and immune regulation. Enlarged PVS (ePVS) are considered sensitive imaging markers of cerebral small vessel disease (CSVD) and may also represent a compensatory mechanism enhancing Aβ clearance. Although PVS burden has been linked to mild cognitive impairment (MCI), most studies rely on visual ratings, limiting assessment of longitudinal change. The relationship between PVS dynamics and cognitive progression remains unclear. This study utilized automated PVS segmentation techniques, combined with longitudinal observational data and two-sample Mendelian randomization (MR) analysis, to systematically investigate the potential role and causal relationship of regional PVS burden dynamics in the progression of MCI. **Methods:** This study included 87 patients with MCI, with MRI and FDG-PET imaging data collected at baseline and at a 12-month follow-up. An improved Frangi filtering algorithm was applied to automatically segment PVS in the white matter (WM), basal ganglia (BG), and hippocampus (HIP) regions. Quantitative and morphological features of PVS were extracted. Multivariable linear regression models were used to assess the longitudinal associations between PVS characteristics and cognitive scale scores, as well as structural and metabolic brain measures. In addition, MR analysis was performed using publicly available genome-wide association study (GWAS) datasets to explore potential causal relationships. **Results:** The increase in the total count and total volume of PVS in the white matter (WM-PVS) was positively correlated with the improvement in ADAS-Cog12 scores (total count: β = -0.226, P = 0.047; total volume: β = -0.242, P = 0.034) and the increase in cingulate gyrus volume (total count: β = 0.300, P =

0.004; total volume: $\beta = 0.346$, P = 0.001). However, the dynamic changes of PVS in the basal ganglia (BG-PVS) and hippocampus (HIP-PVS) showed no significant correlation with cognitive function or multimodal brain imaging changes. Moreover, MR analysis indicated that a high WM-PVS burden might reduce the risk of disease onset (IVW OR = 0.963; 95% CI, 0.929-0.999; P = 0.0428) and was causally associated with an increase in the cortical surface area of the middle temporal gyrus ($\beta = 0.223$, P = 1.29E-04). The causal relationship analysis for BG-PVS and HIP-PVS yielded similarly nonsignificant results. **Conclusions:** Longitudinal expansion of WM-PVS may be associated with cognitive improvement in patients with MCI and may causally reduce the risk of MCI onset, suggesting a potential neuroprotective adaptive response. **Keywords:** Perivascular spaces, mild cognitive impairment, longitudinal observational study, mendelian randomization. **Disclosures:** This study was supported by the National Key R&D Program of China (No. 2017YFC1310103), STI2030-Major Projects (No. 2021ZD0201802), and the General Program of the National Natural Science Foundation of China (No. 82471450). The authors declared no competing interests.

COGNITIVE ASSESSMENTS AND CLINICAL TRIALS

LB16- COMPILATION AND VALIDATION OF THE SIMPLIFIED CHINESE VERSION OF THE COHEN-MANSFIELD AGITATION INVENTORY AND ITS CORRELATION WITH BLOOD BIOMARKERS OF ALZHEIMER'S DISEASE.

B. Jin[1], A. Li[1], H. Liu[1] *(1. First Hospital of China Medical University - Shenyang (China))*

Objective: To compile a simplified Chinese version of the Cohen Mansfield Agitation Inventory (CMAI) based on the Chinese language and cultural background, verify its reliability and validity in the Alzheimer's disease (AD) population, validate the diagnostic efficacy of blood biomarkers based on chemiluminescence, and explore the correlation between agitation behavior and blood biomarkers in AD patients. **Method:** First, the Chinese short form of the CMAI scale (CMAI-cs) was compiled through direct translation, back-translation, and compilation based on the CMAI scale, adapted to Chinese culture. Patients with AD who met the revised diagnostic criteria of the National Institute of Aging (NIA) and Alzheimer's Association (AA) published in 2011 and exhibited agitated behaviors were selected to validate the reliability and validity of the CMAI-cs scale. Reliability testing primarily involved calculating and evaluating the internal consistency, test-retest reliability, and inter-rater reliability of the scale as a whole, as well as its components. Validity testing included: exploratory factor analysis for structural validity, expert review for content validity, and Spearman correlation coefficient for concurrent validity testing between the CMAI-cs and NPI scales. Second, the AD population with positive β-amyloid Positron Emission Tomography (Aβ-PET) and non-AD patients with cognitive impairment and negative Aβ-PET were selected to test the diagnostic efficacy of blood biomarkers based on the chemiluminescence method. Finally, Spearman analysis and Mann-Whitney U test were used to explore the correlation between AD blood biomarkers and the cognitive impairment and agitated behaviors of AD patients. **Results:** Firstly, the CMAI-cs scale was finally compiled into 18 items and validated with 47 cases of mild AD, 51 cases of moderate AD, and 45 cases of AD-related mild cognitive impairment (MCI). Among the included AD patients, the top three behaviors of agitation

were repeating the same words or asking the same question (86.01% of participants), inappropriate dressing or use of tools (72.03% of participants), and negative and pessimistic emotions (72.03% of participants). In the reliability analysis, the internal consistency of the Cronbach's alpha coefficient was 0.723, the test-retest reliability Spearman correlation coefficient was 0.879, and the inter-rater reliability intraclass correlation coefficient was 0.975, all of which indicated good reliability of the scale. In the validity analysis, the content validity index (CVI) of each item ranged from 0.779 to 1.000, and the S-CVI/Ave was 0.889, indicating good content validity. The concurrent validity results showed that the total score of CMAI-cs was significantly correlated with NPI (frequency × intensity) (r = 0.887, P < 0.001) and with NPI (distress to caregivers) (r = 0.793, P < 0.001), indicating good concurrent validity. A total of 167 patients were selected, including 114 AD patients with positive Aβ-PET and 53 non-AD cognitive impairment patients with negative Aβ-PET, to validate the diagnostic efficiency of blood biomarkers: p-Tau181 (AUC: 0.917, sensitivity: 0.876, specificity: 0.906, cutoff value: 2.62); p-Tau217 (AUC: 0.926, sensitivity: 0.866, specificity: 0.944, cutoff value: 3.27); Aβ42/40 (AUC: 0.869, sensitivity: 0.892, specificity: 0.870, cutoff value: 0.059). 3. Based on the above blood test results, 114 AD patients who met the new AD diagnostic and staging criteria proposed by NIA-AA in 2024 with agitation symptoms were selected for Spearman analysis. The results showed MMSE scores had moderate correlation with p-Tau181(p<0.001, r=0.446), and had moderate correlation with p-Tau217(p<0.001, r=0.505); MoCA scores had weak correlation with p-Tau181 (p<0.001, r=0.396), and had moderate correlation with p-Tau217(p<0.001, r=0.460). In addition, the Mann-Whitney U test revealed significant differences in CMAI-cs scores between the negative and positive Aβ42/40 groups (p < 0.05, z = 2.080). **Conclusions:** The CMAI-cs scale demonstrates good reliability and validity in detecting agitation in AD patients, with comprehensive items and concise content, making it suitable for assessing agitation in AD. The blood biomarker detection method used in this study, based on chemiluminescence, exhibits good diagnostic performance, significantly reducing detection costs, extending sample storage time, and may be more suitable for large-scale screening of AD potential risk populations compared to single-molecule methods. In addition, we found that the severity of cognitive impairment in AD patients is related to the levels of blood p-Tau181 and p-Tau217, indicating that blood p-Tau levels may, to some extent, reflect disease progression. The CMAI-cs score significantly increases when patients have plasma Aβ42/40 positivity, suggesting that plasma Aβ42/40 positivity may be associated with a higher likelihood of agitation. This study aims to provide a convenient and efficient tool for evaluating agitation in Chinese clinical AD patients and to gather clinical data on the correlation between agitation symptoms and blood biomarkers. We are looking forward to more extensive clinical applications and scientific exploration in the future. **Keywords:** Alzheimer's disease, agitation, CMAI, blood biomarkers.

BEHAVIORAL DISORDERS AND CLINICAL TRIALS

OC25- IRON METABOLISM CHANGES AND RELATED NEUROINFLAMMATION AND NEUROPATHOLOGICAL MECHANISMS OF OLFACTORY DYSFUNCTION IN PATIENTS WITH ALZHEIMER'S DISEASE. R. Wang[1], T. Lian[1], P. Guo[1], J. Li[1], J. Qi[1], J. Li[1], D. Luo[1], H. Yue[1], Z. Zheng[1], Z. Liu[1], F. Zhang[1], Y. Meng[1], W. Zhang[1,2] *(1. Department of Neurology, Beijing Tiantan Hospital, Capital Medical University - Beijing (China), 2. Center for Cognitive Neurology, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University - Beijing (China))*

Objective: Olfactory dysfunction (OD) is a common and important symptom in the early stage of Alzheimer's disease (AD). There was growing evidence that the metabolic disorder of iron was the key to the pathology of AD and played an important role in the onset and development of AD. Moreover, it was proved that iron and neuroinflammation interacted in a bidirectional relationship. Studies showed that abnormal iron metabolism was related to proteins involved in AD pathology such as amyloid-beta peptide and neurofibrillary tangles. However, there was no study on the relationship between OD and iron metabolism changes in AD patients. There was no study on the changes in iron metabolism in AD with OD (AD-OD) patients and their relationship with neuroinflammation and proteins involved in AD pathology. The specific role and potential mechanisms of abnormal iron metabolism in AD with OD (AD-OD) patients were still unclear. This study aimed to explore the iron metabolism changes in brain and the potential neuroinflammation and neuropathological mechanisms of AD-OD patients. **Methods:** AD patients who met the inclusion and exclusion criteria in Beijing Tiantan Hospital were collected continuously. Olfactory function of all patients was evaluated by the Sniffin' Sticks test and demographic information were recorded. AD patients were divided into AD-OD and AD with no OD (AD-nOD) groups according to overall olfactory function (TDI score) assessed by the Sniffin' Sticks test. All enrolled patients completed CSF collection. Anti-AD drugs were withdrawn for 12-14 hours prior to CSF collection. The levels of iron metabolism-related proteins, neuroinflammatory factors, and neuropathological biomarkers of AD in cerebrospinal fluid (CSF) from AD patients were measured by enzyme linked immunosorbent assay. **Results:** Of the total 116 patients with AD, 70 cases (60.3%) were diagnosed with OD and the other 46 cases were allocated to the AD-nOD group. The levels of ferritin, tumor necrosis factor-α (TNF-α), and phosphorylated tau (P-tau) (S199) in CSF from the AD-OD group was significantly higher than that from the AD-nOD group [2.253 (1.323, 3.491) ng/ml vs. 1.784 (1.004, 2.755) ng/ml, 7.806 (3.916, 18.928) pg/ml vs. 5.308 (3.083, 9.362) pg/ml, 9.591 (5.440, 15.310) pg/ml vs. 5.721 (4.170, 9.140) pg/ml, P <0.05]. The TDI score was significantly and negatively associated with the levels of ferritin, TNF-α, and P-tau (S199) in CSF in AD patients after adjusting for sex and age [B (95%CI)=-1.043 (-1.865, -0.221), -0.172 (-0.294, -0.050), -0.431 (-0.671, -0.192), P<0.05]. The ferritin level was significantly and positively correlated with the levels of P-tau (S199) and TNF-α in CSF from the AD-OD group (r=0.513, 0.267, P<0.05). The TNF-α level showed a significant and positively correlation to the P-tau (S199) level in CSF from the AD-OD group (r=0.513, P<0.05). Mediation analysis showed that the TNF-α mediated 29.2% of the effect of ferritin on P-tau (S199). **Conclusions:** AD-OD is correlated with increased levels of ferritin, TNF-α, and P-tau (S199) in CSF. In AD-OD patients, the ferritin, TNF-α, and P-tau (S199) in CSF mutually promote and work together to cause and exacerbate OD with TNF-α partially mediated of the effect of ferritin on P-tau (S199). **Keywords:** Alzheimer's disease, olfactory function, iron metabolism, neuroinflammation, neuropathology

NEW THERAPIES AND CLINICAL TRIALS

OC07- TREATMENT OF ALZHEIMER'S DISEASE WITH ORAL EDARAVONE--FROM PRECLINICAL STUDY TO PHASE II TRIAL (ERASE-AD). Y.J. Wang[1], J. Wang[1], X.F. Zhou[2] *(1. Daping Hospital, Third Military Medical University - Chongqing (China), 2. Shanghai Auzone Biotech - Shanghai (China))*

Background: Alzheimer's disease (AD) is a public health problem worldwide. It is imperative to develop safe, effective and affordable drugs to prevent and halt the progression of early AD. Amyloid beta (Abeta) is the main pathogenic factor initiating AD pathogenesis and oxidative stress (OS) plays a critical role in AD progression. **Method:** Edaravone, a free radical scavenger, was tested for its therapeutic potential in APP/PS1 AD mice. To facilitate its long-term use for AD, a solid dispersion formula of edaravone was developed and its bioavailability and safety were examined in animals and healthy volunteers. Based on the efficacy and safety data of preclinical and clinical studies, we designed a phase II clinical trial in patients with early symptomatic AD. **Results:** We discovered that a small molecule drug edaravone is effective in the treatment of AD in animal models by suppressing oxidative stress and inhibiting Abeta deposition [1]. For the efficacy trials in AD patients, we have developed oral tablet formula {2, 3} which is more compliant for patients with AD or other chronic diseases. We have performed phase I clinical trials for its safety and bioavailability in Australia, China and USA. The solid dispersion formula (TTYP-01 tablets) is stable in room temperature for at least 2 years and with NOAEL at 30 mg/kg in dogs for 6 months administration. Single ascending doses of oral intake from 30 mg to 240 mg in a phase I trial on adult volunteers in Australia showed an excellent tolerability without significant difference in adverse events between the control and TTYP-01 groups. Compared to intravenous dripping formula of 30 mg edaravone (Radicut), 60 mg TTYP-01 tablets taken orally showed 59% bioavailability. Similar results were obtained from repetitive dosages of TTYP-01 up to 120 mg bid for 7 days in Chinese volunteers with an excellent tolerability. In a cross-over bioequivalence study in 30 healthy volunteers compared with both Radicava and edaravone oral suspension (ORS), 90 mg of TTYP-01 (3 tables) is almost bioequivalent with 60 mg Radicava (iv) and 105 mg ORS without significant difference in adverse events. The positive preclinical and Phase I clinical data allow to move TTYP-01 into Phase II clinical trials in AD. In this study we will recruit 180 early symptomatic AD patients (MCI due to AD and mild AD dementia) at multiple centers from China, USA and Australia. Patients will be randomly treated with placebo, low dosage (TTYP-01 60 mg bid) and high dosage (90 mg bid) groups for 18 months and followed up every three months. The safety and tolerance and CDR-SB will be the primary end points and the changes of brain Abeta-PET, Tau-PET and MRI imaging will be the secondary end points at 18 months. We will also examine the correlation between the drug exposure and the efficacy. **Conclusions:** Edaravone solid dispersion formulation (TTYP-01) was efficacious in AD animal models and had an excellent tolerance and safety profile in healthy volunteers. A phase II clinical trial from multiple centers is designed to test its safety and dose-dependent efficacy

in 180 early AD patients. **Keywords:** Edaravone, Alzheimer's disease, disease-modifying drug, solid dispersion. Clinical trial registrations: CT-2020-CTN-01186-1; CTR20220495; NCT06107205. **Disclosure:** XF Zhou is an employee of Suzhou Auzone Biotech and one of the inventors of Edaravone solid dispersion patents. **References:** 1. Jiao SS et al., PNAS 2015; 112(16):5225-30. 2. Parikh A, Drug Des Devel Ther. 2018;12:2051-2069. 3. Parikh A et al Drug Des Devel Ther. 2018;12:2111-2128.

OC10- SODIUM OLIGOMANNATE IMPROVES COGNITIVE FUNCTION VIA REMODELING GUT MICROBIOME IN PATIENTS WITH MILD-TO-MODERATE ALZHEIMER'S DISEASE DEMENTIA. H. Chu[1], H. Chuyi[2], G. Qihao[1] *(1. Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine - Shanghai (China), 2. Renji Hospital, School of Medicine, Shanghai Jiaotong University - Shanghai (China))*

Background: Sodium oligomannate (GV-971) is approved for treating Alzheimer's disease (AD). Our ongoing real-world study including 700 AD patients has revealed that patients who had not previously received treatment with acetylcholinesterase inhibitors (AChEIs) and/or the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, showed significantly greater improvement in cognitive function compared to those with prior exposure to these medications. We hypothesize that conventional AD medications may alter gut microbiome composition, potentially affecting GV-971's ability to remodel the gut microbiome and improve cognitive function improvement. However, no research to date has investigated how GV-971 regulates the gut microbiome in patients with AD, especially biological AD.Here, we investigated whether and how previous exposure to conventional AD medications affects GV-971's therapeutic effects. **Methods:** Participants according with the clinical and biological diagnostic criteria of mild-to-moderate AD were enrolled in a 48-week study, divided into Naive (n=7) and Non-Naive groups (previously treated with acetylcholinesterase inhibitors and/or memantine; n=41). Participants were further stratified into GV-971 responsive and non-responsive subgroups based on changes in Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) 11 scores. We analyzed cognitive function and activities of daily living. Also, the gut microbiome composition in each subgroup at baseline and follow-up visits was measured through 16S rRNA sequencing. The short-chain fatty acid (SCFA) production was tested by microbiota in vitro culture. Moreover, the 18F-florbetapir PET scan was performed to assess the brain Aβ burden. **Results:** GV-971 showed higher response rates in naive versus non-naive patients (57.1% vs 33.3% at 48 weeks), with better cognitive improvement (ADAS-Cog 11 change: -0.9±4.0 vs. 3.6±6.30, p < 0.05). At baseline, naive patients exhibited higher abundance of beneficial bacteria, particularly SCFA producers. After GV-971 treatment, responders showed predominant increases in beneficial microbiota, especially SCFA-producing bacteria, such as Turicibacter, Clostridium_sensu_stricto_1, Intestinibacter, Collinsella stercoris and Romboutsia ilealis, while non-responders developed conditionally pathogenic bacteria, such as Streptococcus oralis and Streptococcus anginosus. In vitro culture studies demonstrated that GV-971 significantly increased SCFAs such as acetic acid, propionic acid and butyric acid only in Naive group microbiota. Improved cognitive outcomes corresponded with reduced Aβ deposition in the brain regions including prefrontal lobe, parietal lobe, temporal lobe, posterior cingulate and precuneus, particularly in Naive patients. **Conclusions:**

These findings reveal that prior exposure to conventional AD medications influences GV-971's efficacy through gut microbiome-dependent mechanisms, with treatment-naive status associated with better microbiome profiles and treatment outcomes. Our results suggest potential benefits of using GV-971 as initial therapy and highlight how treatment sequencing affects gut microbiome-mediated drug efficacy in AD management. **Keywords:** Sodium oligomannate, GV-971, Alzheimer's disease, gut microbiome, short-chain fatty acid, 16S rRNA sequencing. **Disclosures:** The authors declared no competing interests.

PRE-CLINICAL TRIALS/TRANSLATIONAL RESEARCH FOR ALZHEIMER DRUG DEVELOPMENT INTERVENTIONS

LB10- RBM8A PROMOTES MICROGLIAL SURVIVAL AND REDUCE Aβ DEPOSITION VIA WNT/B-CATENIN SIGNALING ACTIVATION IN ALZHEIMER'S DISEASES. T. Cao[1], Q. Huang[1], W. Song[1], Y. Xie[1], C. Zou[1], D. Zou[1] *(1. The Second Affiliated Hospital of Guangxi Medical University - Nanning (China))*

Background: Excessive β-amyloid (Aβ) deposition in brain is the hallmark pathological feature of Alzheimer's disease (AD). Our previous studies demonstrated decreased expression of RNA Binding Motif Protein 8A (RBM8A) in AD patient brains. Furthermore, we found microglial activation were suppressed when RBM8A was knockdown. However, the specific mechanistic role of RBM8A in regulating microglial function during AD progression remains unclear. Therefore, the study mainly explores the neuroprotective effect of RBM8A, aiming to provide theoretical basis for early AD intervention and treatment. **Methods:** Firstly, we established lentivirus-mediated RBM8A knockdown and overexpression models in primary microglia. Then we tested the microglial proliferation and apoptosis using flow cytometry (FCM), cell cycle analysis, 5-ethynyl-2'-deoxyuridine (EdU) staining, and cell counting kit8 (CCK8). Secondly, by establishing an organotypic hippocampal slice culture model, we compared the microglial Aβ internalization efficiency between wild-type mice and RBM8A-overexpressing mice by immunofluorescence (IF). To further elucidate the underlying molecular mechanism of RBM8A on microglial activation, we treated RBM8A-overexpressing primary microglia with Wnt pathway inhibitor LF3, and tested the protein expression of β-catenin, C-Myc, Cyclin D1, Survivin and Bcl-2 using Western Blot (WB). Finally, we evaluated TCF/LEF transcriptional activity by dual-luciferase reporter assay, and further tested the microglial proliferation and apoptosis using FCM, cell cycle analysis, EdU and CCK8 again. **Results:** Firstly, at the cellular level, RBM8A overexpression in microglia significantly reduced apoptosis and enhanced proliferation, whereas RBM8A knockdown exerted opposite effects, increasing apoptosis while suppressing proliferative activity. These findings demonstrate that RBM8A expression levels positively promote microglial viability and activation. Secondly, at the tissue level, RBM8A-overexpression mice exhibited significantly reduced Aβ deposition in hippocampus region compared with control group. Thirdly, RBM8A overexpression in microglia enhanced TCF/LEF transcriptional activity and increased the protein expression of β-catenin, C-Myc, Cyclin D1, Survivin and Bcl-2. Finally, RBM8A overexpression in microglia significantly increased its apoptosis and suppressed the proliferation while treating with Wnt pathway inhibitor LF3.

At the same time, the level of protein expression of β-catenin, C-Myc, Cyclin D1, Survivin and Bcl-2 were decreased. **Conclusions:** Our study demonstrates that RBM8A promotes microglial viability and activation and reduces Aβ deposition through the activation of Wnt/β-catenin signal pathway. These findings providing new theoretical basis and potential therapeutic target for precision medicine approaches in AD. **Keywords:** Alzheimer's disease, RBM8A, microglia, Wnt signal pathway. **Disclosures:** The study received grants from the National Natural Science Foundation of China (82460267), the Joint Project on Regional High-Incidence Diseases Research of Guangxi Natural Science Foundation(2024GXNSFDA010001). The authors declared no competing interests.

LB17 - PRELIMINARY SAFETY AND BASELINE CHARACTERISTICS OF LECANEMAB IN ALZHEIMER'S DISEASE: A REAL-WORLD, MULTI-CENTER OBSERVATIONAL COHORT STUDY IN CHINA.

L. Leng[1], Z. Liao[2], P. Lu[3], Y. Sun[1], Q. Weng[4], W. Fan[5], H. Zhu[6], W. Wu[7], P. Liu[1], X. Liu[1], K. Zhang[1], W. Wang[1], B. Luo[8], Z. Wang[9], G. Peng[1] *(1. Department of Neurology, the First Affiliated Hospital, Zhejiang University School of Medicine - Hangzhou (China), 2. Department of Psychiatry, Zhejiang Provincial People's Hospital - Hangzhou (China), 3. Department of Neurology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine - Hangzhou (China), 4. Department of Neurology, The First Affiliated Hospital of Ningbo University - Ningbo (China), 5. Department of Neurology, the Ningbo No.2 Hospital - Ningbo (China), 6. Department of Neurology, Huzhou Central Hospital, the Affiliated Central Hospital of Huzhou University - Huzhou (China), 7. Department of Neurology, the Second Affiliated Hospital of Wenzhou Medical University - Wenzhou (China), 8. Department of Neurology, the First Affiliated Hospital, Zhejiang University School of Medicine - Hangzhou (China) - Hangzhou (China), 9. Department of Geriatrics, the First Affiliated Hospital of Wenzhou Medical University - Wenzhou (China))*

Background: Lecanemab is the Aβ monoclonal antibody to demonstrate significant slowing the cognitive decline in AD [1]. There is a lack of data regarding its efficacy and safety in the Chinese AD population. This study aims to evaluate baseline characteristics, preliminary safety, and potential of plasma biomarkers for early screening of AD in a Chinese cohort. **Methods:** This real-world, multi-center, observational study enrolled 190 patients with AD from eight centers in Zhejiang Province, who completed baseline assessments and received lecanemab treatment with close follow-up. **Results:** The study included 176 participants with early AD and 14 with moderate AD. In the early AD with a mean age of 68.04 years, a total of 124 participants (70.5%) were female. The majority (n=127, 72.2%) were junior high school education level or less. Cognitive assessments showed a mean MMSE score of 20.03, and a mean MoCA score of 14.93. APOE4 heterozygote was predominant (48.3%), and APOE4 homozygote was 11.9%. A total of 137 participants (77.8%) received lecanemab with conventional AD medications. The most common comorbidities were hypertension (31.8%), hypercholesterolemia (10.8%), and diabetes mellitus (14.2%). Logistic regression for distinguishing early AD from the Aβ negative cognitively unimpaired (Aβ-CU) populations showed that the model consisting p-Tau 217 independently provided better classification efficacy (area under the curve (AUC) =0.9983, P <0.0001). In the early AD, 29 (16.5%) participants experienced infusion-related reactions (IRR) after the first-dose lecanemab, and amyloid-related imaging abnormalities (ARIA) [2] were identified in 17 patients (9.7%), while 3 (21.4%) with IRR and none ARIA observed in the moderate AD. **Conclusions:** The real-world lecanemab treatment cohort shows unique characteristics including more females, lower educational level, and higher disease burden compared with the clinical trial cohort. Overall lecanemab exhibited a favorable safety profile. The plasma biomarker p-Tau 217 showed high accuracy in screening the early AD population, who were likely to benefit from lecanemab. **Keywords:** Alzheimer's disease, lecanemab, real-world, disease-modifying therapies. **Disclosures:** This work was supported by the Zhongguancun Foundation. They had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The authors declare no competing interests. **References:** 1. Van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med. 2023 Jan 5;388(1):9–21. doi:10.1056/nejmoa2212948. 2. Cogswell PM, Andrews TJ, Barakos JA, Barkhof F, Bash S, Benayoun MD, et al. Alzheimer Disease Anti-Amyloid Immunotherapies: Imaging Recommendations and Practice Considerations for Monitoring of Amyloid-Related Imaging Abnormalities. AJNR Am J Neuroradiol. 2025 Jan;46(1):24–32. doi:10.3174/ajnr.A8469

OC12- DE NOVO DESIGNED TFR1 BINDING PEPTIDE FOR DELIVERING THERAPEUTIC ANTIBODIES ACROSS BLOOD BRAIN BARRIER.

H. Wu[1], X. Zhang[1], Y. Qiu[1], F. Sheng[1], Y. Wu[1] *(1. ChainGen Bio - Shanghai (China))*

Background: Despite the approval of Aβ-clearing antibodies for Alzheimer's Disease (AD), their efficacy is significantly limited by poor penetration across the blood-brain barrier (BBB). To overcome this, TfR1 binders, including antibodies, antibodies fragments, and single-domain antibodies, have been extensively explored as BBB-crossing facilitators. Trontinemab, leveraging a Fab TfR binder, stands out as the first BBB-crossing antibody to enter and show promise in early-stage clinical trials. However, existing TfR1 binders often face challenges such as large size, poor protein expression, and reliance solely on N-terminal complementary determining regions (CDRs) for TfR1 binding. To address these limitations, we report a de novo designed TfR1-binding peptide that offers a small size, a differentiated paratope, optimal protein expression, and efficient delivery of Aβ-clearing antibodies across the BBB. **Methods:** We de novo designed over 200,000 TfR1-binding peptides using open-source algorithms and screened them via yeast display. A lead peptide of approximately 70 amino acids was selected and expressed either alone or as a antibody-peptide fusion protein. The binding epitope and paratope were precisely determined by HDX-MS and validated through ELISA. The brain transport capability of the antibody-peptide fusion protein was rigorously tested both in vitro using a transcytosis assay and in vivo in human TfR1 transgenic mice and non-human primates. **Results:** The lead peptide demonstrated single-digit nM binding affinity to the apical domain of human TfR1, exhibiting a desirable «fast-on, fast-off» kinetic profile. Uniquely, the peptide bound via its C-terminal in a novel beta extension conformation. The antibody-peptide fusion protein achieved high expression titers, while retaining both its hTfR1 binding affinity and the ability to bind and clear human Aβ plaque. Critically, intravenous injection of the antibody-peptide fusion protein in both human TfR1 transgenic mice and non-human primates resulted in substantial parenchymal delivery. **Conclusions:** Our de novo designed TfR1-binding peptide presents a compelling alternative approach for delivering therapeutic antibodies across the BBB.

This peptide offers advantages including smaller size, ease of protein engineering, flexibility in epitope/paratope choices, optimal developability, and superior parenchymal delivery efficiency. These attributes underscore its potential to evolve into a platform technology for CNS drug delivery. **Keywords:** de novo design, peptide, TfR1, blood brain barrier (BBB), CNS, drug delivery. **Disclosures:** HW, XZ, YQ, FS and YW are employees and receive compensation and stock options from ChainGen Bio. The authors declared no competing interests.

OC20- ASSOCIATION BETWEEN MULTIMORBIDITY AND LONGITUDINAL BRAIN AB DEPOSITION IN ALZHEIMER'S DISEASE. X.L. Bu[1], Y.J. Wang[1] *(1. Daping Hospital, Third Military Medical University - Chongqing (China))*

Aims: Increasing studies showed that multiple systemic comorbidities were associated with Alzheimer's disease (AD) and dementia risk. However, whether multimorbidity accelerates brain beta-amyloid (Aβ) deposition, the molecular driver of AD, in humans remains largely unknown. To investigate whether participants with higher comorbidity burden are associated with faster rates of brain Aβ accumulation, and provide human evidence to underlie the mechanism behind the increased risk of AD in individuals with high multimorbidity burden. **Methods:** We selected 435 brain Aβ-positive participants with available longitudinal Aβ-PET data (Aβ PET scans at 2 or more timepoints) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Multimorbidity is defined as any combination of chronic disease with at least one other disease in the same individual. Twenty-two chronic disorders were considered as a measure of the severity of multimorbidity. **Results:** Of a total 435 participants, there were 210 females (48.3%) and 225 males (51.7%), and the mean (SD) age was 74.6 (7.1) years. These participants had a mean follow-up of 3.9 years. Participants with hypertension, hyperlipidemia, atrial fibrillation, coronary heart disease, anemia, hearing loss, cancer, or depression presented faster rates of longitudinal Aβ accumulation in the brain during follow-up. After adjustment for age, sex, education level, APOE-ε4 status and cognitive diagnosis, individuals with a high or medium multimorbidity burden had faster rates of brain Aβ accumulation than individuals with a low multimorbidity burden. Moreover, both the central nervous system and peripheral system multimorbidity burdens were associated with longitudinal brain Aβ deposition. **Conclusions:** This longitudinal study provides the first demonstration that greater multimorbidity burden at baseline is associated with faster longitudinal brain Aβ accumulation. These results indicate that non-brain organ and tissue dysfunctions contribute to AD pathogenesis and may help researchers better understand AD pathogenesis and tailor interventions for AD from a systemic view.

POSTERS

CLINICAL TRIALS: METHODOLOGY

P01- DESIGN OF 50561-II-01: A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF 50561 TABLETS IN ALZHEIMER'S DISEASE PATIENTS.

M. Wu[1], R. Ni[1], X. Zhao[1], T. Wang[1], W. Ma[1] *(1. Beijing Joekai Biotechnology LLC, Synnex - Beijing (China))*

Background: We aim to investigate the efficacy and safety of 50561 tablets, a first-in-class small molecule for the treatment of mild to moderate Alzheimer's Disease (AD). The primary objective is to assess the preliminary efficacy of 50561 over 24 weeks, while the secondary objectives focus on safety, tolerability, and pharmacokinetics (PK). **Methods:** This randomized, double-blind, placebo-controlled study will enroll 60 participants. The study will enroll subjects with mild to moderate AD dementia (age 50-85, MMSE 11-25, CDR 1-2), in good general health, diagnosed with AD according to the 2011 NIA-AA criteria. Subjects will be randomly assigned to one of three groups—low-dose 50561, high-dose 50561, or placebo—in a 1:1:1 ratio. The study consists of screening (up to 2 weeks), lead-in (4-5 weeks), baseline (D-3 to D0), double-blind treatment (24 weeks), and safety follow-up (2 weeks). Primary and secondary efficacy endpoints include ADAS-cog/13, CDR-SB, MMSE, ADCS-ADL, and NPI scores. Safety and tolerability will be assessed with clinical and laboratory tests. PK of 50561 and its metabolite in plasma and CSF will be measured. Pharmacodynamic (PD) profile including inflammatory markers, Aβ, Tau, and Nfl in blood and CSF will also be evaluated, if feasible. An Independent Data Monitoring Committee (IDMC) will oversee the trial to ensure safety. **Results:** With measurable efficacy, safety, PK, and PD results, the study is well-positioned to provide proof of concept (PoC) for 50561's clinical impact, safety and drug exposure. **Conclusions:** This trial aims to establish PoC for 50561, offering insights into its dose-response relationship and safety profile, and provide evidence for future development. **Keywords:** Alzheimer's disease, Rac1 activity, phase II clinical trail. **Clinical Trial Registry:** NCT05811442. **Disclosures:** The authors declared no competing interests. **References:** 1. Wu W, Du S, Shi W, Liu Y, Hu Y, Xie Z, et al. Inhibition of Rac1-dependent forgetting alleviates memory deficits in animal models of Alzheimer's disease. Protein Cell. 2019;10(10):745-59.

P02- CLINICAL EVALUATION OF BLOOD-BASED ASSAYS FOR RAPID DETECTION OF AMYLOID-β PATHOLOGY IN ALZHEIMER'S DISEASE (CLEAR-AD).

X. Lv[1], S. Jiong[1] *(1. Department of Neurology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China - Hefei (China))*

Background: Blood-based biomarkers show promise in predicting Alzheimer's disease (AD) pathology and progression; however, inconsistencies in detection standards hinder clinical application. A head-to-head comparison of commercially available biomarkers is crucial for optimizing the clinical pathway for AD screening and diagnosis. **Method:** The CLEAR-AD study is a population-based prospective cohort study currently enrolling 400 participants across ten centers in China. The study includes cognitively normal controls, individuals with mild cognitive impairment (MCI) - categorized as amyloid-positive and amyloid-negative — as well as patients with dementia, also divided into amyloid-positive and amyloid-negative groups. All participants undergo amyloid PET scans using tracers such as AV1, AV45, and PIB. Blood samples are collected within three months prior to the PET scan or from existing samples collected after January 1, 2024, that meet quality standards. After collection, these samples are analyzed at a central laboratory under blinded conditions using multiple detection methods to measure plasma levels of Aβ40, Aβ42, t-tau, and p-tau181/217. The detection technologies included single-molecule immunoassay, digital immunoassay chips, magnetic particle chemiluminescence, and flow cytometry fluorescence. The objective is to assess the sensitivity and specificity of different plasma biomarker levels in predicting amyloid pathology confirmed by Aβ-PET. **Result:** The study uses Aβ-PET as the reference standard to evaluate the sensitivity and specificity of various AD plasma biomarkers across different detection methods in diagnosing amyloid pathology. The analysis included generating receiver operating characteristic (ROC) curves, determining optimal cut-off values, and developing a predictive model that integrates multiple biomarker parameters and clinical data. Results is considered statistically significant with a p-value of less than 0.05. **Conclusions:** CLEAR-AD study provided crucial data on the effectiveness of commercially available blood biomarkers for predicting amyloid pathology and inform the optimization of early AD screening in the Chinese population. The findings will guide future developments in diagnostic tools. **Keywords:** Alzheimer's disease, blood biomarkers, cerebral amyloid pathology, Aβ-PET, cognitive impairment, Chinese population

P03- FEASIBILITY OF USING INSTRUMENTAL ACTIVITIES OF DAILY LIVING (IADL) TO STAGE ALZHEIMER'S DISEASE PROGRESSION BY CROSSWALKING WITH MMSE.

Y. Wang[1], A.A. Tahami Monfared[2], Q. Zhang[2], J. Reisman[3], B. Mittler[4], D. Berlowitz[3], P. Morin[5], R. Zhang[2], W. Xia[5] *(1. Wentworth Institute of Technology - Boston (United States), 2. Eisai, Inc - Nutley (United States), 3. U Massachusetts - Lowell (United States), 4. UTHealth - San Antonio (United States), 5. Boston University - Boston (United States))*

Introduction: Clinical guidelines recommend MMSE or other cognitive screening instrument with a score compatible with early AD to be used for patient evaluation for anti-amyloid therapy (AAT). MMSE may exhibit a ceiling effect in early stages of disease and floor effects in advanced stages, limiting its utility as a standalone tool for longitudinal assessment of disease progression. The literature reports a strong correlation between MMSE and functional measures, however, MMSE does not assess function. This study aims to cross walk MMSE and IADL to expand the clinical tools to classify Alzheimer's disease severity, stage Alzheimer's progression, and support clinical trials and patient identification for AAT. **Methods:** Patients with mild cognitive impairment (MCI) or Alzheimer's dementia (AD) were identified in the United States Veteran's Affairs Healthcare System (2020-2024). Paired MMSE (range 0-30) and Lawton-IADL (range 0-8) scores that were ≤6 months apart were identified. Piece-wise linear regression with spline transformation and repeated measures analysis with mixed-effects were both performed, adjusting for patient demographics, consistent with prior research. **Results:** The study sample (N=2,609) had a mean age of 81.1 years (97.9% men, 14.9% black, and 30.5% Hispanic). The most common comorbidity was hypertension (79.8%). The MMSE and IADL score distributions trended with different patterns. Functional

deterioration appears to accelerate after MCI staged by MMSE. IADL scores corresponding to mild AD had the greatest variability (widest score range). IADL scores corresponding to severe AD had a skewed distribution with outliers, suggesting retained function among a few patients despite severe MMSE scores. Five regression slopes were estimated using a spline transformation corresponding to each MMSE cut-off score to allow robust estimation of variations in slopes. Projected IADL scores declined linearly between MMSE-staged MCI to moderate AD (P<0.01), indicated by comparable slopes (0.16-0.18) corresponding to these stages. MMSE <13 was not associated with continued declines in projected IADL (β=0.02, P=0.35), suggesting a severity ceiling of MMSE, namely, unable to detect or differentiate patients at the most severe end of IADL (0-3); likewise, projected IADL scores plateaued at MMSE $\geq$29 (β=0.06, P=0.75) suggested lacking patient differentiation with the high end of IADL scores (6-8). **Conclusions:** This study identified distinct IADL thresholds corresponding to clinical stages from normal to severe AD measured by MMSE. Among patients with MCI or mild AD, projected IADL scores (4.5-5.8) declined linearly with MMSE (MMSE scores 21-28), suggesting that IADL may be considered as an alternative to MMSE for identifying patients potentially eligible for AATs when MMSE is not available, or used alongside MMSE to provide additional information on patient status. Projected IADL scores did not reach <3 or >6 over the full MMSE score range, supporting the potential utility of IADL for assessing Alzheimer's disease progression over a broader severity range relative to MMSE. Overall, findings from the crosswalk between cognitive and functional testing suggest that IADL can provide information on disease staging, complementing cognitive screening to help guide specialist referral for AAT evaluation. AT, QZ, RZ are Employees of Eisai. WX receives funding support from Eisai for epidemiological research.

CLINICAL TRIALS: RESULTS

P04- RELATIONSHIP BETWEEN POST-TREATMENT AMYLOID LEVELS AND CLINICAL OUTCOMES IN TRAILBLAZER-ALZ 2 PHASE 3 CLINICAL TRIAL.
M. Lu[1], M.J. Kim[1], E. Collins[1], Y. Yokoi[1], D.A. Brooks[1], J. Sims[1], M.A. Mintun[1], S. Cai[2] *(1. Eli Lilly and Company, Indianapolis, USA - Indianapolis (United States), 2. Eli Lilly and Company, China - Shanghai (China))*

Background: Evaluate the association between amyloid reduction and clinical outcomes in participants with early symptomatic Alzheimer's disease (AD) following treatment with donanemab, an amyloid-targeting therapy. **Methods:** Data were from TRAILBLAZER-All 2 (NCT04437511), a phase 3 study of participants with early symptomatic AD (mild cognitive impairment/mild dementia) with amyloid and tau pathology based on positron emission tomography (PET) imaging. Participants were randomized 1:1 to receive donanemab or placebo intravenously every 4 weeks for 72 weeks, with outcomes assessed at 76 weeks. Presented post-hoc analyses include participants with baseline and at least one post-baseline assessment. Participants were classified into decile groups based on the lowest amyloid values (Centiloids) observed post - baseline. Mixed models using repeated measures estimated the 76-week least-square mean changes in the integrated Alzheimer's Disease Rating Scale (iADRS) and Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) for each decile group. Relationships between mean clinical changes and the median amyloid value from each decile group were

assessed using correlation analyses and bubble plots. **Results:** Analyses included 1582 participants, with n=158 or 159 in each decile group based on lowest observed post¬ baseline amyloid value. Donanemab-treated participants were mostly classified into decile groups with lower post¬ baseline amyloid burden compared to placebo participants. Median amyloid values correlated with 76-week least-square mean changes in both the iADRS and CDR-SB, with R-square values of 0.73 and 0.87, respectively. In general, lower observed amyloid burden correlated with slower decline on combined cognitive and functional assessments. **Conclusions:** These findings of strong relationships between post-treatment amyloid level and clinical benefit support the clinical utility of donanemab and the use of amyloid PET as a surrogate biomarker in amyloid-targeting therapies. **Keywords:** Alzheimer's disease, amyloid clearance, clinical outcomes. **Disclosures:** 1. This data was initially presented at International Conference on Alzheimer's and Parkinson's Diseases; Vienna, Austria, and Online; April 1-5, 2025. 2. Ming Lu, Min Jung Kim, Emily Collins, Yuma Yokoi, Dawn Brooks, John Sims, Mark Mintun are full-time employees and minor shareholders of Eli Lilly and Company.

P06- A HIGHLY SENSITIVE EARLY DIAGNOSTIC REAGENT FOR ALZHEIMER'S DISEASE SUITABLE FOR CONSUMERS TO SELF-TEST.
L. Shen[1] *(1. AILEX (Hunan) Medical Equipment Co.,Ltd. - Changsha (China))*

Objective: Alzheimer's Disease (AD) is a chronic and progressive neurodegenerative disease, accounting for 60%-80% of cases of senile dementia. Its main characteristics are the abnormal deposition of β-amyloid protein in the brain to form plaques, and the excessive phosphorylation of tau protein leading to neurofibrillary tangles, which trigger neuronal death and brain atrophy. AD places a heavy economic and psychological burden on both families and society. Early diagnosis enables patients to receive early intervention, which can delay the development of AD by 5-10 years, reduce the risk of complications, and alleviate the burden on families and society. Therefore, we are committed to developing an AD detection product suitable for consumers to self-test at home (Registration certificate number 20252400387), characterized by high sensitivity and high specificity, Can be used for early assessment of the risk of AD dementia and mild cognitive impairment, providing auxiliary information for physicians in diagnosing Alzheimer's disease in clinical practice. **Methods:** Human urine was used as the detection sample, and β1-42, β1-40 and Aβ oligomers were used as detection markers. The lateral flow immunochromatography method based on the double-antibody sandwich was adopted as the detection method. Through project cooperation with the Department of Geriatrics of Shanghai Sixth People's Hospital, a large number of AD patient samples at different stages were used for verification, and the process was continuously optimized and adjusted to finally determine the appropriate detection limit. At the same time, diets, medications, etc. that might cause interference were screened out through the design of interference experiments. And the anti-interference design was carried out by adjusting the antibody coating concentration of the reagent, the pH environment of the sample pad, and the ion concentration. The situation of false positives caused by interference was greatly reduced. Finally, the stability of the reagent was predicted through a thermal acceleration experiment. In addition, through testing 228 individuals aged 60 and above, the results showed characteristics consistent

with epidemiology. **Results:** By comparing with 60 samples diagnosed by Aβ-PET in Shanghai Sixth People's Hospital, the sensitivity of the comparison results was 75%; the specificity was 87.5%; and the accuracy was 83.3%;By comparing with 96 samples diagnosed by MoCA Scale in Shanghai Sixth People's Hospital, the sensitivity of the comparison results was 82.93%; the specificity was 83.64%; and the accuracy was 83.3%. Through the clinical trials carried out in Shaoxing People's Hospital and Luoyang First People's Hospital, a total of 384 samples were tested by comparing with the results of scales such as MoCA. The sensitivity of the results was 89.06%; the specificity was 91.15%; and the accuracy was 90.10%. At the same time, through the national standard substance (GBW09875), the minimum detection limit of β1-42 of our company's reagent was determined to be 65pg/ml. In the interference experiment, we found that when people consume some foods, such as vegetables or fruits with high VC content, their metabolites will make the urine more acidic, resulting in false positive situations. We adjusted the pH environment of the sample pad to keep the pH at 7.0~7.4 in most cases, reducing the false positive rate by 91%. In addition, we found that increasing the ion concentration in the sample pad can reduce the false positive rate. When 0.9% NaCl was added to the sample pad, the false positive rate was reduced by 71%. The test results of 228 subjects are shown in Table 1 below. In the thermal acceleration experiment, after the reagent was thermally accelerated at 45°C for 35 days, the reagent had good stability. **Conclusions:** In this study, we developed a lateral flow immunochromatography product with high sensitivity and high specificity, which can be used for early screening of Alzheimer's disease and self-testing at home, and the reagent has good anti-interference ability.

P08- PRELIMINARY STUDY ON THE EFFECTS OF LECANEMAB THERAPY ON MOOD DISORDERS IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE. Y. Chang[1], Y. Cao[2], X. Liu[1], X. Li[3], H. Li[4], H. Qian[4], J. Jia[5], R. Wang[1] *(1. Department of Nuclear Medicine, the First Medical Centre, Chinese PLA General Hospital - Beijing (China), 2. Central Research Institute, United Imaging Healthcare Group Co, Ltd - Beijing (China), 3. Department of Cadres' Outpatient, The First Medical Center of Chinese PLA General Hospital - Beijing (China), 4. Department of Neurology, the Third Medical Centre, Chinese PLA General Hospital - Beijing (China), 5. Institute of Geriatrics, National Clinical Research Center of Geriatrics Disease, the Second Medical Center of PLA General Hospital - Beijing (China))*

Background: Alzheimer's disease (AD) and its precursor, mild cognitive impairment (MCI), are characterized not only by cognitive decline but also by frequent neuropsychiatric symptoms, including mood disorders like depression and anxiety1. The accumulation of amyloid-beta (Aβ) plaques is a core pathological feature of AD. Lecanemab, a monoclonal antibody targeting Aβ protofibrils, has demonstrated efficacy in reducing brain Aβ burden and slowing cognitive decline in early AD 2. However, its specific impact on comorbid mood symptoms remains less explored. Understanding whether lecanemab's anti-amyloid action translates to improvements in anxiety and depression is crucial for comprehensive patient care. This preliminary study aimed to evaluate the effects of standard-dose lecanemab therapy on mood disorder symptoms (specifically depression and anxiety) in patients with MCI or AD. Furthermore, it sought to investigate potential correlations between improvements in these symptoms and reductions

in regional Aβ deposition, as measured by positron emission tomography (PET). **Methods:** Fourteen subjects meeting the diagnostic criteria for MCI or AD were enrolled and received standard-dose lecanemab treatment. All subjects underwent baseline Aβ positron emission tomography (Aβ-PET), tau-PET, and comprehensive neuropsychological assessments, including the Hamilton Depression Rating Scale (HAMD), and Hamilton Anxiety Rating Scale (HAMA). Following six months of treatment, the mood disorder scales and Aβ-PET scans were repeated. Primary analyses included: 1) Comparison of pre- and post-treatment HAMD and HAMA scores; 2) Comparison of pre- and post-treatment standardized uptake value ratio (SUVR) changes—using cerebellar gray matter as the reference region—across brain regions defined by the Automated Anatomical Labeling (AAL) atlas based on Aβ-PET images; 3) Analysis of the correlation between changes in mood scale scores and changes in SUVR, focusing on brain regions exhibiting significant SUVR reduction during treatment. **Results:** After six months of treatment, only HAMA scores showed a significant decrease compared to baseline (p<0.05), while changes in HAMD, MMSE, and MoCA scores were not statistically significant (p>0.05). Lecanemab significantly reduced global brain Aβ burden, as measured by Centiloid values (CL) (p<0.05). However, there was no significant correlation between the degree of CL reduction and changes in HAMD, HAMA scores (p>0.05). Comparison of mean SUVR values within AAL-defined brain regions before and after treatment revealed significant SUVR reductions (p<0.05, FDR-corrected) in multiple regions following lecanemab treatment, including the prefrontal lobe, parietal lobe, posterior cingulate cortex/precuneus, and temporal lobe. Specifically, significant SUVR reductions were observed in the right hippocampus, bilateral amygdala, and right thalamus. The magnitude of SUVR reduction in these regions positively correlated with the decrease in HAMA scores (p<0.05). In contrast, changes in HAMD scores negatively correlated with SUVR reductions in the left calcarine cortex, bilateral cuneus, left postcentral gyrus, and bilateral paracentral lobule (p<0.05). **Conclusions:** This preliminary study suggests that lecanemab treatment significantly improves anxiety symptoms in patients with MCI/AD, while exhibiting limited efficacy in ameliorating depressive symptoms and overall neuropsychiatric symptoms. The anxiolytic effect may be closely associated with a reduction in Aβ pathological burden in key emotion-processing regions, such as the hippocampus, amygdala, and thalamus. **Keywords:** Lecanemab, mild cognitive impairment, anxiety symptoms, amyloid beta. **Disclosures:** The authors report no potential conflicts of interest relevant to the manuscript. **References:** 1. Forrester SN, et al. Am J Geriatr Psychiatry 2016 Feb;24(2):117-25. doi: 10.1016/j.jagp.2015.05.007. 2. van Dyck CH, et al. N Engl J Med 2023 Jan 5;388(1):9-21. doi: 10.1056/NEJMoa2212948.

P09- VALIDATION OF THE ROBUSTNESS OF BOOD-BASED BIOMARKERS FOR PREDICTING AMYLOID-β POSITIVITY IN CHINESE POPULATIONS. Y. Wang[1], C. Liang[1], P. Feng-Feng[1], Z. Zhen[1], H. Lin[1], M. Ya[1], G. Yi-Hui[1], G. Qi-Hao[1] *(1. Shanghai Sixth People's Hospital - Shanghai (China))*

Background: Blood-based biomarkers (BBBs) of Alzheimer's disease (AD) provide a promising alternative for detecting amyloid-β (Aβ) pathology. However, the lack of robust validation across different platforms and populations have impeded the widespread application of BBBs. **Objective:** We aimed to validating the robustness of BBBs for predicting Aβ positivity in Chinese populations. **Methods:** The whole

cohort (N=1,254) of AD clinical spectrum underwent cognitive assessments, cranial MRI scans, and Aβ PET scans. Sub-cohort 1 (N=504) underwent Simoa-based quantification of peripheral blood Aβ40, Aβ42, p-tau181, and NfL. Subcohort 2 (N=262) underwent additional single molecule assays (Simoa) based quantification of p-tau217 and GFAP. The whole cohorts (Subcohort 1, Subcohort 2, and the remaining population) were measured for the aforementioned six biomarkers (Aβ40, Aβ42, p-tau181, p-tau217, NfL, and GFAP) using light-initiated chemiluminescent assays (LiCA). We validated the robustness of BBBs for predicting Aβ positivity in Chinese populations, with a focus on p-tau217. **Results:** The BBBs of Aβ42/40, p-tau181, p-tau217, GFAP, and NfL have demonstrated remarkable robustness in identifying Aβ positivity within the Chinese population, as evidenced by both LiCA and Simoa assays. Among these markers, p-tau217 has emerged as the most accurate, performing robustness in both the whole cohort and cognitively normal individuals. Utilizing a dual-threshold approach for p-tau217, only 16% of samples fell into the intermediate range, thus requiring additional Aβ PET testing. **Conclusions:** BBBs have demonstrated good robustness in predicting Aβ positivity among the Chinese population, with plasma p-tau217 emerging as the most promising biomarker, exhibiting exceptional potential for detecting AD pathophysiology.

CLINICAL TRIALS: IMAGING

P11- REGIONAL CEREBRAL HYPOMETABOLISM AND PATHOLOGICAL HETEROGENEITY IN SPORADIC EARLY ONSET ALZHEIMER'S DISEASE: CHINA AGING AND NEURODEGENERATIVE INITIATIVE (CANDI).

Z. Zhu[1], N. Ming[1], L. Xinyi[2], P. Jiyong[2], G. Feng[2], P. Bo[1], S. Yong[2], S. Jiong[2] *(1. Department of Nuclear Medicine, The First Affiliated Hospital of USTC - Hefei (China), 2. Department of Neurology, The First Affiliated Hospital of USTC - Hefei (China))*

Introduction: Although EOAD patients constitute a minority of AD cases, they occupy pivotal familial and societal roles, frequently serving as primary household providers. The study aims to explore the underlying mechanism of sEOAD. **Methods:** This is a sub-study of the CANDI, which is a prospective cohort on AD and related cognitive disorders. It included 112 patients with sEOAD, 88 with late-onset AD, and 32 controls. Participants underwent biomarker assessment, structural MRI, and multi-probe PET/CT. PET images were analyzed by SPM12, and SUVRs were calculated. **Results:** In sEOAD, the cerebral hypometabolism pattern was observed in bilateral angular, precuneus, and posterior cingulate gyri. This pattern was associated with higher levels of tau pathology, especially in the bilateral angular and precuneus. **Discussion:** Regional cerebral hypometabolism, not Aβ plaques, strongly correlates with tau pathology in sEOAD, suggesting hypometabolism drives tau accumulation and underpins disease mechanisms.

P12- HEAD-TO-HEAD COMPARISON OF THE ASSOCIATIONS BETWEEN IMAGING AND PLASMA A-T-N BIOMARKERS WITH SYNAPTIC DENSITY IN ALZHEIMER'S DISEASE.

F. Xie[1], J. Wang[1] *(1. Huashan Hospital, Fudan University - Shanghai (China))*

Objective: To compare the associations between imaging and plasma A-T-N biomarkers with synaptic density assessed by 18F-SynVesT-1 PET/MRI in Alzheimer's disease. **Methods:** This study enrolled 193 participants: 62 with Alzheimer's disease (AD), 56 with mild cognitive impairment (MCI), and 75 normal controls (NC). All underwent 18F-SynVesT-1 PET/MRI scans to assess synaptic density and T1-weighted imaging for hippocampal volume. 18F-Florbetapir PET/CT and 18F-MK6240 PET/CT scans were used to evaluate amyloid-β and tau pathology, respectively. Cognitive function was assessed using neuropsychological tests. Plasma Aβ42, Aβ40, p-Tau181, and neurofilament light chain (NfL) levels were measured. Correlations between synaptic density and "A-T-N" biomarkers from imaging and plasma were analyzed at the volume of interest (VOI)and voxel levels, with comparisons made between the strengths of these correlations. **Results:** For «A», synaptic density in the medial temporal lobe was negatively correlated with global Aβ deposition (r = -0.272, p < 0.001) and positively correlated with plasma Aβ42/40 levels (r = 0.307, p < 0.001). In the AD group, only global Aβ deposition showed a negative correlation with medial temporal synaptic density (r = -0.284, p = 0.028). For «T», tau burden was negatively associated with synaptic density in the medial temporal lobe and widespread neocortex across the whole population, as well as within the AD and MCI groups. Plasma p-Tau181 levels were also negatively correlated with synaptic density in the medial temporal lobe and widespread neocortex in both the whole population and the NC group. For «N», hippocampal volume was positively correlated with synaptic density in the medial temporal lobe and widespread neocortex in the whole population and NC group, and showed positive correlations with synaptic density in both the lateral and medial temporal lobes in the AD and MCI groups. Plasma NfL levels were negatively correlated with synaptic density in the lateral temporal lobe across the whole population, and with medial temporal synaptic density as well. Notably, the correlation between synaptic density and hippocampal volume was stronger than that between synaptic density and plasma NfL levels. **Conclusions:** Synaptic density showed varying degrees of correlation with imaging and plasma A-T-N biomarkers, with stronger associations observed for imaging biomarkers. Among the A-T-N components, T-related biomarkers exhibited the strongest correlation with synaptic density. Given their accessibility, plasma biomarkers may serve as convenient surrogate indicators of synaptic density changes throughout the course of Alzheimer's disease in the future.

P13- IMPAIRED GLYMPHATIC FUNCTION IS ASSOCIATED WITH SYNAPTIC LOSS IN ALZHEIMER'S DISEASE.

K. He[1], J. Wang[1], W.Y. Wang[1], T.Y. Hu[1], Q. Huang[1], Y.H. Guan[1], F. Xie[1] *(1. Huashan Hospital Fudan University - Shanghai (China))*

Objective: To investigate the correlation between glymphatic impairment and synaptic loss and to explore whether this relationship is affected by amyloid-β (Aβ) pathology or reactive astrocytes in AD. **Methods:** We investigated the value of the diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) index as a biomarker of the glymphatic system. The participants underwent synaptic vesicle glycoprotein 2A (SV2A) and Aβ positron emission tomography (PET) imaging, and the plasma Aβ42/40 ratio and glial fibrillary acid protein (GFAP) levels were measured. Controlling for age, sex, years of education, and cognitive status, we investigated the relationships between glymphatic system impairment and synaptic density, along with other biomarkers. Mediation models were used to assess whether synaptic density mediates the relationship between the ALPS index and cognitive performance. **Results:** The ALPS index

was significantly correlated with synaptic loss. The ALPS index was also significantly positively associated with the residual SV2A PET standardized uptake value ratio (SUVr) in the hippocampus of participants with Aβ deposition or greater plasma GFAP concentrations. The correlation between hippocampal synaptic loss and centiloids was stronger in participants with a lower ALPS index. In addition, the ALPS index fully mediated the association between global cognition and hippocampal synaptic density. **Interpretation:** Glymphatic system impairment is significantly correlated with synaptic density loss. GFAP levels and cerebral Aβ plaques strengthened this association. Our results indicate that impaired glymphatic function reflects synaptic loss and is a promising biomarker for further monitoring of therapy in AD.

P15- CEREBRAL PERFUSION CORRELATES WITH AMYLOID DEPOSITION IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT DUE TO ALZHEIMER'S DISEASE.

N. Zhang[1] *(1. Tianjin Medical University General Hospital - Tianjin (China))*

Background: Changes in cerebral blood flow (CBF) may contribute to the initial stages of the pathophysiological process in patients with Alzheimer's disease (AD). Hypoperfusion has been observed in several brain regions in patients with mild cognitive impairment (MCI). However, the clinical significance of CBF changes in the early stages of AD is currently unclear. **Methods:** The differences in CBF and expression of the AD-related perfusion pattern (ADRP), established by spatial covariance analysis in our previous study, were compared between the PiB+ MCI group and the CUC group and between the PiB+ and PiB- MCI groups. The diagnostic accuracy and correlations with cognitive function scores for CBF and ADRP expression were further analyzed. **Results:** Hypoperfusion in the precuneus and posterior cingulate cortex (PCC) was more characteristic of patients with MCI due to AD than of those with non-AD-related MCI. The relative regional CBF value of the left precuneus best distinguished patients with MCI due to AD from CUCs and patients with MCI due to non-AD conditions. Cerebral perfusion, as indicated by either the relative regional CBF or the expression score of the ADRP, was strongly correlated with certain cognitive function scores. **Conclusions:** Here, we show that changes in CBF in the precuneus/PCC are promising MRI biomarkers for the identification of an AD etiology in patients with MCI. ASL, a noninvasive and cost-effective tool, has broad application prospects in the screening and early diagnosis of AD. **Keywords:** Mild cognitive impairment, Alzheimer's disease, cerebral blood flow, arterial spin labeling, AD-related perfusion pattern. **Disclosures:** The authors declare no conflicts of interest. **References:** 1. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. The Lancet Public health 2022;7:e105-e125. 2. Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's & dementia: the journal of the Alzheimer's Association 2018;14:535-562. 3. Govindpani K, McNamara LG, Smith NR, et al. Vascular Dysfunction in Alzheimer's Disease: A Prelude to the Pathological Process or a Consequence of It? Journal of clinical medicine 2019;8.

P16- DEEP ADAPTIVE LEARNING PREDICTS AND DIAGNOSES CSVD-RELATED COGNITIVE DECLINE USING RADIOMICS FROM T2-FLAIR: A MULTI-CENTRE STUDY.

L. Huang[1], Z. Li[2], K. He[2], Y. Xu[1] *(1. Nanjing Drum Tower Hospital - Nanjing (China), 2Nanjing University - Nanjing (China))*

Early identification of cerebral small vessel disease related cognitive impairment (CSVD-CI) is crucial for timely clinical intervention. We developed a Transformer-based deep learning model using white matter hyperintensity (WMH) radiomics features from T2-fluid-attenuated inversion recovery images to detect CSVD-CI. A total of 783 subjects (161 longitudinally followed) were enrolled from three centres for model development and external validation, using a domain adaptation strategy. The model achieved AUCs of 0.841 (training) and 0.859/0.749 (validation cohorts), outperforming conventional machine learning models. The gradient-weighted class activation mapping approach highlighted WMH textural features, particularly the logarithm-transformed gray level size zone matrix features, as key contributors. These features were significantly correlated with CSVD macro- and microstructural changes, mediated age-cognition relationships and predicted longitudinal cognitive decline. Our findings indicate that WMH radiomics features, reflecting CI-related biological changes in CSVD, combined with a Transformer-based deep learning model, constitute a feasible, automated, and non-invasive tool for CSVD-CI detection.

P17- LECANEMAB'S IMPACT ON BRAIN STRUCTURE: REVEALING THE DYNAMICS OF ALZHEIMER'S TREATMENT.

Y. Li[1], Y. Wang[1], A. Yang[1], L. Song[1], T. Gong[1], G. Wang[1] *(1. Shandong First Medical University Affiliated Provincial Hospital - Jinan (China))*

Objective: Lecanemab, a humanized monoclonal antibody, selectively targets aggregated β-amyloid (Aβ) and has been demonstrated to reduce Aβ deposition, thereby mitigating cognitive decline in the early stages of Alzheimer's disease (AD) [1]. Emerging evidence indicates that Aβ deposition not only induces neurotoxicity but also disrupts cerebrospinal fluid (CSF) circulation and glymphatic clearance [2], leading to impaired metabolic waste removal and accelerated neurodegeneration [3]. Consequently, Aβ-targeted therapies may offer additional neuroprotective benefits by modulating CSF dynamics beyond merely reducing amyloid burden. Nonetheless, the extent to which lecanemab affects CSF-related brain structures remains inadequately understood. Current assessments of AD treatments predominantly rely on clinical cognitive scales, which are subjective and often lack sensitivity to early structural changes [4]. Although amyloid positron emission tomography (PET) provides direct pathological insights, its high cost and associated radiation exposure limit its routine use. In contrast, magnetic resonance imaging (MRI) presents a safe, noninvasive, and reproducible method for objectively quantifying brain volumetric and microstructural changes, offering potential biomarkers for monitoring disease progression. This study aimed to longitudinally assess the effects of lecanemab on CSF-related structural changes, including total brain volume, PVS, and CP, in patients with AD using serial MRI, with the goal of identifying potential imaging biomarkers indicative of therapeutic response. **Methods:** In this study, we enrolled 11 patients diagnosed with amyloid-positive AD, confirmed through amyloid PET, who were administered lecanemab at a dosage of 10 mg/kg via intravenous infusion biweekly. Serial structural MRI was conducted at baseline

and at irregular intervals throughout a treatment duration of 3 to 9 months. A cohort of patients with MCI and early PD, who received lecanemab therapy, was compared with an age- and education-matched control group consisting of MCI and early AD patients who did not receive lecanemab treatment. The control group underwent longitudinal MRI assessments over a period of 6 to 12 months. MRI was conducted using 3 Tesla (3T) scanners in accordance with a standardized protocol, with subsequent scans performed on the same equipment to maintain consistency. Volume measurements were derived from T1-weighted three-dimensional gradient echo sequences. Segmentation of brain, CSF, and hippocampal volumes was executed utilizing FreeSurfer and FSL software, ensuring reproducibility of results. The PVS-VF was calculated through Frangi filtering, supplemented by manual corrections. Additionally, CP volume was segmented with high precision using a three-dimensional U-Net deep learning algorithm. Baseline volumes were adjusted relative to intracranial volume. Longitudinal alterations within the AD cohort were analyzed utilizing paired t-tests or Wilcoxon signed-rank tests, contingent upon the distribution of the data. Temporal dynamics across multiple time points were depicted through line plots. MCI cohort was subjected to an identical baseline-to-follow-up paired analysis. A two-sided p-value of less than 0.05 was deemed to indicate statistical significance. ARIA were assessed by two neuroradiologists in a blinded manner. **Results:** During the follow-up period of 3 to 9 months, patients receiving lecanemab treatment exhibited significant longitudinal volumetric changes in various brain structures (all p<0.05). Specifically, there was a decrease in total brain volume by $-6.43 \pm 3.01\%$ (p=0.0002), accompanied by an increase in CSF volume by $4.11 \pm 1.37\%$ (p=0.0085). PVS volume increased significantly by $6.75 \pm 2.13\%$ (p=0.0039), while CP volume exhibited a marked increase of $20.6 \pm 6.20\%$ (p=0.0146). Notably, volumes of the hippocampus and gray matter consistently decreased, whereas the CSF volume increased proportionally. The volume fraction of the PVS, particularly within the white matter, demonstrated a significant reduction over time, whereas CP volume showed a progressive increase throughout the treatment period. Conversely, the control group, monitored for 6–12 months without anti-amyloid therapy, did not exhibit significant longitudinal changes in these structural measures (all p>0.05). Additionally, no ARIA were detected in either group throughout the observation period. **Conclusions:** This pioneering longitudinal MRI investigation indicates that lecanemab treatment in Alzheimer's disease may influence cerebrospinal fluid-associated structures, potentially enhancing glymphatic clearance and thereby contributing to its neuroprotective effects. Although reductions in brain and hippocampal volumes were observed, likely attributable to the resolution of inflammation and alterations in cerebrospinal fluid homeostasis, initial cognitive improvements were modest. Volumetric measurements derived from structural MRI offer objective biomarkers for assessing early treatment effects and may serve as a complement to clinical scales. Furthermore, imaging-based predictive models have the potential to enhance personalized treatment evaluations and elucidate the mechanisms underlying anti-amyloid therapy in AD. **References:** 1. Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate Use Recommendations. J Prev Alzheimers Dis. 2023;10(3):362-377. doi: 10.14283/jpad.2023.30. 2. Plog BA, Nedergaard M. The Glymphatic System in Central Nervous System Health and Disease: Past, Present, and Future. Annu Rev Pathol. 2018;13:379-394. doi:10.1146/annurev-pathol-051217-111018. 3. Thal DR, Rüb

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P18- THE SUB-VOXEL QUANTITATIVE SUSCEPTIBILITY MAPPING (QSM) REVEALS IRON AND PATHOLOGICAL PROTEIN ALTERATIONS IN EARLY ALZHEIMER'S DISEASE WITH LECANEMAB TREATMENT. A. Yang[1], Y. Li[1], Y. Wang[2], L. Song[1], T. Gong[1] *(1. Shandong Provincial Hospital Affiliated to Shandong First Medical University - Jinan (China), 2. Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University - Jinan (China))*

Background: Alzheimer's disease (AD) involves Aβ plaques, tau tangles, and cholinergic neuron loss, with disrupted brain iron homeostasis playing a key role in disease progression. Lecanemab, an anti-Aβ monoclonal antibody, reduces Aβ burden in early AD. However, a non-invasive imaging biomarker for tracking treatment response is lacking. Quantitative Susceptibility Mapping (QSM) is an MRI technique that quantifies tissue magnetic susceptibility at the voxel level. In deep gray matter (DGM), susceptibility mainly reflects paramagnetic iron, making QSM highly sensitive to iron accumulation. In AD, elevated QSM signals have been reported in cortical regions [1]. However, pathological proteins such as amyloid-β and tau are diamagnetic, producing negative susceptibility values. As QSM reflects the net effect of both paramagnetic and diamagnetic sources [2], opposing contributions within the same voxel may confound interpretation. Therefore, in this study, we investigate the longitudinal alterations of paramagnetic component susceptibility (PCS) and the diamagnetic component susceptibility (DCS) in AD and mild cognitive impairment (MCI) patients with Lecanemab treatment using an advanced susceptibility separation method, hoping to monitor the iron and pathological protein perturbations separately in DGM and cortical regions. **Methods:** Eight patients with amyloid-positive AD or aMCI (mean age 66.1±8.3) received biweekly intravenous Lecanemab (10 mg/kg). Serial 3T MRI (T1, 3D-mGRE) was acquired over 1–9 months. QSM images were reconstructed from the phase and magnitude images of the 3D-mGRE data using the STI Suite software, and the PCS and |DCS| were generated by APART-QSM method [3]. The individual T1-weighted structural images were first normalized to the standard MNI space using the ANTs. Then, the first-echo magnitude images were rigidly co-registered to the corresponding T1 images, and then the QSM, PCS and |DCS| images were subsequently warped to the MNI space using the above combined transformations. Region of interest (ROI) were selected from a specific QSM Atlas [4], including 30 DGM and 94 cerebral cortical regions. The mean value of QSM, PCS and |DCS| in ROIs were extracted using fslmeants in FSL. The linear mixed effects (LME) model was used to evaluate the susceptibility source signal changes in DGM and cortical regions across time after Lecanemab treatment. The P values of β in LME model less than 0.05 were considered statistically significant. **Results:** For QSM, significant susceptibility reductions were observed in subcortical nuclei,

including the left Globus Pallidus (β = –0.00340, p = 0.044), right Substantia Nigra pars reticulata (β = –0.00382, p = 0.025), and left TL-Medial nucleus (β = –0.00208, p = 0.043), while an increase was detected in the right hippocampus (β = 0.00207, p = 0.005). PCS, representing iron deposition, also showed significant decreases in the left Globus Pallidus (β = –0.00415, p = 0.013) and right Substantia Nigra (β = –0.00468, p = 0.015), suggesting reduced iron load post-treatment. In contrast, |DCS|, associated with diamagnetic pathological proteins, showed increases in the right medial and anterior orbitofrontal cortices (β = 0.00208–0.00210, p < 0.05), and decreases in visual and temporal regions including the left calcarine, right lingual gyrus, and bilateral superior temporal cortices (β = –0.00030 to –0.00052, p < 0.05), reflecting region-specific dynamics of protein aggregation. **Conclusions:** Separated susceptibility components (PCS, |DCS|) provide complementary insights into iron and pathological protein changes during Lecanemab treatment. This approach may serve as a promising non-invasive imaging biomarker for therapeutic monitoring in AD. **Keywords:** Lecanemab, Alzheimer's disease (AD), Quantitative Susceptibility Mapping (QSM), iron deposition, pathological protein aggregation. **Disclosures:** The authors declared no competing interests. **References:** 1. Yang A, Du L, Gao W, Liu B, Chen Y, Wang Y, Liu X, Lv K, Zhang W, Xia H, Wu K, Ma G. Associations of cortical iron accumulation with cognition and cerebral atrophy in Alzheimer's disease. Quant Imaging Med Surg. 2022 Sep;12(9):4570-4586. doi: 10.21037/qims-22-7. 2. Gong NJ, Dibb R, Bulk M, van der Weerd L, Liu C. Imaging beta amyloid aggregation and iron accumulation in Alzheimer's disease using quantitative susceptibility mapping MRI. Neuroimage. 2019 May 1;191:176-185. doi: 10.1016/j.neuroimage.2019.02.019. 3. Li Z, Feng R, Liu Q, Feng J, Lao G, Zhang M, Li J, Zhang Y, Wei H. APART-QSM: An improved sub-voxel quantitative susceptibility mapping for susceptibility source separation using an iterative data fitting method. Neuroimage. 2023 Jul 1;274:120148. doi: 10.1016/j.neuroimage.2023.120148. 4. Zhang Y, Wei H, Cronin MJ, He N, Yan F, Liu C. Longitudinal atlas for normative human brain development and aging over the lifespan using quantitative susceptibility mapping. Neuroimage. 2018 May 1;171:176-189. doi: 10.1016/j.neuroimage.2018.01.008.

NEW AD BIOMARKERS IN CLINICAL TRIALS

P19- PERFORMANCE OF BLOOD BIOMARKERS IN INTERNAL JUGULAR VEIN FOR ALZHEIMER DISEASE PATHOLOGIES: THE DELTA STUDY. J. Wang[1], D.Y. Fan[1], S. Huang[1], Y.J. Wang[1] *(1. Daping Hospital - Chongqing (China))*

Background: Systemic factors confound blood tests for the diagnosis of Alzheimer disease (AD). The Delta study explored whether blood biomarkers from the vein proximal to the brain perform better in detecting cerebral AD pathologies. **Methods:** Blood was collected from the internal jugular vein (IJV) and median cubital vein (MCV) in the discovery (n=371) and validation (n=92) cohorts from 3 hospitals in China. AD biomarkers were measured with Lumipulse G and Simoa methods. Aβ and tau PET imaging and cerebrospinal fluid (CSF) biomarkers were used to evaluate brain pathologies. **Results:** The levels of Aβ42, Aβ40, p-tau217, p-tau181, GFAP and NfL were higher in the IJV than MCV and highly correlated between the two sites. IJV-Aβ42/40 had stronger correlations with Aβ PET Centiloids and tau PET meta-temporal SUVR than MCV-Aβ42/40. In detecting cerebral Aβ positivity, IJV-Aβ42/40 demonstrated a significantly higher accuracy (79.9% to 92.9% vs. 72.4% to 88.8%) and a lower percentage of uncertain individuals (17.8% to 54.5% vs. 31.3% to 70.1%) than MCV-Aβ42/40. Moreover, the diagnostic accuracy of Lumipulse G IJV-Aβ42/40 (88.2% to 92.9%) was statistically equivalent to that of MCV-p-tau217 (90.2% to 94.3%), although the intermediate percentage of IJV-Aβ42/40 was higher (17.8% to 34.0% vs. 0.7% to 17.5%) than MCV-p-tau217. These findings were verified in the validation cohort. **Discussion:** IJV-Aβ42/40 performs better than MCV-Aβ42/40 in detecting cerebral AD pathologies, offering a novel perspective to reduce the impacts of systemic factors and comorbidities on blood tests. (IJV-AD-24 ClinicalTrials.gov number, NCT06754254).

P20- BEYOND THE RETINA: CHOROIDAL BIOMARKERS AND AMYLOID BURDEN IN SUBJECTIVE COGNITIVE DECLINE. R. Gao[1], S. Rao[1], S. Cheng[1], Z. Gong[1], B. Bu[1], L. Ba[1], X. Sun[1], M. Zhang[1,2] *(1. Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology - Wuhan (China), 2. Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University - Taiyuan (China))*

Background: Subjective cognitive decline (SCD) serves as an initial symptom of preclinical Alzheimer's disease (AD). The accumulation of amyloid-beta (Aβ) is acknowledged as a critical risk factor for the eventual progression to mild cognitive impairment or dementia in individuals with SCD, highlighting the necessity for early detection and intervention. Previous studies have identified the retina and choriocapillaris as potential biomarkers for AD; however, these investigations have not thoroughly examined large and medium-sized choroidal vessels. Ultra-wide swept-source optical coherence tomography angiography (SS-OCTA), an innovative noninvasive imaging modality, facilitates rapid and precise quantitative assessment of retinal and choroidal boundaries and vasculature through dynamic scanning, encompassing large and medium-sized choroidal vessels [1]. This study aims to characterize the outer retinal and choroidal vasculature and structure in individuals with SCD, examine the correlation between altered choroidal vasculature parameters and amyloid burden, and the presence of the apolipoprotein E (APOE) ε4 allele in SCD participants, to identify potential ocular biomarkers for high-risk SCD screening. **Methods:** 57 individuals with SCD and 45 matched normal controls were enrolled. Ultra-wide SS-OCTA was employed to assess the thickness of the outer retina and choroid and the blood flow within the choriocapillaris and large, medium-sized choroidal vessels. 18F-Florbetapir positron emission tomography scans were performed to classify amyloid-positive-SCD (Aβ+ SCD) and amyloid-negative-SCD (Aβ-SCD) groups. Plasma Aβ42/40 and APOE ε4 genotypes were also measured. **Results:** Compared with normal controls, individuals with SCD exhibited a significant increase in the choroidal vessel index and a reduction in outer retinal thickness. The Aβ+ SCD group demonstrated an elevated choriocapillaris flow area relative to the Aβ- SCD group. Moreover, a negative correlation was observed between the choriocapillaris flow area and plasma Aβ42/40 levels in the SCD cohort. Among SCD participants, APOE ε4 carriers displayed increased choriocapillaris flow area and choroidal vessel volume compared to APOE ε4 non-carriers. **Conclusions:** Our findings provide intriguing insights into the relationship between amyloid pathology and changes in the choriocapillaris flow area. The choroid may serve as a potential biomarker for screening Aβ+ SCD. **Keywords:** Subjective cognitive decline, optical coherence tomography angiography, amyloid, choroid.

P21- RESEARCH PROGRESS IN ALZHEIMER'S DISEASE AND BONE-BRAIN AXISS. F. Zhang[1], W. Zhang[1] (*1. Department of Neurology, Beijing Tiantan Hospital, Capital Medical University - Beijing (China)*)

Objective: Understanding the relationship between AD and orthopedic diseases, bone-brain axis mechanisms of AD, and AD therapy by targeting bone-brain axis, in order to deepen the understanding of bone-brain communication, promote early diagnosis and explore new therapy for AD patients. **Materials and methods:** Pubmed, CNKI, Wanfang and other databases were searched to review the literature related to AD and orthopedic diseases such as osteoporosis and osteoarthritis, as well as the mechanisms of the bone-brain axis in AD, and the advances of the bone-brain axis in the treatment of AD. **Results:** 1. AD and osteoporosis: (1) AD mice showed significantly reduced osteogenic gene expression, decreased bone mineral density, and impaired bone remodeling; AD pathology and impaired learning memory were observed in the brain of mice that selectively expressed the APP mutant gene in osteoblasts. (2) AD and osteoporosis are risk factors for each other, and the association may be due to the related neuroanatomical basis of the two. 2. AD and Osteoarthritis: (1) Surgery-induced knee osteoarthritis accelerated β-amyloid deposition and neurodegeneration in the brain of AD mice. AD also aggravated the deterioration of articular cartilage and osteoarthritis symptoms in osteoarthritic rats. (2) Osteoarthritis patients have a significantly higher risk of developing AD, which is particularly evident in patients with concomitant pain. Osteoarthritis patients had faster deposition of β-amyloid and more tau production in the brain. 3. AD and rheumatoid arthritis: (1) Collagen-induced proliferation of microglial cells and astrocytes in the brain of rheumatoid arthritis rats was markedly enhanced, and blood-brain barrier permeability was enhanced. (2) Patients with rheumatoid arthritis had significantly decreased cognitive function compared with healthy controls, and the incidence of dementia due to AD was increased. 4. Bone-brain axis mechanism of AD: AD and bone tissues can engage in bone-brain communication through mechanisms such as the Wnt signaling pathway, peripheral and central inflammation, calcium imbalance, bone-secreted proteins (osteocalcin, osteopontin, and sclerostin), and extracellular vesicles. 5. Prospects of bone-brain axis in AD therapy: Calcium metabolism-related hormones (parathyroid hormone and vitamin D), bone-secreted proteins, and extracellular vesicles are expected to fulfill their potential in treating AD through the bone-brain axis. **Conclusions:** AD and orthopedic diseases, including osteoporosis, osteoarthritis and rheumatoid arthritis, are the risk factors for each other. AD and bone tissue can communicate through bone-brain by multiple mechanisms. Calcium metabolism-related hormones, bone-secreted proteins, and extracellular vesicles are expected to exert their therapeutic potential for AD through the bone-brain axis. In-depth clinical studies and randomized controlled trials should be conducted in multi-centers with large sample sizes, and the intervention window should be moved forward to the prodromal stage and even the pre-clinical stage of AD, so as to further explore the underlying mechanisms and therapeutic prospects of bone-brain axis in the occurrence and development of AD, and eventually realize the early prevention and treatment of AD.

P22- CONCORDANCE BETWEEN THE UPDATED ELECSYS CSF IMMUNOASSAYS AND AMYLOID PET FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE: FINDINGS FROM THE APOLLO STUDY. H. Schinke[1], Y. Feng[2], M. Jonsson[3], M. Gummesson[3], R. Nilsson[3], S. Gaupp[1], E. Manuilova[1], S. Mcilwrick[1], M. Carboni[4], E. Stomrud[5] (*1. Roche Diagnostics GmbH - Penzberg (Germany), 2. Roche Diagnostics (Shanghai) Ltd. - Shanghai (China), 3. Department of Clinical Chemistry and Pharmacology, Skåne University Hospital - Lund (Sweden), 4. Roche Diagnostics Int. AG - rotkreuz (Switzerland), 5. Clinical, Memory Research Unit, Department of Clinical Sciences Malmö, Lund University - Malmö (Sweden)*)

Background: Cerebrospinal fluid (CSF) biomarkers play a crucial role in the timely and accurate diagnosis of Alzheimer's disease (AD). The Elecsys® β-Amyloid(1-42) CSF II, Elecsys® Phospho-Tau(181P) CSF and Elecsys® total-Tau CSF (Roche Diagnostics Int. AG, Rotkreuz, Switzerland), are electrochemiluminescence immunoassays that use a quantitative sandwich principle to detect amyloid pathology. The aim of this study was to assess the concordance between amyloid status classification based on the Elecsys Abeta42 and its ratios with pTau and tTau, and the visual evaluation of amyloid positron electromagnetic tomography (PET) scans. **Methods:** The Apollo study is a prospective study designed to verify clinical performance of the updated Abeta42, pTau and tTau Elecsys assays in samples prepared according to the routine-use pre-analytical procedure [1]. Participants with a diagnosis of subjective cognitive decline (SCD) or mild cognitive impairment (MCI) were recruited from the Swedish BioFINDER-2 study, following the previously described eligibility criteria [2]. Eligible participants were required to have their amyloid status tested via Elecsys CSF assays and an amyloid PET scan. The main study objectives were to demonstrate concordance of the Elecsys CSF pTau/Abeta42 and tTau/Abeta42 ratios with visual amyloid PET. Cutoff values for biomarker classification were determined previously (pTau/Abeta42 ratio > 0.023, tTau/Abeta42 ratio > 0.28), and amyloid PET results were assessed by three blinded independent expert readers. The Acceptance Criterion for the point estimates of positive and negative percent agreement (PPA and NPA) was set at >0.75. Elecsys measurements were performed in fresh CSF samples. After the measurements, some samples were frozen at -20°C and re-measured to investigate the effect of freezing. **Results:** A total of 108 subjects were enrolled in the study, out of which 91 met the eligibility criteria. The mean age of the participants was 70.3 (43-90). At the time of the visit, 31 participants (34.1%) were diagnosed with MCI, and 41 (45.1%) were diagnosed with SCD. However, detailed information regarding the SCD or MCI status was missing for 19 subjects (20.9%). The primary analysis population consisted of 40 PET+ (44.0%) and 51 PET- (56.0%) subjects. For the Elecsys CSF pTau/Abeta42 ratio, the PPA was 0.800 (95% CI: 0.652-0.895) and the NPA was 0.882 (95% CI: 0.766-0.945). For the Elecsys CSF tTau/Abeta42 ratio, the PPA was 0.775 (95% CI: 0.625-0.877) and the NPA was 0.902 (95% CI: 0.790-0.957). 33 out of the 91 samples (36%) were frozen at -20°C and re-measured after 1-13 weeks of storage. In samples (n=6) stored 1-8 weeks, the concentration recoveries were within 100% ±10%. **Conclusions:** Both pTau/Abeta42 and tTau/Abeta42 ratios showed evident concordance

with amyloid PET. The new routine-use pre-analytical procedure, along with the adjusted cutoffs for the updated Elecsys assays, are recommended for use in clinical practice. CSF samples can be stored at -20°C for up to 8 weeks before testing, as they maintain good stability under such conditions. **Keywords:** Diagnosis, cerebrospinal fluid biomarkers, CSF, fluid biomarkers, amyloid pathology, clinical performance, sample stability, clinical practice. **Disclosures:** HS, EM and SM are full-time employees of Roche Diagnostics GmbH, Penzberg, Germany, and shareholders of F. Hoffmann-La Roche Ltd. YF is a full-time employee of Roche Diagnostics (Shanghai) Ltd., Shanghai, China. MFJ, MG, RN and ES have no conflicts of interest. SG is an employee of TRIGA-S GmbH contracted by Roche Diagnostics GmbH, Penzberg, Germany. MC is a full-time employee of Roche Diagnostics International Ltd, Rotkreuz, Switzerland and a shareholder of F. Hoffmann-La Roche Ltd. **References:** 1. Hansson O, et al. Alzheimers Dement (Amst). 2020;12(1):e12137. doi: 10.1002/dad2.12137. Erratum in: Alzheimers Dement (Amst). 2021;13(1):e12176. 2. The Swedish BioFINDER 2 Study (BioFINDER2). Study details, eligibility criteria. Accessible: https://classic.clinicaltrials.gov/ct2/show/NCT03174938 Last accessed: May 2024.

P23- EVALUATING FUTURE IVD PLASMA P-TAU 181 IMMUNOASSAYS ALONE AND IN COMBINATION WITH APOE4 IMMUNOASSAY FOR RULE OUT OF AMYLOID PATHOLOGY IN A MULTI-CENTER STUDY REFLECTIVE OF ROUTINE CLINICAL PRACTICE.

I. Kirste[1], S. Hortsch[2], S. Baez-Torres[3], M. Boada[4], M. Crane[5], K. Steen Frederiksen[6], K. Hanson[7], J. Liss[8], J. Norton[9], M. Suárez-Calvet[10], C. Ritchie[11], S. Rutrick[12], D. Watson[13], K. Yokum[14], Y. Feng[15] *(1. Roche Molecular Solutions - Indianapolis (United States), 2. Roche Diagnostics GmbH - Penzberg (Germany), 3. K2 Medical Research - Maitland (United States), 4. ACE Alzheimer Center - Barcelona (Spain), 5. Genesis Neuroscience Clinic/Tennessee Memory Disorders Foundation - knoxville (United States), 6. Danish Dementia Research Centre, Department of Clinical Medicine - copenhagen (Denmark), 7. Eastside Research Associates - Redmond (United States), 8. Columbus Memory Center - columbus (United States), 9. Charter Research Lady Lake - The Villages (United States), 10. Barcelona Beta Brain Research Center - Barcelona (Spain), 11. Brain Health Scotland - Edinburgh (United States), 12. Adams Clinical - Watertown (United States), 13. Alzheimer's Research and Treatment Center - Wellington (United States), 14. K2 Medical Research, LLC - Tampa (United States), 15. Roche Diagnostics (Shanghai) Ltd. - Shanghai (China))*

Background: Early detection of amyloid pathology using blood-based biomarkers have emerged as powerful tools in the AD patient journey. This study investigates the clinical performance of plasma pTau181 alone and in combination with plasma ApoE4 as a potential IVD to detect amyloid pathology in a broad population as seen in routine clinical practice. **Methods:** In this prospective multicenter study, we enrolled 604 patients aged 55-80 with SCD, MCI, or mild dementia being evaluated for Alzheimer's disease or other causes of cognitive decline. Plasma samples from eligible patients were analyzed using Elecsys® pTau181 and ApoE4 plasma assays (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). The discriminative ability of pTau181 alone, or in combination with ApoE4 with respect to amyloid PET visual read status and to CSF ratio of the Elecsys Phospho-Tau (181P) and Elecsys Amyloid (1-42) II CSF was evaluated. **Results:** The study population was heterogeneous regarding sex, race, and comorbidities, reflective of a real-world setting. The AUC of a combination of pTau181 and ApoE4 was 0.896, while for pTau181 alone was 0.873.

Given an amyloid positivity prevalence of 23.0% (based on amyloid PET), the negative predictive value (NPV) was 96.5%, paired with a positive predictive value of 49.8% (sensitivity: 91.3%, specificity: 72.5%). The performance was only minimally impacted by age, sex, body mass index or impaired kidney function. The rule-out performance of pTau181 alone was similar (NPV: 97.3%, PPV: 43.5%). However, the combination with ApoE4 made the clinical performance more robust towards analytical variability. **Conclusions:** The observed clinical performance in this study highlights the potential of plasma pTau181 alone and in combination with ApoE4 as robust and accurate tools for ruling out individuals with a low likelihood of amyloid pathology in the early stages of the AD continuum. **Keywords:** Fluid biomarkers, plasma, phosphorylated tau, pTau181, ApoE4, amyloid pathology, clinical practice, rule-out, clinical performance. **Disclosures:** IK is an employee, and shareholder, of Roche Molecular Solutions. SH is an employee of Roche Diagnostics GmbH. KSF has given lectures in symposia sponsored by, and served on advisory boards for (fees paid to institution), Novo Nordisk. JL has received consultancy fees and/or research trial income from Abbvie, Accumen, Biogen, Cassava, Eisai, Eli Lilly, Merck, Prothena and Roche. MC received direct research income from the American College of Radiology and the Center for Biomedical Research. MS-C has given lectures in symposia sponsored by Almirall, Eli Lilly, Novo Nordisk, Roche Diagnostics and Roche Pharma, has received consultancy (fees paid to institution) from Roche Diagnostics, and served on advisory boards of Roche Diagnostics and Grifols. MS-C was also granted a project by, and is a site investigator for a clinical trial (funded to his institution) for Roche Diagnostics. In-kind support for research (fees paid to institution) was received from ADx Neurosciences, Alamar Biosciences, Avid Radiopharmaceuticals, Eli Lilly, Fujirebio, Janssen Research & Development and Roche Diagnostics. CR is the CEO, founder and majority stakeholder of Scottish Brain Sciences, has received consultancy fees from Abbvie, Actinogen, Biogen, Eisai, Eli Lilly, MSD, Novo Nordisk and Roche, and has received payment/honoraria for presenting from Eisai and Roche. YF is an employee of Roche Diagnostics (Shanghai) Ltd. CQ-R is an employee of Roche Diagnostics International Ltd. The remaining authors have no conflicts of interest to report.

P24- ECONOMIC EVALUATION OF CEREBROSPINAL FLUID BIOMARKERS VS Aβ-PET FOR DIAGNOSIS OF ALZHEIMER'S DISEASE IN CHINA. J. Xin[1,2], J. Yu[3], X. Li[4,5], M. Guan[6], J. Meng[7], W. Zhang[8,9], C. Wei[10], Z. Pei[11], B. Gu[12], X. Chen[1,2], S. Hu[1,3] *(1. Department of Neurology, Fujian Medical University Union Hospital, Fujian Key Laboratory of Molecular Neurology and Institute of Neuroscience, Fujian Medical University - Fuzhou (China), 2. Institute of Clinical Neurology, Fujian Medical University - Fuzhou (China), 3. Department of Neurology and National Center for Neurological Disorders, Huashan Hospital, State Key Laboratory of Medical Neurobiology and Ministry of Education Frontiers Center for Brain Science, Shanghai Medical College, Fudan University - Shanghai (China), 4. Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine - Shanghai (China), 5. Alzheimer's Disease and Related Disorders Center, Shanghai Jiao Tong University - Shanghai (China), 6. Department of Laboratory Medicine, Huashan Hospital, Fudan University - Shanghai (China), 7. Department of Laboratory Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine - Shanghai (China), 8. Center for Cognitive Neurology, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University - Beijing (China), 9. Innovation Center for Neurological Disorders, Department of Neurology, Xuanwu Hospital, Capital Medical University - Beijing (China), 10. Department of Neurology, the First Affiliated Hospital of Sun Yat-Sen University - Guangzhou (China), 11. Department of Clinical Laboratory, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences - Guangzhou (China), 12. School of Public Health, Fudan University - Shanghai (China))*

Background: Alzheimer's disease (AD) poses a growing health and economic burden in China, with an estimated 17 million affected by 2030 and costs projected to reach ¥2.96 trillion by 2050 [1]. Despite this burden, diagnosis rates remain low (<5%), delaying treatment initiation of amyloid targeting disease modifying therapies (DMTs). Positron emission tomography (PET) is the current diagnostic gold standard but is costly and not widely accessible in China [2]. Cerebrospinal fluid (CSF) biomarkers (pTau181, tTau, Aβ42) offer a lower-cost alternative and have shown strong concordance with PET in diagnosing AD. This study evaluated the economic benefits of CSF compared with Aβ-PET for confirmatory diagnosis of amyloid pathology in China. **Methods:** A cohort decision-tree model was developed to simulate the diagnostic pathway in a public healthcare setting, with an attached Markov model to include the treatment pathway. A 5-year time horizon and a societal and payer perspective were adopted. Simulated patients aged 72.4 suspected of mild cognitive impairment (MCI) and mild dementia due to AD entered the model for initial assessments with cognitive and blood-based biomarkers testing as well as Magnetic Resonance Imaging (MRI) [3]. Patients with positive results got referred to subsequent assessments with either CSF or Aβ-PET for amyloid confirmation. Patients with Aβ-positive were treated with DMTs per local practice. Patients with false negatives would reiterate the diagnostic pathway and receive delayed diagnosis, while true negative patients were ruled out. The Markov model included MCI, mild AD, moderate AD, and severe AD health states. Model inputs of the decision tree included patient characteristics, performance of CSF and Aβ-PET, resource use, lab testing and image examination costs, and utilities. Costs (including direct and indirect costs), and resource use were from the medical services price of various provinces in China. Other inputs were sourced from published literature or clinician interviews. One-way deterministic sensitivity analysis (DSA) was also conducted to identify the main drivers of the model. **Results:** The rates of timely correct AD diagnosis were similar in both arms (CSF: 10.36% vs. Aβ-PET: 10.48%). However, the cost per timely accurate AD diagnosis with CSF (¥17,435.37) was lower compared to Aβ-PET (¥27,338.43), resulting in a cost reduction of 36.22%. CSF yielded cost savings of ¥1,891.39 in the diagnostic pathway (CSF: ¥3,103.40 vs. Aβ-PET: ¥4,994.79) and ¥188.98 in the treatment pathway (CSF: ¥135,099.00 vs. Aβ-PET: ¥135,287.98) respectively, primarily driven by the lower cost of CSF testing. Quality-adjusted life-years (QALYs) were almost the same across the two strategies (CSF: 5.5562 QALYs vs. Aβ-PET: 5.5563 QALYs). DSA identified that the cost of Aβ-PET and CSF testing has the biggest impact on the net-monetary benefit (NMB). **Conclusions:** CSF biomarkers provide comparable clinical outcomes to Aβ-PET at a significantly lower cost per accurate diagnosis. This results in meaningful cost savings in the diagnosis and management of AD and supports the broader adoption of CSF testing in China. **Keywords:** Cerebrospinal fluid, amyloid-β positron emission tomography, Alzheimer's disease, economic evaluation. **Disclosures:** All authors declared no competing interests. **References:** 1. Chen S, et al. The global macroeconomic burden of Alzheimer's disease and other dementias: estimates and projections for 152 countries or territories. The Lancet Global Health 2024;12(9): e1534-e1543. doi:10.1016/S2214-109X(24)00264-X. 2. Tian J, et al. Chinese guideline for the diagnosis and treatment of Alzheimer's disease dementia (2020). Chin J Geriatr, March 2021;40(3). doi:10.3760/cma.j.issn.0254-9026.2021.03.001. 3. Jia L, et al. Dementia in China: epidemiology, clinical management, and research advances. Lancet Public Health. 2020;5(12):e661-e671. doi:10.1016/S2468-2667(20)30185-7

P26- APPLICATION OF A CYTOMETRIC BEAD ARRAY–BASED ASSAY TO QUANTIFY PLASMA BIOMARKERS FOR THE DIAGNOSIS AND DISCRIMINATION OF ALZHEIMER'S DISEASE. Y. Sun[1], W. Wu[2], G. Peng[1] *(1. Department of Neurology, the First Affiliated Hospital, Zhejiang University School of Medicine - Hangzhou, Zhejiang (China), 2. State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, National Medical Center for Infectious Diseases, the First Affiliated Hospital, Zhejiang University School of Medicine - Hangzhou, Zhejiang (China))*

Background: Background: In recent years, blood-based markers have got increasing attention for their potential in the diagnosis and assessment of Alzheimer's disease (AD), offering a promising avenue for early detection and disease progression monitoring. This study aims to further investigate and validate the diagnostic and differential efficiency of seven AD-related plasma biomarkers in Eastern Chinese populations, utilizing a newly developed cytometric bead array (CBA)-based multiplex assay. **Methods:** Following comprehensive clinical evaluations and auxiliary examinations, all eligible participants were divided into two cohorts. Cohort 1 included AD patients with positive amyloid β (Aβ)-positron emission tomography results and cognitively unimpaired (CU) controls with negative Aβ state. Cohort 2 included individuals clinically diagnosed with probable AD, probable frontotemporal dementia (FTD), amnestic mild cognitive impairment (aMCI), and CU. Plasma p-tau217, p-tau181, Aβ40, Aβ42, neurofilament light (NfL), glial fibrillary acidic protein (GFAP) and α-synuclein levels were measured in all participants using the CBA-based assay. After adjusting for age, sex, and years of education, inter-group differences in biomarker levels were assessed. Correlation

among biomarkers was analyzed, and receiver operating characteristic curves were generated to evaluate the diagnostic and differential performance of the biomarkers for AD. **Results:** Twenty-nine biological-diagnosed AD patients and 32 CU were included in the cohort 1; forty-one CU, 51 probable AD, 37 probable FTD and 62 aMCI patients were included in the cohort 2. Significant differences were found in plasma p-tau217, p-tau181, Aβ42, NfL, GFAP, α-synuclein and p-tau217/Aβ42 between AD and CU groups in the cohort 1. Plasma p-tau217/Aβ42 achieved the highest accuracy in diagnosing AD (AUC = 0.9330), closely followed by p-tau217 (AUC = 0.9149) and p-tau181 (AUC = 0.9133). In the cohort 2, plasma p-tau217, p-tau181, p-tau217/Aβ42 and Aβ40 were higher in the FTD patients than CU controls; plasma p-tau217, Aβ40 and NfL were higher than aMCI patients, and α-synuclein was lower than aMCI patients. No individual plasma biomarker showed the ability of distinguishing AD from FTD. The combination of p-tau217, Aβ40, NfL and α-synuclein presented the best performance in the differentiation of AD (AUC = 0.760). **Conclusions:** Individual plasma biomarkers measured using the CBA-based assay, especially p-tau217, exhibited great potential for the diagnosis of AD. The combination of AD core biomarkers, non-specific biomarkers and co-pathological biomarkers assisted in the discrimination of AD and FTD. **Keywords:** Alzheimer's disease, frontotemporal dementia, plasma biomarkers, cytometric bead array, diagnosis, differential diagnosis. **Disclosures:** The authors declare no competing interests. **References:** 1. Jack CR Jr, et al. Alzheimers Dement. 2024;20(8):5143-5169. doi:10.1002/alz.13859. 2. Liu Y, et al. Sci Rep. 2025;15(1):9767. doi:10.1038/s41598-024-83919-x

P27- ASSOCIATIONS BETWEEN IMMUNOSENESCENCE AND COGNITIVE DECLINE IN OLDER ADULTS. Y.X. Luo[1], D. Song[1], X.H. Zhou[1], T. Heng[1], L.L. Yang[1], L.H. Gong[1], N. Liu[1], X.Q. Yao[1] *(1. Department of Rehabilitation, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China - Chongqing (China)))*

Background: The reevaluation of the brain's immune privilege concept is driven by preclinical research emphasizing the dual role of peripheral immune cells in cognitive impairment. The relationship between immunosenescence and cognitive function in humans remains unclear, it is essential to establish a clear understanding of the relationships between immunosenescence and cognitive decline due to its current ambiguity. **Methods:** Using data from the US Health and Retirement Study (HRS), particularly the Venous Blood Study (VBS) during Wave 2016, the study investigated the relationship between immunosenescence markers and cognitive function in adults aged 50 years and older. Peripheral blood samples were analyzed via flow cytometry to evaluate immunosenescence markers, including the percentage of Naïve CD4+ T cells, Naïve CD8+ T cells, TemRA CD4+ T cells, TemRA CD8+ T cells, and the CD4+/CD8+ T cell ratio. Cognitive function was evaluated through episodic memory, working memory, processing speed, and attention tests administered at both Wave 2016 and 2020. Cross-sectional associations between baseline immunosenescence markers and cognitive function were analyzed using Spearman correlation analysis and linear regression models. Longitudinal associations between baseline immunosenescence markers and cognitive decline were assessed using mixed linear models. **Results:** A total of 6,911 individuals (59.7% females) with a median age of 66 years (IQR: 60-75) were included in the study, with an average follow-up duration of 3.93 years (SD 0.34 years). The majority of participants were non-Hispanic White (64.9%) and non-Hispanic Black (17.1%). In the cross-sectional analysis, there were no significant associations found between immunosenescence markers and baseline global cognitive function after adjusting for covariates. In the longitudinal analysis, significant age-specific associations were observed between global cognitive function and two immunosenescence markers: CD4+/CD8+ T cell ratio (estimate = 0.229, SE 0.099, P = 0.021, P for interaction with age = 0.016) and Naïve CD8+ T cell percentage (estimate = -0.068, SE 0.018, P < 0.001, P for interaction with age < 0.001). **Conclusions:** This study identified significant associations between immunosenescence phenotypes and cognitive decline in middle-aged and older adults. Specifically, a robust age-specific relationship was observed between Naïve CD8+ T cells and subsequent cognitive function decline. Further investigation into the age-related reshaping of Naïve CD8+ T cell immunosenescence and its role in cognitive decline may provide valuable insights into the brain aging. **Keywords:** Immunosenescence, T lymphocyte, cognitive function, dementia. **Clinical Trial Registry:** Not Applicable. **Data Deposition:** Not Applicable. **Disclosures:** The authors declared no competing interests.

P28- BIOMARKER MODELING OF ALZHEIMER'S DISEASE USING REVISED PET-BASED BIOLOGICAL STAGING FRAMEWORK. Y. Zhao[1], Y.J. Wang[1] *(1. Department of Neurology, Daping Hospital, Third Military Medical University - Chongqing (China))*

Background: Previous PET-based biomarker studies on Alzheimer's disease (AD) predominantly focused on the intensity values of Aβ and tau for quantifying pathological burden [1], neglecting their spatial distribution patterns across brain regions. The 2024 Alzheimer's Association revised biological staging framework (A–D) integrates both intensity thresholds and regional distribution criteria to enhance disease classification precision [2]. Therefore, this study aimed to evaluate the feasibility of the updated biological staging scheme, with a focus on exploring its potential clinical implications. **Methods:** The 2018 syndromal staging framework, which employed binary biomarker classification, was applied to 535 participants from the Alzheimer's Disease Neuroimaging Initiative. In contrast, the updated 2024 numeric clinical staging framework that incorporating biomarker-based staging was restricted to 221 AD continuum cases. **Results:** The 2024 biological staging framework demonstrated high diagnostic accuracy, correctly classifying 90.5% of AD cases. Cognitive performance progressively declined across biological stages (A–D), with significant longitudinal deterioration confirmed via mixed linear models. Biomarker profiles exhibited stage-dependent stratification: CSF Aβ42/40 decreased, while CSF p-tau181/Aβ42 and t-tau/Aβ42 ratios increased markedly. Notably, the 2018 framework showed limited precision in differentiating progression risks. Within the A+T− group, cognitive trajectories diverged between stage A and B. In the A+T+ group, stages B, C, and D exhibited distinct progression rates, highlighting the enhanced granularity of the 2024 framework in capturing AD heterogeneity. **Conclusions:** Our findings support the utility of the 2024 revised biological staging framework as a reliable tool for modeling the natural history of AD and monitoring in vivo disease severity in conjugating cognitive progression. By integrating both biomarker intensity thresholds and spatial distribution patterns, this updated framework captures the dynamic interplay between Aβ, tau pathology, and regional

neurodegeneration, thereby enhancing prognostic accuracy. The alignment of this framework with clinical trajectories highlights its potential to guide personalized therapeutic strategies and improve clinical trial stratification. Future studies are warranted to validate these staging thresholds in diverse cohorts and assess their responsiveness to disease-modifying interventions. **Keywords:** Alzheimer's disease diagnosis, Alzheimer's disease staging. **Disclosures:** None. **References:** 1. Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimer's Dement. 2018;14:535-562. 2. Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. 2024; 20:5143-5169.

P29- GLYMPHATIC SYSTEM DYSFUNCTION AS A PREDICTOR OF COGNITIVE DECLINE AND INCIDENT DEMENTIA. C. Li[1], L. Wen-Xin[1], L. Zi-Yue[1], Z. Fei-Fei[1], H. Fei[1], L. Ming-Li[1], Z. Li-Xin[1], N. Jun[1], Y. Ming[1], Z. Shu-Yang[1], C. Li-Ying[1], J. Zheng-Yu[1], P. Bin[1], Z. Yi-Cheng[1]

(1. Peking Union Medical College Hospital - Beijing (China))

Background: Cognitive decline and incident dementia in ageing populations have been linked to brain parenchymal injury and the ALPS index (ALPS-I). This investigation aimed to elucidate whether the baseline ALPS-I could predict incident dementia and cognitive decline in this population. **Methods:** In total, 973 dementia-free participants from the Shunyi Study (mean age, 57 years; 37% male) received MRI between 2013 and 2016 to quantify the ALPS-I. The longitudinal relationships between the ALPS-I and cognitive deterioration in various cognitive areas were evaluated via linear mixed models. Cox proportional hazard models were utilized to explore the link between the index and incident dementia. Mediation assessments were carried out to identify the potential mediating effects of brain parenchymal injury on the link between the ALPS-I and cognition. **Results:** The baseline ALPS-I predicted longitudinal changes in global cognition (Montreal Cognitive Assessment), language (verbal fluency test), visuospatial perception (block design subtest of Wechsler intelligence scale), and executive function (Trail Making Test). A lower score was markedly associated with a higher incident dementia risk. Mediation analysis revealed that fractional anisotropy mediated the associations between the ALPS-I and executive function (mediation effect: 21.9%) and visuospatial perception (mediation effect: 68.8%). The white matter hyperintensity fraction was found to mediate the link between the ALPS-I and global cognition (mediation effect: 55.0%). **Conclusions:** This longitudinal evidence supports a link between the ALPS-I and cognitive degeneration. Furthermore, the link is mediated by subcortical parenchymal injury. **Keywords:** Glymphatic dysfunction, diffusion tensor image analysis along the perivascular space, cognitive decline, incident dementia, subcortical parenchymal injury. **Disclosures:** This work was supported by grants from the CAMS Innovation Fund for Medical Sciences (CIFMS 2022-I2M-1-001), National High Level Hospital Clinical Research Funding (grant number: 2022-PUMCH-D-007), National Natural Science Foundation of China (No. 82371347 and No.82401557) and the Fundamental Research Funds for the Central Universities (No. 3332024112). The authors declared no competing interests. **Ethics Committee approval:** The Peking Union Medical College Hospital Ethics Committee approved the study (B-160 and JS-2822). All participants provided written informed consent.

P30- A STUDY ON THE CORRELATION BETWEEN THE NEUTROPHIL-TO-LYMPHOCYTE RATIO AND BLOOD BIOMARKERS WITH COGNITIVE FUNCTION IN ALZHEIMER'S DISEASE. C. Liang[1], X. Yan[1], X. Xiao[1]

(1. Shenzhen City, Guangdong Province (China))

Background: In recent years, increasing evidence has indicated that inflammatory responses play a significant role in the onset and progression of Alzheimer's disease (AD). The neutrophil-to-lymphocyte ratio (NLR) is a readily available and cost-effective inflammatory marker. Therefore, this study aims to investigate the associations between NLR, AD-related blood biomarkers, and cognitive function. **Materials and Methods:** A total of 117 cognitively unimpaired individuals (CU) and 111 individuals with AD-related cognitive impairment (CI) were enrolled in this study. Baseline characteristics and cognitive scores were collected for all participants. Fasting blood samples were obtained in the morning for complete blood count analysis and measurement of AD-related blood biomarkers. Complete blood counts were performed using an automated hematology analyzer. Plasma levels of $A\beta42/40$, GFAP, NfL, and p-tau181 were measured using the single-molecule array (SIMOA) technique. Differences in complete blood count parameters, NLR, and AD-related biomarkers were compared across individuals with varying cognitive statuses. The correlations between NLR, cognitive scores, and AD biomarkers were assessed using Spearman's rank correlation. Participants were stratified into high and low NLR groups based on the median NLR value. Comparisons of baseline characteristics, cognitive scores, and AD biomarkers between the two groups were conducted to evaluate whether NLR mediates the relationship between AD biomarkers and cognitive function. **Results:** White blood cell and neutrophil counts were significantly higher in the CI group compared to the CU group. Similarly, the NLR in the CI group (2.183 ± 1.207) was significantly higher than that in the CU group (1.783 ± 0.881). NLR and AD-related blood biomarkers were significantly associated with MMSE and MoCA cognitive scores. Except for plasma $A\beta42/40$, which showed a significant positive correlation with cognitive scores, NLR, GFAP, NfL, and p-tau181 levels were significantly negatively correlated with cognitive performance, with the strongest correlation observed between NLR and MoCA scores. When stratified by the median NLR value of 1.668, the high NLR group had a higher proportion of males, was older, had lower educational attainment, and included more smokers. Cognitive scores (MMSE and MoCA) were significantly lower in the high NLR group compared to the low NLR group. However, no significant differences were observed in AD-related biomarkers between the two groups. Spearman correlation analysis revealed that NLR was significantly positively correlated with GFAP, NfL, and p-tau181 levels, with the strongest correlation observed for NfL (r = 0.260). NLR did not mediate the relationship between $A\beta42/40$ and cognitive function but showed a partial mediating effect between the other three AD biomarkers and cognitive performance. **Conclusions:** NLR is positively correlated with plasma GFAP, NfL, and p-tau181 levels, which are all effective predictors of cognitive function. Higher NLR values are associated with more severe cognitive impairment. Additionally, male gender, older age, lower educational attainment, and smoking were identified as risk factors for elevated NLR. **Keywords:** Neutrophil-to-lymphocyte ratio, blood biomarkers, cognitive function, Alzheimer's disease. **Disclosures:** None of the authors have any conflicts of interest related to this article.

P32- VALIDATION AND EVALUATION OF PERIPHERAL BLOOD TRF-37-WURMJKYOSR99RHJ AS AN EARLY NON-INVASIVE DIAGNOSTIC BIOMARKER FOR ALZHEIMER'S DISEASE. H.H Yu[1] *(1. Ningbo (China))*

Objective: This study aimed to investigate the differences in the presence of tRNA-derived small RNAs (tsRNAs) in peripheral blood between Alzheimer's disease (AD) patients and healthy controls, and to explore their expression levels as potential early diagnostic biomarkers for AD. Additionally, we assessed the clinical value of tsRNAs in AD diagnosis. **Materials and Methods:** High-throughput sequencing was conducted to analyze the plasma tsRNA expression profiles of 3 AD patients and 3 healthy controls, identifying the tsRNAs for further study. Reverse transcription primers and amplification primers were designed for the selected tsRNA. The sample size was expanded to include 77 early-stage AD patients and 77 healthy controls, and quantitative reverse transcription-polymerase chain reaction (qRT-PCR) was used to validate the expression of the selected differential tsRNAs. The diagnostic value and potential of these tsRNAs were evaluated through receiver operating characteristic (ROC) curves. Furthermore, correlations between differential tsRNA expression levels and clinical assessments, such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCa), Activities of Daily Living (ADL), and Clinical Dementia Rating (CDR), were analyzed using Spearman's rank correlation. tRF-37-WURMJKYOSR99RHJ was identified as a highly valuable clinical marker. Logistic regression analysis of clinical data was performed to select valuable indicators for constructing an AD diagnostic model. **Results:** High-throughput sequencing of plasma samples from 3 AD patients and 3 healthy controls revealed 7196 differentially expressed tsRNAs (1.5-fold change), with 3524 upregulated and 3672 downregulated. Among these, 18 tsRNAs showed significant statistical differences, with one upregulated and 17 downregulated (preliminary AUC = 0.90). A specific tsRNA, tRF-37-WURMJKYOSR99RHJ (sequence: TCTGAGGGTCCAGGGTTCAAGTCCCTGTTCGGGCGCC), was selected for further investigation using the MINTbase database. The expression level of tRF-37-WURMJKYOSR99RHJ was significantly higher in the plasma of diagnosed AD patients compared to the control group (P < 0.0001), and the AUC of the ROC curve was 0.948 (95% CI: 0.912–0.983). No significant difference in the expression levels of tRF-37 was found in the plasma of 30 Parkinson's disease (PD) patients and 30 vascular dementia (VD) patients compared to the control group. The expression of tRF-37-WURMJKYOSR99RHJ in AD patients was positively correlated with MMSE and MoCa scores (P < 0.001) and negatively correlated with CDR and ADL scores (P < 0.001). Logistic regression analysis identified that tRF-37-WURMJKYOSR99RHJ, body mass index (BMI), alcohol consumption history, high-density lipoprotein levels, and depression scores were associated with AD. Decision curve analysis (DCA) demonstrated that tRF-37-WURMJKYOSR99RHJ outperformed other clinical indicators in diagnostic potential. Model-building using AD-related tRF-37-WURMJKYOSR99RHJ, BMI, high-density lipoprotein, and depression scores achieved an AUC of 0.943 for tRF-37-WURMJKYOSR99RHJ alone, and 0.954 for the combined model with clinical indicators. These values were comparable to the AUC of p-tau217 (0.93–0.96). **Conclusions:** This study revealed that plasma tRF-37-WURMJKYOSR99RHJ is significantly upregulated in early-stage AD patients. The findings suggest that tRF-37-WURMJKYOSR99RHJ could serve as a promising plasma biomarker for early AD diagnosis with strong clinical

application value. Additionally, no significant differences in plasma expression levels of tRF-37 were observed in 30 PD and 30 VD patients compared to controls. The diagnostic potential of tRF-37-WURMJKYOSR99RHJ is comparable to that of p-tau217, indicating its value in clinical practice. **Keywords:** Alzheimer's disease, tsRNA, tRF-37-WURMJKYOSR99RHJ, early diagnostic value, biological marker. **Declaration of interests:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CLINICAL TRIALS: COGNITIVE AND FUNCTIONAL ENDPOINTS

P34- PREDICTING THE REVERSION FROM MILD COGNITIVE IMPAIRMENT TO NORMAL COGNITION BASED ON MAGNETIC RESONANCE IMAGING, CLINICAL, AND NEUROPSYCHOLOGICAL EXAMINATIONS. H.H Yu[1], T. Lan[1], W. Xu[1] *(1. Department of Neurology, Qingdao Municipal Hospital, Qingdao University - Qingdao (China))*

Background: Reversion from mild cognitive impairment (MCI) to normal cognition (NC) is not uncommon and indicates a better cognitive trajectory. This study aims to identify predictors of MCI reversion and develop a predicting model. **Methods:** A total of 391 MCI subjects (mean age = 74.3 years, female = 61 %) who had baseline data of magnetic resonance imaging, clinical, and neuropsychological measurements were followed for two years. Multivariate logistic analyses were used to identify the predictors of MCI reversion after adjusting for age and sex. A stepwise backward logistic regression model was used to construct a predictive nomogram for MCI reversion. The nomogram was validated by internal bootstrapping and in an independent cohort. **Results:** In the training cohort, the 2-year reversion rate was 19.95 %. Predictors associated with reversion to NC were higher education level (p = 0.004), absence of APOE4 allele (p = 0.001), larger brain volume (p < 0.005), better neuropsychological measurements performance (p < 0.001), higher glomerular filtration rate (p = 0.035), and lower mean arterial pressure (p = 0.060). The nomogram incorporating five predictors (education, hippocampus volume, the Alzheimer's Disease Assessment Scale-Cognitive score, the Rey Auditory Verbal Learning Test-immediate score, and mean arterial pressure) achieved good C-indexes of 0.892 (95 % confidence interval [CI], 0.859–0.926) and 0.806 (95 % CI, 0.709–0.902) for the training and validation cohort. **Conclusions:** This prediction model could facilitate risk stratification and early management for the MCI population. **Keywords:** Mild cognitive impairment, reversion, predictors, normogram. **Disclosures:** The authors declared no competing interests.

P35- ASSOCIATIONS BETWEEN CARDIOMETABOLIC MULTIMORBIDITY AND CEREBROSPINAL FLUID BIOMARKERS OF ALZHEIMER'S DISEASE PATHOLOGY IN COGNITIVELY INTACT ADULTS. Q. Li[1] *(1. Qingdao University - Qingdao (China))*

Background: Cardiometabolic multimorbidity is associated with an increased risk of dementia, but the pathogenic mechanisms linking them remain largely undefined. We aimed to assess the associations of cardiometabolic multimorbidity with cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) pathology to enhance our understanding of the underlying mechanisms linking cardiometabolic multimorbidity

and AD. **Methods:** This study included 1,464 cognitively intact participants from the Chinese Alzheimer's Biomarker and LifestylE (CABLE) database. Cardiometabolic diseases (CMD) are a group of interrelated disorders such as hypertension, diabetes, heart diseases (HD) and stroke. Based on the CMD status, participants were categorized as CMD-free, single CMD, or CMD multimorbidity. CMD multimorbidity is defined as the coexistence of two or more CMDs. The associations of cardiometabolic multimorbidity and CSF biomarkers were examined using multivariable linear regression models with demographic characteristics, the APOE ε4 allele, and lifestyle factors as covariates. Subgroup analyses stratified by age, sex, and APOE ε4 status were also performed. **Results:** A total of 1,464 individuals (mean age, 61.80 years; age range, 40–89 years) were included. The markers of phosphorylated tau-related processes (CSF P-tau181: β=0.165, P=0.037) and neuronal injury (CSF T-tau: β=0.065, P =0.033) were significantly increased in subjects with CMD multimorbidity (versus CMD-free), but not in those with single CMD. The association between CMD multimorbidity with CSF T-tau levels remained significant after controlling for Aβ42 levels. Additionally, significantly elevated tau-related biomarkers were observed in patients with specific CMD combinations (i.e., hypertension and diabetes, hypertension and HD), especially in long disease course. **Conclusions:** The presence of cardiometabolic multimorbidity was associated with tau phosphorylation and neuronal injury in cognitively normal populations. CMD multimorbidity might be a potential independent target to alleviate tau-related pathologies that can cause cognitive impairment. **Keywords:** Alzheimer's disease, cerebrospinal fluid, cardiometabolic multimorbidity

P36- DEFINING STAGES OF ALZHEIMER'S DISEASE USING IADL: A CROSSWALK WITH MMSE SCORES.

Y. Wang[1,2], A.A. Tahami Monfared[3,4], Q. Zhang[3], J. Reisman[5,6], B. Mittler[7], D. Berlowitz[8], P. Morin[9], R. Zhang[3], W. Xia[6,10] *(1. Research Service, VA Bedford Healthcare System - Bedford (United States), 2. Wentworth Institute of Technology - Boston (United States), 3. Eisai Inc. - Nutley (United States), 4. McGill University - Montreal (Canada), 5. Center for Healthcare Optimization and Implementation, VA Bedford Healthcare System - Bedford (United States), 6. Department of Biological Sciences, University of Massachusetts Lowell - Lowell (United States), 7. Geriatric Research Education and Clinical Center, VA South Texas Healthcare System - San Antonio (United States), 8. Department of Public Health, Zuckerberg College of Health Sciences, University of Massachusetts Lowell - Lowell (United States), 9. Department of Neurology, Boston University, Chobanian and Avedisian School of Medicine - Boston (United States), 10. Geriatric Research Education and Clinical Center, Bedford VA Healthcare System - Bedford (United States))*

Background: Clinical guidelines recommend MMSE «or other cognitive screening instrument with a score compatible with early AD"1 to be used for patient evaluation for anti-amyloid therapy (AAT). MMSE may exhibit a ceiling effect3 in early stages of disease and floor effects in advanced stages, limiting its utility as a standalone tool for longitudinal assessment of disease progression. The literature reports a strong correlation between MMSE and functional measures4, however, MMSE does not assess function. This study aims to cross walk MMSE and IADL to expand the clinical tools to support patient identification for AAT and preliminarily evaluate the potential suitability of using IADL for assessment of disease progression. **Methods:** Patients with mild cognitive impairment (MCI) or Alzheimer's dementia

(AD) were identified in the United States Veteran's Affairs Healthcare System (2020-2024). Paired MMSE (range 0-30) and Lawton-IADL (range 0-8) scores that were ≤6 months apart were identified. Piece-wise linear regression with spline transformation and repeated measures analysis with mixed-effects were both performed, adjusting for patient demographics, consistent with prior research5. **Results:** The study sample (N=2,609) had a mean age of 81.1 years (97.9% men, 14.9% black, and 30.5% Hispanic). The most common comorbidity was hypertension (79.8%). The MMSE and IADL score distributions trended with different patterns. Functional deterioration appears to accelerate after MCI staged by MMSE. IADL scores corresponding to mild AD had the greatest variability (widest score range). IADL scores corresponding to severe AD had a skewed distribution with outliers, suggesting retained function among a few patients despite severe MMSE scores. Five regression slopes were estimated using a spline transformation corresponding to each MMSE cut-off score to allow robust estimation of variations in slopes. Projected IADL scores declined linearly between MMSE-staged MCI to moderate AD (P<0.01), indicated by comparable slopes (0.16-0.18) corresponding to these stages. MMSE <13 was not associated with continued declines in projected IADL (β=0.02, P=0.35), suggesting a severity ceiling of MMSE, namely, unable to detect or differentiate patients at the most severe end of IADL (0-3); likewise, projected IADL scores plateaued at MMSE ≥29 (β=0.06, P=0.75) suggested lacking patient differentiation with the high end of IADL scores (6-8). **Conclusions:** This study identified distinct IADL thresholds corresponding to clinical stages from normal to severe AD measured by MMSE. Among patients with MCI or mild AD, projected IADL scores (4.5-5.8) declined linearly with MMSE (MMSE scores 21-28)* with a strong correlation, suggesting that IADL may be considered as an alternative to MMSE for identifying patients potentially eligible for AATs when MMSE is not available, or used alongside MMSE to provide additional information on patient status. Projected IADL scores did not reach <3 or >6 over the full MMSE score range, supporting the potential utility of IADL for assessing Alzheimer's disease progression over a broader severity range relative to MMSE. Overall, findings from the crosswalk between cognitive and functional testing suggest that IADL can provide information on disease staging, complementing cognitive screening to help guide specialist referral for AAT evaluation. **Keywords:** Alzheimer's disease, crosswalk, IADL, MMSE, disease severity, staging. **Disclosures:** Amir Abbas Tahami Monfared is an employee of Eisai Inc. and holds the position of Adjunct Professor of Epidemiology, Biostatistics, and Occupational Health at McGill University. He also serves as an Associate Editor for the Journal of Alzheimer's Disease but does not receive honoraria for this role. Quanwu Zhang and Raymond Zhang are employees of Eisai Inc. The other authors, Ying Wang, Joel Reisman, Brant Mittler, Dan Berlowitz, Peter J Morin, and Weiming Xia declare no conflict of interest. This study was funded by Eisai Inc.

VASCULAR CONTRIBUTION IN AD INCLUDING CEREBRAL SMALL VESSEL DISEASE (SVD)

P37- COUPLING ANALYSIS OF CARDIOVASCULAR RISK BURDEN WITH CEREBRAL BLOOD FLOW IN PATIENTS WITH AMNESTIC MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE. L. Zhuang[1], L. Yuan[2], X. Liu[1], G. Peng[1], B. Luo[1] *(1. The First Affiliated Hospital, College of Medicine, Zhejiang University - Hangzhou (China), 2. School of Physics, Zhejiang University - Hangzhou (China))*

Background: About one third of Alzheimer's disease (AD) cases can be attributed to hypertension, diabetes, obesity, smoking and other cardiovascular risk factors, suggesting the contribution of vascular factors to the development of AD. At present, the specific role of the aggregation of vascular factors in the pathogenesis of AD is still unclear. This study aims to explore the coupling between the cardiovascular risk burden and the cerebral blood flow (CBF) in patients with amnestic mild cognitive impairment (aMCI) and AD. **Methods:** A total of 224 subjects from the memory clinic cohort of the First Affiliated Hospital of Zhejiang University School of Medicine were enrolled in this cross-sectional cohort study, including 65 cognitively normal (CN) individuals, 100 aMCI and 59 AD patients. The cardiovascular risk burden was assessed by the Framingham General Cardiovascular Risk Score (FGCRS), and CBF was calculated based on arterial spin labeling (ASL) magnetic resonance imaging. One-way analysis of variance was used to compare the differences of FGCRS and CBF in different diagnostic levels (CN, aMCI vs. AD), Further, the coupling of FRS and CBF at the whole brain voxel level and brain network level was calculated by the general linear model. **Results:** AD patients exhibited significantly higher FGCRS (19%) than CN (13%, p=0.009), while aMCI (17%) showed no difference from CN. AD patients demonstrated hypoperfusion in the default mode network (DMN, 33.95% of affected regions), frontoparietal network (FPN, 22.42%), and dorsal attention network (DAN, 18.22%) compared to CN/aMCI. No CBF differences were observed between aMCI and CN. In CN/aMCI, higher FGCRS correlated with lower CBF in prefrontal, parietal, and cingulate regions (p<0.05). At the network level, CN showed FGCRS-CBF negative correlations in visual, motor, DAN, FPN, and DMN, while aMCI only in visual and DAN. In AD, localized negative correlations were found in the right superior/middle temporal gyri and postcentral gyrus (p<0.05), with no network-level associations. **Conclusions:** Elevated cardiovascular risk in AD suggests vascular factors may accelerate progression from aMCI to AD. AD-specific hypoperfusion in DMN/FPN aligns with core pathological changes, while diminished FGCRS-CBF coupling in AD implies dominance of non-vascular mechanisms (e.g., amyloidosis). Managing vascular risks during the prodromal stage (e.g., aMCI) may preserve CBF and delay AD onset, highlighting a critical window for prevention. Longitudinal studies are needed to validate causality and therapeutic potential. **Keywords:** Amnestic mild cognitive impairment, Alzheimer's disease, Framingham General Cardiovascular Risk Score, cerebral blood flow, coupling. **Disclosures:** The authors declared no competing interests. **References:** - Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet Comm. 2017;390:2673-2734. http://dx.doi.org/10.1016/. - Peloso GM, Beiser AS, Satizabal CL, et al. Cardiovascular health, genetic risk, and risk of dementia in the Framingham Heart Study. Neurology. 2020;95(10):e1341-e1350. doi:10.1212/WNL.0000000000010306. - Iturria-Medina Y, Sotero RC,

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P38- THE PREDICTIVE EFFECT OF PEAK-WIDTH OF SKELETONIZED MEAN DIFFUSIVITY ON COGNITIVE CHANGE AND DEMENTIA TRANSFORMATION IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT. X. Hou[1], H. Hong[1], B. Xiong[1], C. Wang[1], Y. Tang[1] *(1. The Second Affiliated Hospital of Zhejiang University School of Medicine, - Hangzhou (China))*

Background: Alzheimer's disease is often associated with cerebral small vessel pathology, including cerebral amyloid angiopathy and hypertensive arteriopathy. The index of peak-width of skeletonized mean diffusivity derived from diffusion tensor imaging can sensitively detect white matter microstructure damage, but the effect of different SVD subtypes on cognitive decline in AD is still unclear. This study aims to explore the differences between cerebral amyloid angiopathy and hypertensive arteriopathy in AD patients based on PSMD indicators, and analyze their predictive value for the decline of each cognitive domain, so as to provide a basis for early diagnosis and intervention of AD complicated with SVD. **Methods:** Based on the open database of ADNI (Alzheimer's Disease Neuroimaging Initiative), this study collected baseline DTI imaging data and 4-year longitudinal cognitive follow-up data of 124 MCI patients, and used PSMD indicators to explore its relationship with cognitive function changes and disease progression. At the same time, Aβ-PET was used as the gold standard for AD pathology, and the prediction performance of PSMD was compared throughout the process. In addition, according to the visual evaluation like Fazekas score and distribution of cerebral microhemorrhage, MCI patients were divided into four subgroups: CAA, HA, mixed pathology and no pathology (pure group) for further subgroup analysis. **Results:** In terms of baseline, baseline PSMD values were significantly different between groups, and TMTB, which stands for executive ability, was significantly greater in the mixed group than in the pure group. In the CAA group, the baseline PSMD value was significantly positively correlated with TMTA, representing processing speed, and significantly positively correlated with TMTB, and the baseline Aβ load was negatively correlated with logical memory score. In the mixed group, there was a significant positive correlation between baseline PSMD and TMTA, and a significant negative correlation between baseline Aβ load and logical memory score. In terms of longitudinal cognition, baseline PSMD values in the mixed group could predict TMTB, and baseline PSMD values in the pure group could predict logical memory, but neither could be corrected. At the same time, baseline Aβ load predicts overall cognition and each cognitive domain. Positive results were present in all groups. In terms of dementia conversion, baseline PSMD values were not predictive in the whole group or in each group. Baseline Aβ load showed predictive value in the whole group, HA group, and pure group. **Conclusions:** PSMD value was affected by vascular pathological burden, which was significantly related to processing speed and execution ability. Although PSMD did not perform well in the longitudinal prediction, it showed value in different cognitive domains compared with Aβ. **Keywords:** Peak-width of skeletonized mean diffusivity, longitudinal. **Disclosures:** The authors declared no competing interests. **References:** 1. Author J, et al. JoBaykara E, Gesierich B, Adam R, et al. A Novel Imaging Marker for Small Vessel Disease Based on Skeletonization of

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P41- LARGER LESION DIAMETER AND RETINAL MICROVASCULAR IMPAIRMENT JOINTLY INFLUENCE COGNITIVE DECLINE IN LACUNAR INFARCTION.

Z. Wang[1], J. Shen[1] *(1. The First Affiliated Hospital of Wenzhou Medical University - Whenzhou (China))*

Background: Lacunar infarction (LI), a subtype of ischemic stroke caused by cerebral small vessel disease (SVD), is strongly associated with post-stroke cognitive impairment (PSCI). While neuroimaging biomarkers are critical for diagnosis, their accessibility and cost limit routine use. The retina, as an extension of the central nervous system, offers a non-invasive window to study microvascular pathology. This study investigates the synergistic impact of infarct lesion volume and retinal microvascular metrics on cognitive decline in LI patients. **Methods:** We prospectively enrolled 112 LI patients and 128 controls. Retinal vascular parameters (tortuosity, vessel density, fractal dimension) were quantified from color fundus photographs, and lesion diameter was measured via MRI. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA). Linear regression models with generalized estimating equations (GEE) evaluated associations between retinal metrics, lesion diameter, and MoCA scores, adjusting for covariates (age, vascular risk factors). Interaction terms tested the moderating effects. **Results:** LI patients exhibited sparser, more tortuous retinal microvasculature compared to controls ($p < 0.001$). Poorer cognitive performance in LI was associated with larger lesion diameter ($p < 0.001$) and retinal microvascular impairment. A significant interaction was observed between retinal microvasculature and lesion diameter on MoCA scores (fractal dimension: ß = 1.532, p for interaction = 0.026; vessel density: ß = 0.53, p for interaction = 0.041) suggesting that the relationship between lesion diameter and MoCA scores may be more pronounced in LI with severe retinal microvascular impairment. **Conclusions:** The diameter of the lesion infarct and severity of retinal microvascular damage may jointly reflect global cognitive performance in LI, signifying ischemia as a potential shared mechanism. Integrating retinal imaging with neuroimaging may enhance early risk stratification and personalized intervention strategies. **Keywords:** Lacunar infarction, retinal microvasculature, cognition, retinal biomarkers.

COGNITIVE ASSESSMENTS AND CLINICAL TRIALS

P43- ASSOCIATION OF MODIFIED DEMENTIA RISK SCORE WITH CEREBROSPINAL FLUID BIOMARKERS AND COGNITION IN ADULTS WITHOUT DEMENTIA.

Q. Li[1] *(1. Qingdao University - Qingdao (China))*

Background: This study aimed to investigate the cognitive profile and prospective cognitive changes in non-demented adults with elevated Modified Dementia Risk Scores (MDRS), while also exploring the potential relationship between these associations and cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) pathology and neuroinflammation. **Methods:** Within the Chinese Alzheimer's Biomarker and LifestylE (CABLE) database, 994 participants without dementia were assessed on MDRS, CSF biomarkers and cognition. We examined the associations of the MDRS with CSF biomarkers and cognitive scores using linear regressions. Causal mediation analyses were conducted to analyze the associations among MDRS, brain pathologies, and cognition. The Alzheimer's Disease Neuroimaging Initiative (ADNI) study was used to validate the mediation effects and to investigate the longitudinal association between MDRS and cognitive decline. **Results:** The results revealed that higher MDRS were linked to poorer cognitive performance (Model 1: PFDR<0.001; Model 2: PFDR<0.001) and increases in CSF levels of phosphorylated tau (P-tau, Model 1: PFDR<0.001; Model 2: PFDR<0.001), total tau (T-tau, Model 1: PFDR<0.001; Model 2: PFDR<0.001), P-tau/Aβ42 ratio (Model 1: PFDR=0.023; Model 2: PFDR=0.028), T-tau/Aβ42 ratio (Model 1: PFDR<0.001; Model 2: PFDR<0.001) and soluble triggering receptor expressed on myeloid cells 2 (sTrem2, Model 1: PFDR<0.001; Model 2: PFDR<0.001) in the CABLE study. The impact of MDRS on cognition was partially mediated by neuroinflammation and tau pathology. These mediation effects were replicated in the ADNI study. Baseline MDRS were significantly associated with future cognitive decline, as indicated by lower scores on the Mini-Mental State Examination (MMSE, Model 1: PFDR=0.045; Model 2: PFDR<0.001), ADNI composite memory score (ADNI-MEM, Model 1: PFDR=0.005; Model 2: PFDR<0.001), ADNI composite executive function score (ADNI-EF, Model 1: PFDR=0.045; Model 2: PFDR<0.001) , and higher score on the Alzheimer's Disease Assessment Scale (ADAS13, Model 1: PFDR=0.045; Model 2: PFDR<0.001). **Conclusions:** The findings of this study revealed significant associations between MDRS and cognitive decline, suggesting a potential role of tau pathology and neuroinflammation in the link between MDRS and poorer cognitive performance in individuals without dementia. Consequently, the MDRS holds promise as a tool for targeted preventive interventions in individuals at high risk of cognitive impairment. **Keywords:** Modified dementia risk scores, Alzheimer's disease, cognition, amyloid-β, tau, neuroinflammation.

P44- ASSOCIATIONS OF METABOLIC SYNDROME WITH RISKS OF DEMENTIA AND COGNITIVE IMPAIRMENT: A SYSTEMATIC REVIEW AND META-ANALYSIS.

S.D Qiu[1,2], L. Tan[1,2] *(1. Nanjing Medical University - Qingdao (China), 2. Qingdao Municipal Hospital - Qingdao (China))*

Background: Previous studies have linked metabolic syndrome (MetS) to dementia risk. We conducted a systematic review and meta-analysis to assess the association between MetS and dementia as well as cognitive impairment, with additional focus on individual MetS component. **Methods:** We systematically searched the PubMed, Embase, and Cochrane Library databases from inception through July 2024. We used random-effects models to calculate relative risks (RRs) and odds ratios (ORs) with 95% confidence intervals (CIs). Publication bias was evaluated using the Egger's test, while potential sources of heterogeneity were investigated through meta-regression, subgroup, and sensitivity analyses. **Results:** Our analysis included 21 studies with a total of 411,810 participants. MetS was associated with increased risks of all-cause dementia (RR =1.33, 95% CI =1.03–1.71, I² =85.8%) and vascular dementia

(RR =2.07, 95% CI =1.32–3.24, I² =10.1%), but not Alzheimer's disease (RR =1.10, 95% CI =0.64–1.91, I² =81.8%). Regarding cognitive impairment, longitudinal studies showed an increased risk (OR =1.38, 95% CI =1.24–1.53, I²=3.3%), with similar findings in cross-sectional studies (OR=1.65, 95% CI =1.19–2.28, I² =85.3%). **Conclusions:** This study found that MetS is significantly associated with increased risks of dementia and cognitive impairment, with each component potentially being a modifiable factor. These findings may help guide clinicians in recommending lifestyle interventions to prevent cognitive decline and promote brain health. **Keywords:** Alzheimer's disease, cognitive impairment, dementia, meta-analysis. **Disclosures:** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

P45- LECANEMAB TREATMENT FOR ALZHEIMER'S DISEASE OF VARYING SEVERITIES AND ASSOCIATED SERUM BIOMARKERS MONITORING: A REAL-WORLD STUDY IN CHINA. S. Chen[1], Q. Wei[1], R. Ou[1], S. Wei[1], C. Li[1], X. Chen[1], H. Shang[1] *(1. West China hospital - Chengdu (China))*

Introduction: We updated real-world efficacy and safety data of lecanemab in a Chinese Alzheimer's disease (AD) population and evaluated dynamic monitoring of AD-related serum biomarkers for efficacy assessment. **Methods:** A prospective cohort study enrolled 58 AD patients (CDR 0.5–1.0, n=45). Assessments were conducted at baseline (V0), 2.5 months (V1), and 7 months (V2). Cognitive function was measured using the Alzheimer's Disease Assessment Scale – Cognitive Subscale (14-item version) (ADAS-Cog 14), Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), and Frontal Assessment Battery (FAB). Serum biomarkers, including neurofilament light chain (NFL), glial fibrillary acidic protein (GFAP), amyloid-β (Aβ) 1–40, Aβ 1–42, phosphorylated tau 181 (p-tau 181), and p-tau 217, were monitored by at each visit. **Results:** 77.59% had mild cognitive impairment or mild dementia, and 60.34% carried the APOE4 (ε4). At V1, significant improvements were observed in ADAS-Cog 14 (-7.32, p<0.001) and MoCA (+4.62, p<0.001), while no changes were seen in MMSE and FAB. Only serum p-tau 181 showed a significant decrease (p=0.031). At V2, improvements in ADAS-Cog 14 (-7.34, p<0.001) and MoCA (+2.52, p=0.007) were observed. Serum p-tau181 significantly decreased (p<0.001). Subgroup analysis showed that males benefitted more than females, while carrying ε4 had no significant effect on treatment efficacy. Correlation analysis showed significant relationships between ADAS-Cog 14 and p-tau181 (r=0.281, p = 0.044) and GFAP (r=0.276, p = 0.048). The mixed-effects model showed a significant association between p-tau 181 and ADAS-Cog 14 (β = 0.4049, p = 0.003). No serious adverse events were reported. Infusion reactions occurred in 6.90%, and 8.62% discontinued treatment due to asymptomatic amyloid-related imaging abnormalities (ARIA). One patient with severe white matter lesions (Fazekas III) experienced psychiatric worsening and stopped treatment. **Discussion:** Lecanemab is safe and effective, with better efficacy in male and mild AD. Monitoring ADAS-Cog14 and p-tau 181 may aid treatment assessment. Patients with severe cognitive impairment and white matter lesions need to closely monitored for adverse events such as ARIA. **Conflicts of interest:** All authors declare no conflicts of interest. **Keywords:** Alzheimer's disease, Lecanemab, serum biomarkers, real-world study.

P46- ABNORMAL EYE MOVEMENT AND BRAIN ACTIVATION IN COGNITIVE DISORDERS: EVIDENCE OF BIOMARKERS AND BRAIN ACTIVATION. C. Du[1], J. Shi[1] *(1. Department of Neurology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China - Hefei (China))*

Background: Eye-tracking analysis shows promise in distinguishing cognitive impairment, yet comprehensive understanding of relationships between oculomotor patterns, cognitive domains, and neuropathological biomarkers across the Alzheimer's disease (AD) spectrum remains incomplete. **Aims:** This study investigated correlations between eye movement parameters and AD biomarkers, evaluated their diagnostic utility across clinical stages, and compared frontal eye field activation patterns between cognitively impaired individuals and healthy controls. **Methods:** From the China Aging and Neurodegenerative Initiative (CANDI) cohort, 162 participants were stratified into cognitively normal (CN, n=45), mild cognitive impairment (MCI, n=66), and dementia (n=51) groups. Functional near-infrared spectroscopic (fNIRS) measurements were performed on the subjects during the execution of the eye movement task(smooth pursuit, pro-saccade, anti-saccade). Individuals were examined with neurocognitive scales, plasma and cerebrospinal fluid biomarkers, and 18F-flobetapir PET scans. **Results:** Compared with the MCI group, the dementia group had longer completion time and lower accuracy rate on smooth pursuit, pro-saccade, and anti-saccade tasks. Accuracy and error correction rate on anti-saccade tasks of CN were higher than MCI (P < 0.05). There was a strong correlation between eye movement parameters and Trail Making Test Part A (TMTA) and Boston Naming Test (BNT) scales In CN and MCI. Accuracy on anti-saccade tasks are strongly correlated with CSF-Aβ40 and CSF-Aβ40 in dementia patients (P < 0.05). MCI and dementia were divided into negative and positive groups according to 18F-flobetapir (AV-45) PET-CT. It was found that there were significant differences in anti-saccade completion time and error correction rate between the two groups. The diagnostic model combining anti-saccade completion time, error correction rate and BNT score exhibited favorable diagnostic efficacy in discriminating AV-45 positive PET-CT from the negative (AUC = 0.764, p < 0.001). Near infrared results show that the MCI patients when performing a smooth track on the right side of the frontal eye area activated than dementia group, but lower than normal group. **Conclusions:** Eye-tracking features are correlated with biomarkers of cognitive impairment. Eye movement assessment combined with cognitive scale is feasible for the detection of AD.

P47- MECHANISMS OF ALZHEIMER'S DISEASE PROMOTED BY PERIODONTITIS: THE RELATIONSHIP BETWEEN CLINICAL SYMPTOMS, VIRULENCE FACTORS, AND BRAIN STRUCTURE. J.H. Li[1], T.H. Lian[1], J. Li[1], P. Guo[1], J. Qi[1], D.M. Luo[1], H. Yue[1], Z.J. Zheng[1], Z. Liu[1], F. Zhang[1], W. Zhang[1] *(1. Beijing Tiantan Hospital - Beijing (China))*

Background: Periodontitis is a prevalent condition among patients with Alzheimer's disease (AD), whose causative agent is known to secrete the virulence factor gingipain. The objective of this study was to investigate the clinical manifestations of AD with periodontitis, the correlation between the virulence factor and the brain structure, and to elucidate the mechanism by which periodontitis contributes to the progression of AD. **Methods:** 1. The study included 110 patients with mild cognitive impairment and dementia due to AD (AD-MCI and

AD-D). 2. A series of neuropsychological scales were employed for the evaluation of clinical symptoms, including cognitive function, neuropsychiatric symptoms, and the ability to perform activities of daily living. Cerebrospinal fluid levels of the virulence factor gingipain K (K-GP) were quantified by enzyme-linked immunosorbent assay. 4. Cerebral cortex volume was calculated by voxel-based brain morphometry. 5. Differences in cerebral cortex volume were compared between groups. 6. The relationship between cerebral cortex volume and virulence factors and clinical symptoms was investigated by using bivariate correlation methods and regression analyses. **Results:** 1. Changes in cerebral cortex volume in patients with periodontitis at different stages of AD: compared with the AD-MCI without periodontitis group, the volume of the precuneus lobe in the AD-MCI with periodontitis (AD-MCI-P) group was significantly reduced. Compared with the AD-D without periodontitis group, the volume of the precentral gyrus, inferior frontal gyrus, superior frontal gyrus and orbitofrontal cortex in the AD-D with periodontitis (AD-D-P) group was significantly reduced (all P<0.05). 2. In the AD-MCI-P group, the higher the K-GP level, the smaller the precuneus lobe volume, the worse the overall cognitive function, and the more obvious the memory impairment (all P<0.05). In the AD-D-P group, the higher the K-GP level, the smaller the volume of the inferior frontal gyrus and orbitofrontal cortex. The smaller the volume of the inferior frontal gyrus, the worse the overall cognitive function and language function. The smaller the volume of the orbitofrontal cortex, the worse the memory and the worse the overall mental and behavioral symptoms (all P<0.05). **Conclusions:** AD Patients with periodontitis had significant reductions in cortical volume of brain regions. In the MCI stage, elevated K-GP levels caused a significant reduction in precuneus volume, leading to a significant decline in overall cognitive function and significant memory impairment. In the dementia stage, elevated K-GP levels caused volume reductions in the inferior frontal gyrus and orbitofrontal cortex. The significant volume reductions in the inferior frontal gyrus were associated with significant decreases in overall cognitive function and impaired language function, while significant volume reductions in the orbitofrontal cortex may accelerate memory impairment and lead to the emergence of neuropsychiatric symptoms. **Keywords:** Alzheimer's disease, periodontitis, porphyromonas gingivalis, gingipain, neuroimaging. **Disclosures:** The authors declared no competing interests.

P48- RESEARCH PROGRESS ON MALNUTRITION AND NUTRITIONAL SUPPORT IN ALZHEIMER'S DISEASE.
Z. Liu[1], M. He[1], W. Zhang[2] *(1. Department of Neurology, Beijing Tiantan Hospital, Capital Medical University - Beijing (China), 2. Center for Cognitive Neurology, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University - Beijing (China))*

Objective: Alzheimer's disease (AD) and malnutrition are common diseases in old age and are closely related to each other. This review focuses on the relationship between the two diseases and the role of nutritional support in AD to provide a basis for the search of new targets for AD prevention and treatment. **Materials and Methods:** The data were analyzed by Pubmed, CNKI using the databases of "Alzheimer's disease", "malnutrition", "vitamins", and "dietary patterns". The databases were searched using the terms "Alzheimer's disease", "malnutrition", "vitamins" and "dietary patterns" to review the relevant literature and summarize the latest research progress. **Results:** 1. Malnutrition is a risk factor for the occurrence and progression of AD, and AD patients who are malnourished and at nutritional risk suffer from faster cognitive decline and more rapid progression of behavioral and psychological symptoms. 2. AD increases the risk of malnutrition, and patients with AD suffer from a variety of nutrient deficiencies. The two promote each other and damage the health of patients. 3. Mechanisms by which malnutrition and AD interact: (1) Pathological changes in AD affect hypothalamic neurons, inhibit feeding, and cause dysfunction in leptin-related conduction pathways, resulting in lower body weight and fat mass. (2) Decreased appetite in AD patients was associated with hypoperfusion in the anterior cingulate gyrus and orbital frontal cortex, and eating disorders were associated with decreased blood perfusion in the left inferior temporal gyrus, suggesting that blood perfusion in the relevant brain regions has an impact on eating. (3) Weight loss in AD patients was associated with reduced glucose metabolism in the medial prefrontal cortex region, and decreased fat mass was the main cause of weight loss. (4) Clinical symptoms reduce eating and increase energy expenditure: cognitive and behavioral symptoms affect food intake and increase energy expenditure, causing malnutrition in patients with AD. 4 The Mediterranean diet, MIND diet, and others reduce the risk of AD and decrease beta amyloid deposition in the brain. Supplementation of nutritional elements alone can reduce the risk of AD development to varying degrees, improve cognition, and delay the onset of behavioral and psychological symptoms. **Conclusions:** Malnutrition is a risk factor for the development and progression of AD and can aggravate psychobehavioral symptoms, while the risk of malnutrition is elevated in patients with AD, and the two contribute to each other and affect the prognosis. Pathological changes in AD affect the regulation of feeding-related neurons and leptin loops, which are closely related to the occurrence of malnutrition. Healthy dietary patterns reduce AD pathology and risk, and nutrient supplementation has a positive effect on reducing AD risk and improving prognosis. Future studies are expected to further elucidate the mechanisms by which malnutrition and AD interact, as well as high-quality trials to determine the therapeutic and preventive effects of specific nutrients on AD. **Keywords:** Alzheimer's disease, malnutrition, research progress.

P50- CLINICAL CHARACTERISTICS, BIOMARKERS AND NEUROIMAGING CHANGES IN PATIENTS WITH ALZHEIMER'S DISEASE AND OBSTRUCTIVE SLEEP APNEA.
L. Dongmei[1], Z. Wei[1] *(1. Beijing Tiantan Hospital - Beijing (China))*

Background: To explore the clinical characteristics, biomarkers, structural neuroimaging changes in patients with Alzheimer's disease (AD) and obstructive sleep apnea (OSA). **Methods:** 213 AD patients were divided into AD with OSA (AD-OSA) group and AD without OSA (AD-nOSA) group. Demographics, cognition function, fluid and imaging biomarkers were compared between two groups. Multiple linear regression and mediation analyses were used to explore associations between OSA, biomarkers, and clinical symptoms. **Results:** 80 AD-OSA patients (37.6%) were included. AD-OSA group was older, had higher BMI, and showed worse cognitive performance and higher neuropsychiatric scores compared to AD-nOSA group. CSF analysis revealed altered levels of biomarkers (e.g., MMP-9, NO, P-tau, Orexin) in AD-OSA patients. Mediation analyses suggested that certain biomarkers, such as IL-1β, NO and P-tau(T181), mediated the relationship between OSA and cognitive decline. Brain imaging showed

reduced GMV in temporal, cerebellar, and visual regions. Cortical thickness decreased in the right cuneus and left temporal pole. **Conclusions:** OSA exacerbates AD pathology through neuroinflammation, tau hyperphosphorylation, and brain atrophy, contributing to accelerated cognitive and functional deterioration. These findings highlight the potential impact of OSA on the progression of AD and suggest that targeting OSA may offer therapeutic potential for AD patients. **Keywords:** Alzheimer's disease, obstructive sleep apnea, cognitive impairment, biomarker, neuroimaging. **Disclosures:** The authors declared no competing interests. **References:** Fernandes M, et al. Nocturnal Hypoxia and Sleep Fragmentation May Drive Neurodegenerative Processes: The Compared Effects of Obstructive Sleep Apnea Syndrome and Periodic Limb Movement Disorder on Alzheimer's Disease Biomarkers. Journal of Alzheimer's disease: JAD. 2022;88(1):127-39. https://doi.org/10.3233/JAD-215734.

P51- A CONVERSION FRAMEWORK FOR CDR-SB AND MOCA SCORES IN ALZHEIMER'S DISEASE AND RELATED DEMENTIA.

B. Haji[1], Q. Zhang[1], A.A. Tahami Monfared[1,2] *(1. Eisai Inc. - Nutley (United States), 2. McGill University - Montreal (Canada))*

Background: Accurate assessment of cognitive impairment is essential for effective Alzheimer's disease (AD) management and research. However, the absence of validated methods to translate scores between widely used instruments—such as the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) in trials and the Montreal Cognitive Assessment (MoCA) in clinical practice-poses a significant barrier. This limits data harmonization, impedes cross-study comparability, and complicates the integration of clinical and research evidence. Bridging this gap is critical for consistent staging, longitudinal monitoring, and data-driven decision-making in AD and related dementias. This study aimed to develop and validate bidirectional score conversion tables between CDR-SB and MoCA using a large, diverse cohort spanning the full spectrum of cognitive function. **Methods:** A retrospective, cross-sectional analysis was conducted using data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set, which aggregates standardized assessments from 35 U.S.-based Alzheimer's Disease Research Centers. Individuals were included if they had at least one visit with both CDR-SB and MoCA administered on the same day between January 2015 and September 2024. The final cohort comprised 23,717 individuals (59,871 visits) across normal cognition, mild cognitive impairment (MCI), and dementia. Bidirectional crosswalk tables were derived using equipercentile equating with log-linear smoothing, with optimal smoothing parameters selected by minimizing mean squared error, Akaike Information Criterion, and Bayesian Information Criterion. Concordance between raw and converted scores was assessed using Spearman's rank correlation and Bland-Altman plots. Subgroup analyses were performed in an AD-specific cohort to evaluate generalizability. **Results:** CDR-SB and MoCA scores demonstrated a strong inverse correlation (Spearman's $\varrho = -0.68$; $p < 0.001$). The equipercentile crosswalks enabled direct, bidirectional translation of scores between CDR-SB and MoCA, preserving the relative ranking of individuals and accommodating non-linearities, floor and ceiling effects, and differing score ranges. Bland-Altman analyses confirmed minimal bias and acceptable limits of agreement across the full range of cognitive severity. Subgroup analyses in individuals with a primary diagnosis of AD yielded comparable results, supporting the generalizability of the conversion framework. The crosswalk tables performed consistently across the cognitive spectrum, demonstrating robust agreement in both the full cohort and AD-specific subgroups. **Conclusions:** This study provides the first validated, bidirectional CDR-SB–MoCA crosswalk, supporting data harmonization and consistent interpretation of cognitive severity across research and clinical settings. The availability of empirically derived conversion tables enables clinicians, researchers, and policymakers to bridge the gap between clinical trial endpoints and real-world cognitive screening. This framework facilitates longitudinal monitoring, data pooling, and meta-analyses across studies using different cognitive measures, and has the potential to inform regulatory, reimbursement, and health policy decisions. By enhancing interoperability between cognitive assessment tools, this work supports more precise disease staging, improved patient stratification, and evidence-based decision-making in Alzheimer's disease and related dementias. **Keywords:** Alzheimer's disease, dementia, CDR-SB, MoCA, crosswalk, equipercentile equating, cognitive assessment, NACC database. **Disclosures:** Babak Haji and Quanwu Zhang are employees of Eisai Inc. Amir Abbas Tahami Monfared is also an employee of Eisai Inc. and holds the position of Adjunct Professor in the Department of Epidemiology, Biostatistics, and Occupational Health at McGill University. Additionally, he serves as an Associate Editor for the Journal of Alzheimer's Disease, for which he receives no honorarium. Eisai Inc. provided funding for this study. The authors declare no other competing interests.

P52- CORTICAL ACTIVATION AND NETWORK CONNECTIVITY IN HEALTHY INDIVIDUALS DURING THE MEMTRAX MEMORY TEST USING FNIRS.

J. Qiu[1], Y. Zhang[1], C. Zhang[1], H. Deng[1], J. Zhu[1], Y. Duan[1], X. Liu[1] *(1. The First Affiliated Hospital of Kunming Medical University - Kunming (China))*

Background: MemTrax is a rapid image-recognition task designed to probe episodic memory and multiple other cognitive domains. Although prior work has implicated MemTrax performance in engaging episodic memory, attention, visuospatial processing, and executive function, the domain-specific patterns of cortical activation and inter-regional network connectivity elicited during task execution remain uncharacterized. Functional near-infrared spectroscopy (fNIRS) provides a non-invasive, high-temporal-resolution method for monitoring task-evoked hemodynamic changes in the cerebral cortex. This study, therefore, aimed to delineate the spatial activation profiles and functional connectivity dynamics evoked by MemTrax in a cohort of healthy adults and to assess how age and task performance modulate these neural responses. **Methods:** MemTrax was administered with fNIRS monitoring of task accuracy, reaction time, and oxygenated hemoglobin (HbO) concentration. Individuals were stratified by accuracy and age and underwent independent sample t-tests. Data were processed in NirSpark, where optodes were mapped to Broca's areas based on the cap layout. Functional Connectivity (FC) between predefined regions of interest was quantified, and spatial activation maps were generated in MATLAB R2024a. **Results:** MemTrax elicited robust activation in prefrontal, parietal, and temporal cortices— regions implicated in episodic memory, attention, and executive control. FC during task execution was significantly greater than during rule exposition ($P < 0.001$). Across predefined ROIs, task-state FC increased by 13.01%–64.33%, with the secondary visual cortex (V2), executive function, working memory, attention, visuospatial working memory, and Broca's areas each showing > 50% enhancement.

During rule exposition, individuals achieving 100% accuracy exhibited a superior coordination in the sensory cortex and oculomotor regions, including the frontal lobe, compared with lower accuracy individuals (P < 0.05). Age groups demonstrated significant differences in frontal activation (P < 0.001), bilateral executive and working memory regions (P < 0.05), and bilateral attention areas (P < 0.05) throughout the MemTrax task. **Conclusions:** The MemTrax task elicited extensive cortical activation, most prominently in the prefrontal region. Relative to routine communication activities, it provoked stronger hemodynamic responses and substantially enhanced functional connectivity within networks supporting visual integration, executive function, working memory, and attention, with concomitant increases in motor, sensory, and language areas. These results indicate that the MemTrax recruits multiple higher-order cognitive processes and diverse neural circuits, underscoring its utility for comprehensive cognitive assessment. **Keywords:** Healthy population, brain function, fNIRS, MemTrax task. **Clinical Trial Registry:** ChiCTR2200062493; https://www.chictr.org.cn. **Disclosures:** This work was supported by the Kunming Medical University Innovation Team for Clinical Diagnosis and Treatment of Neuropsychiatric Diseases (Grant No. KYCXTD202104). The authors declared no competing interests.

P53- MEMTRAX MEMORY TEST COMBINED WITH INTELLIGENT EYE-TRACKING SYSTEM IN ALZHEIMER'S DISEASE DIAGNOSIS. Y. Zhang[1], J. Qiu[1], C. Zhang[1], H. Deng[1], J. Zhu[1], X. Liu[1] (*1. The First Affiliated Hospital of Kunming Medical University - Kunming (China)*)

Background: Early Alzheimer's disease (AD) diagnosis is hampered by cultural and educational bias in standard neuropsychological tests and the invasiveness or cost of established biomarkers such as PET. To address these limitations, we developed an integrated screening protocol that combines the MemTrax rapid image-recognition memory test (MTX) with an intelligent eye-tracking system for the efficient detection of cognitive impairment in the community. **Methods:** Participants completed the MemTrax test via an online platform while an eye tracking system recorded pro saccade latency and duration, anti saccade accuracy and error correction rate, and smooth pursuit gain. Characteristic oculomotor features were selected using Lasso regression, and a logistic regression model was built to classify patients with Alzheimer's disease versus cognitively normal controls. We then combined this eye tracking model with MemTrax percent correct metrics to assess incremental diagnostic accuracy. **Results:** Compared with controls, patients with AD exhibited prolonged pro-saccade latency (P = 0.002), increased pro-saccade duration (P < 0.001), reduced anti-saccade accuracy (P < 0.001), and lower error-correction rates (P < 0.001). The eye-tracking classifier achieved an area under the curve of 0.930 (95% CI , 0.888-0.972) with a sensitivity of 0.851 and a specificity of 0.889. Integrating MemTrax performance (%C) raised the combined model AUC to 0.932, significantly outperforming MemTrax alone (AUC 0.861; P < 0.05) and matching MoCA performance (AUC 0.924; P > 0.05). Differentiation between mild cognitive impairment and dementia stages remained moderate (AUC 0.830). **Conclusions:** Eye-movement parameters provide sensitive, noninvasive biomarkers for AD. Combining intelligent eye-tracking with the MemTrax memory test yields a high performance, scalable screening protocol suitable for community deployment. Future multicenter longitudinal studies are needed to validate its generalizability and explore utility in disease monitoring. Eye movement parameters provide sensitive, noninvasive biomarkers for Alzheimer's disease. Combining intelligent eye tracking with the MemTrax memory test yields a high performance, scalable screening protocol suitable for community deployment. Future multicenter longitudinal studies are needed to validate its generalizability and explore utility in disease monitoring. **Keywords:** Alzheimer's disease, machine learning, diagnostic model, auxiliary screening. **Clinical Trial Registry:** ChiCTR2200062493; https://www.chictr.org.cn. **Disclosures:** This work was supported by the Kunming Medical University Innovation Team for Clinical Diagnosis and Treatment of Neuropsychiatric Diseases (Grant No. KYCXTD202104). The authors declared no competing interests.

P54- RAMAN SPECTROSCOPY COMBINED WITH ENSEMBLE LEARNING A NOVEL SCREENING TOOL FOR COGNITIVE IMPAIRMENT. Y. Mo[1], Y. Xu[1] (*1. Affiliated Drum Tower Hospital, Medical School of Nanjing University - Nanjing (China)*)

Background: Early screening and treatment are crucial for improving its prognosis. Currently, cognitive assessments are time-consuming, and their results are susceptible to interference from factors like education level, cooperation, and dialect. There is an urgent need to develop low-cost, easily accessible screening methods, such as blood tests. Raman spectroscopy, a non-destructive analytical technique with simple operation and low cost, is well-suited for large-scale disease screening. Ensemble learning can rapidly process complex spectral data, facilitating the standardized application of Raman spectroscopy. This study aims to utilize serum Raman spectroscopy combined with ensemble learning to provide a novel hematological method for cognitive impairment screening. **Methods:** This study enrolled 220 subjects (93 subjects with normal cognition, 70 subjects with mild cognitive impairment, 57 subjects with dementia) from Nanjing Drum Tower Hospital as the training and testing datasets (modeling dataset), with an additional independent cohort of 40 subjects (14 subjects with normal cognition, 16 subjects with mild cognitive impairment, 10 subjects with dementia) recruited from the community as the validation dataset. All participants underwent Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Activity of Daily Living Scale, along with serum sample collection. Raman spectroscopy testing was performed on the serum samples. After spectral preprocessing, unsupervised clustering and other methods were employed to analyze spectral characteristics and derive additional features. The ensemble learning utilized stacking with data labels determined by voting. Model evaluation metrics included accuracy, sensitivity, and specificity. **Results:** In the modeling dataset, significant differences were found in age, MMSE, and MoCA among participants with normal cognition, mild cognitive impairment, and dementia, while no significant differences were observed in sex or years of education. In the validation dataset, significant differences were identified in MMSE and MoCA among the three groups, with no significant differences in age, sex, or years of education. The ensemble learning model, constructed by stacking a linear discriminant model, an artificial neural network, and a multilayer perceptron, achieved an accuracy of 0.85, average sensitivity of 0.85, and average specificity of 0.92 on the test set. For cognitive classification in the validation dataset, the accuracy was 0.80, with average sensitivity of 0.80 and average specificity of 0.89. Feature weights in the linear discriminant model were ranked,

revealing the top three Raman intensity: 1602 cm⁻¹, 1002 cm⁻¹, and 1666 cm⁻¹. **Conclusions:** Serum Raman spectroscopy combined with ensemble learning can identify cognitive impairment and provide refined grading. The Raman intensity at 1602 cm⁻¹, 1002 cm⁻¹, and 1666 cm⁻¹ are key indicators of cognitive impairment progression. **Keywords:** Raman, ensemble learning, cognitive impairment. **Clinical Trial Registry:** MR-32-25-006642; https://www.medicalresearch.org.cn. **Disclosures:** The authors declared no competing interests.

P55- INTEGRATED PROTEOMIC AND NEUROIMAGING BIOMARKERS OF FRAILTY PREDICT ACCELERATED COGNITIVE DECLINE IN AGING POPULATIONS.

R. Lu[1] *(1. Tiantan Hospital of Beijing City - Beijing (China))*

Background: While frailty is recognized as a risk factor for dementia, its neurobiological mechanisms in pre-dementia stages remain unclear. This study examined how frailty contributes to cognitive decline in non-dementia elderly through multimodal biomarker analysis. **Methods:** We analyzed data from ADNI (n=612) and CLHLS (n=10,053) cohorts. CSF proteomics (SomaScan 7K) and DTI metrics (40 tracts) were used to identify axonal pathology. Differential protein expression was analyzed with Limma, followed by functional enrichment (GO/KEGG/GSEA). Machine learning models (including XGBoost and random forest) with SHAP analysis identified predictive white matter features. **Results:** Frailty significantly increased cognitive decline risk in both cohorts. Proteomics revealed axon integrity disruption, supported by DTI showing microstructural abnormalities in 14 white matter tracts including the cingulum (hippocampus) and corpus callosum. Significant correlations emerged between axonal protein levels, white matter integrity (MD), and cognitive function. **Conclusions:** Our findings demonstrate that frailty accelerates cognitive decline in non-dementia elderly, with axonal degeneration as a potential underlying mechanism. DTI-derived white matter metrics may serve as early biomarkers for cognitive risk prediction. **Keywords:** Frailty, axonal degeneration, diffusion tensor imaging, machine learning, cognitive decline. **Declaration of interests:** The authors declare no competing interests. The authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication.

P56- CLINICAL VALIDATION OF PLASMA BRAIN DERIVED TAU IN ALZHEIMER'S DISEASE: ASSOCIATIONS WITH CORE Aβ AND TAU BIOMARKERS, NEUROFILAMENT LIGHT, AND GFAP.

H. Deng[1], Y. Zhang[1], J. Qiu[1], C. Zhang[1], J. Zhu[1], J. Liu[1], X. Liu[1] *(1. The First Affiliated Hospital of Kunming Medical University - Kunming (China))*

Background: Brain derived tau (BD Tau) is a novel blood biomarker highly specific for Alzheimer's disease, originating exclusively from brain tau and unaffected by peripheral sources. This specificity enables more accurate assessment of AD related neuronal injury and tau pathology. However, its clinical correlations with core AD biomarkers (Aβ₄₂, Aβ₄₀, Aβ₄₂/Aβ₄₀, p Tau217), the neurodegeneration marker NfL, and the neuroinflammation marker GFAP remain unvalidated. **Methods:** A cross-sectional analysis was conducted on patients from the AD cohort at First Affiliated Hospital of Kunming Medical University. Single-molecule array (Simoa) technology was used to measure plasma concentrations of BD-Tau, Aβ42, Aβ40, the Aβ42/40 ratio, p-Tau217, GFAP, and NfL. After excluding Grubbs test outliers (p < 0.05), Spearman correlations were computed. **Results:** A total of 10 patients were enrolled, with 9 included in the final analysis after removal of outliers. Of these, three were male (33.33%) and six female (66.67%), with a mean age of 71 years. Educational attainment was ≤9 years in 4 patients (44.44%), 11 years in 2 (22.20%), and ≥15 years in 3 (33.33%). APOE genotypes included ε2/ε3 in 1 patient (11.11%), ε3/ε3 in 4 (44.44%), ε3/ε4 in 2 (22.22%), and ε4/ε4 in 2 (22.22%). BD-Tau showed no significant correlation with Aβ42 (r = 0.183, p = 0.637), but was significantly positively correlated with Aβ40 (r = 0.733, p = 0.025) and negatively correlated with the Aβ42/Aβ40 ratio (r = −0.698, p = 0.037). No significant correlation was observed with p-Tau217 (r = 0.167, p = 0.693); however, a trend toward a negative correlation with the Aβ42/p-Tau217 ratio was noted (r = −0.500, p = 0.207). Additionally, BD-Tau showed positive correlation trends with GFAP (r = 0.433, p = 0.224) and NfL (r = 0.617, p = 0.077), although these did not reach statistical significance. **Conclusions:** In this AD cohort, BD-Tau correlated with multiple peripheral biomarkers. It showed a significantly positive association with Aβ40 and an inverse relationship with the Aβ42/Aβ40 ratio, indicating its potential to reflect Aβ40-related pathology and Aβ–Tau interactions. Although not statistically significant, trends with the Aβ42/p-Tau217 ratio, NfL, and GFAP suggest BD-Tau may also mirror tau pathology, axonal injury, and astrocyte activation. These results support a multi-biomarker strategy for early AD diagnosis. Given the small sample size and cross-sectional design, larger, multicenter, longitudinal studies are warranted to validate these dynamic associations and to explore BD-Tau's value in predicting disease progression and guiding individualized management. **Keywords:** BD-Tau, p-Tau217, Aβ42/40, biomarker. **Clinical Trial Registry:** ChiCTR2200062493; https://www.chictr.org.cn. **Disclosures:** This work was supported by the Kunming Medical University Innovation Team for Clinical Diagnosis and Treatment of Neuropsychiatric Diseases (Grant No. KYCXTD202104). The authors declared no competing interests.

P57- EVALUATION OF THE CLINICAL EFFICACY OF LECANEMAB IN ALZHEIMER'S DISEASE BASED ON CDR-SB SCORES AND FNIRS: A PROSPECTIVE COHORT STUDY WITH SIX-MONTH FOLLOW-UP ANALYSIS.

C. Zhang[1], Y. Duan[1], J. Qiu[1], Y. Zhang[1], H. Deng[1], W. Ouyang[1], L. Xiaolei[1] *(1. The First Affiliated Hospital of Kunming Medical University - Kunming (China))*

Background: Lecanemab, an anti Aβ monoclonal antibody, has shown promise in slowing cognitive decline in early Alzheimer's disease. The Clarity AD trial used CDR SB as its primary efficacy endpoint. In this six-month prospective real-world cohort, we combined CDR-SB with fNIRS to dynamically assess cognitive changes and brain network alterations after lecanemab treatment, providing multidimensional, objective evidence of clinical efficacy. **Methods:** We enrolled AD patients meeting 2024 NIA AA criteria who received six months of lecanemab and completed baseline and six month CDR SB and fNIRS assessments; those with severe aphasia, major disability or psychiatric illness were excluded. CDR SB changes were tested by Wilcoxon signed rank (α = 0.05). fNIRS connectivity under resting, VFT and MemTrax conditions was extracted via NirSpark and compared by paired t tests with FDR correction (P < 0.05). **Results:** 1. Eight AD patients (three males; mean age, 65.7 ± 10.8 years) completed the study. Education spanned 6 years (12.5%), 9 years (12.5%), 12 years (37.5%) and ≥ 15 years (37.5%); APOE genotypes

were ε2/ε3 (12.5%), ε3/ε3 (37.5%), ε3/ε4 (37.5%) and ε4/ε4 (12.5%). 2. CDR-SB Scores: Scores fell from 3.86 ± 2.20 to 2.88 ± 1.89 over six months (median Δ = 1.00 [IQR 0.13–1.38]; Z = –2.226, P = 0.026). 3. fNIRS Functional Connectivity: a). Resting-state: 87.30% of 63 channels showed increased FC (predominantly prefrontal–limbic), with all 14 ROIs enhanced, notably in language and default mode networks. b). MemTrax task state: 76.32% of 76 channels showed increased FC (mainly in the frontoparietal region); 5 of 7 ROIs also increased. c). Verbal Fluency Task (VFT) state: No channel level changes; 75.00% of 8 ROIs increased. None survived FDR correction, likely due to small sample size. 4. Safety Evaluation: No ARIAs were detected on MRI before infusions on the 5th, 7th, and 14th. No other adverse events occurred during the infusion period. **Conclusions:** Six-month treatment with lecanemab significantly improved CDR-SB scores in patients with early-stage Alzheimer's disease, supporting its potential to slow disease progression. fNIRS analysis revealed a general trend of enhanced functional connectivity under both resting-state and task-related conditions, providing mechanistic insights despite the lack of statistical significance after multiple comparison correction. No ARIA or other adverse events were observed during the treatment period, indicating a favorable safety profile. Further validation of the brain network modulation effects is warranted in larger, multicenter studies with extended follow-up. Additionally, the feasibility of using fNIRS-based metrics as objective biomarkers for treatment monitoring should be explored. **Keywords:** Alzheimer's disease, lecanemab, efficacy evaluation, fNIRS, CDR-SB. **Clinical Trial Registry:** ChiCTR2200062493; https://www.chictr.org.cn. **Disclosures:** This work was supported by the Kunming Medical University Innovation Team for Clinical Diagnosis and Treatment of Neuropsychiatric Diseases (Grant No. KYCXTD202104). The authors declared no competing interests.

P58- ASSOCIATION OF PLASMA P-TAU-217, Aβ42/P-TAU-217 RATIO, NFL, GFAP, AND EYE MOVEMENT SCORES WITH TAU PET PATHOLOGICAL STAGING IN ALZHEIMER'S DISEASE. J. Zhu[1], J. Qiu[1], Y. Zhang[1], C. Zhang[1], H. Deng[1], W. Ouyang[1], X. Liu[1] *(1. The First Affiliated Hospital of Kunming Medical University - Kunming (China))*

Background: The 2024 NIA AA criteria introduce a clinical–pathological staging model for Alzheimer's disease. While plasma Aβ42, Aβ40, p Tau-217, NfL, and GFAP are promising AD biomarkers, their links to Tau PET stages remain underexplored. Composite measures like Aβ42/p Tau217 and eye movement scores may improve staging. This cross sectional study in an AD cohort examines (1) correlations between these peripheral markers and Tau PET stage and (2) the application of the staging framework for early classification. **Methods:** Patients meeting 2024 NIA AA AD criteria with Aβ PET positivity and completed Tau PET, eye movement, and plasma biomarker (Aβ42, Aβ40, Aβ42/40, p Tau-217, GFAP, NfL) assessments were enrolled; those with other cognitive disorders, severe aphasia, significant disability, or psychiatric illness were excluded. Plasma biomarkers were quantified by Simoa. Spearman rank correlations with ordinal Tau PET stages were performed, using two sided α = 0.05. **Results:** Fourteen AD patients (mean age 65.3 ± 12.6 years; 57% male) were enrolled; education spanned ≤ 1 year (7%), 9–11 years (29%) and ≥ 12 years (64%); APOE genotypes were ε2/ε3 (21%), ε3/ε3 (14%), ε3/ε4 (36%), ε4/ε4 (7%) and unknown (21%). Only 1 (7%) followed the expected clinical–pathological trajectory, whereas 13 (93%) exhibited a "comorbidity" trajectory.

Tau PET pathological staging was significantly positively correlated with plasma p-Tau-217 (ϱ = 0.6738, p = 0.0466) and strongly correlated with NfL (ϱ = 0.8085, p = 0.0151). Positive correlations were also observed with GFAP (ϱ = 0.639, p = 0.0881) and age (ϱ = 0.5073, p = 0.0641), although these did not reach statistical significance. Negative correlations were noted for Aβ42/p-Tau-217 ratio (ϱ = –0.5751, p = 0.1052) and eye movement score (ϱ = –0.533, p = 0.0914), although they did not reach statistical significance. **Conclusions:** This study demonstrated that plasma p-Tau-217 is significantly positively correlated with Tau PET-based pathological staging. At the same time, the Aβ42/p-Tau-217 ratio showed a non-significant trend toward a negative correlation, suggesting that p-Tau-217 may be more sensitive to tau deposition burden. NfL also exhibited a strong positive correlation with pathological stage, while GFAP, age, and eye movement scores showed consistent but non-significant trends. These findings support the potential of combining multiple peripheral biomarkers to enhance the accuracy of AD pathological staging. Notably, the majority of patients followed a "comorbidity" clinical–pathological trajectory, possibly influenced by comorbidities, cognitive reserve, and lifestyle factors. The results further highlight the value of the 2024 NIA-AA staging framework, which facilitates early identification of high-risk comorbid states and supports clinicians in developing comprehensive management strategies to optimize outcomes and delay disease progression. **Keywords:** Peripheral biomarkers, Aβ42, p-Tau217, GFAP, NfL, eye movement score, clinical staging, pathological staging, disease trajectory. **Clinical Trial Registry:** ChiCTR2200062493; https://www.chictr.org.cn. **Disclosures:** The authors declared no competing interests.

BEHAVIORAL DISORDERS AND CLINICAL TRIALS

P59- VARIABLES ASSOCIATED WITH COGNITIVE FUNCTION: AN EXPOSOME-WIDE AND MENDELIAN RANDOMIZATION ANALYSIS. Y. Zhao[1], J. Yu[2], L. Tan[1] *(1. Qingdao University - Qingdao (China), 2. Fudan University - Shanghai (China))*

Background: Evidence indicates that cognitive function is influenced by potential environmental factors. We aimed to determine the variables influencing cognitive function. **Methods:** Our study included 164,463 non-demented adults (89,644 [54.51%] female; mean [SD] age, 56.69 [8.14] years) from the UK Biobank who completed four cognitive assessments at baseline. 364 variables were finally extracted for analysis through a rigorous screening process. We performed univariate analyses to identify variables significantly associated with each cognitive function in two equal-sized split discovery and replication datasets. Subsequently, the identified variables in univariate analyses were further assessed in a multivariable model. Additionally, for the variables identified in multivariable model, we explored the associations with longitudinal cognitive decline. Moreover, one- and two- sample Mendelian randomization (MR) analyses were conducted to confirm the genetic associations. Finally, the quality of the pooled evidence for the associations between variables and cognitive function was evaluated. **Results:** 252 variables (69%) exhibited significant associations with at least one cognitive function in the discovery dataset. Of these, 231 (92%) were successfully replicated. Subsequently, our multivariable analyses identified 41 variables that were significantly associated with at least one cognitive function, spanning categories such as education,

socioeconomic status, lifestyle factors, body measurements, mental health, medical conditions, early life factors, and household characteristics. Among these 41 variables, 12 were associated with more than one cognitive domain, and were further identified in all subgroup analyses. And LASSO, rigde, and principal component analysis indicated the robustness of the primary results. Moreover, among these 41 variables, 12 were significantly associated with a longitudinal cognitive decline. Furthermore, 22 were supported by one-sample MR analysis, and 5 were further confirmed by two-sample MR analysis. Additionally, the quality of the pooled evidence for the associations between 10 variables and cognitive function was rated as high. Based on these 10 identified variables, adopting a more favorable lifestyle was significantly associated with 38% and 34% decreased risks of dementia and Alzheimer's disease (AD). **Conclusions:** Overall, our study constructed an evidence database of variables associated with cognitive function, which could contribute to the prevention of cognitive impairment and dementia.

P60- EXPLORING THE RELATIONSHIP BETWEEN BRAIN STRUCTURAL AND ANTIPSYCHOTIC DRUG DOSAGE IN BPSD.

B. Hong[1], H. Zhang[2], J. Chen[3], L. Yue[3] (1. Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine - Shanghai (China), 2. School of Biomedical Engineering, ShanghaiTech University - Shanghai (China), 3. Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine - Shanghai (China))

Introduction: Psychotropic medications are broadly prescribed among Behavioral and psychological symptoms of dementia (BPSD), and the safety of antipsychotic drugs has always been a concern. However, the objective indicators for evaluating drug dosage are still lacking. It is highly desired to investigate the relationship between brain structural alteration and antipsychotic drug dosage for BPSD patients towards precision medicine. **Methods:** This study focuses on the patients with Alzheimer disease (AD) at the Shanghai Mental Health Center, China. Baseline general demographic data were collected. Their cognitive function was evaluated using the Mini Mental State Scale (MMSE) and the behavioral and psychological symptoms were evaluated by the Neuropsychiatric Inventory (NPI). 3D T1w brain structural MRI data were acquired. All patients underwent standardized clinical treatment and were followed up until BPSD remission. The antipsychotic drugs were converted using a defined daily dose (DDD) method to obtain the final daily dose. We divided the patients into three groups: DDDs=0, 0<DDDs<0.3, and DDDs≥0.3, representing a non-antipsychotic group (NAP), a low-dose group (LAP), and a high-dose group (HAP). Region-wise comparisons on cortical thickness and sub-cortical volume were conducted across different groups. Finally, we investigated the relationship between the altered brain regions and the DDDs. **Results:** A total of 86 AD patients who met the ICD-10 diagnostic criteria were enrolled (NAP, n=28, LAP, n=26, HAP, n= 32). Among the three groups, NAP group showed less NPI score than LAP and HAP, while no difference was observed in age, gender, education level and MMSE score. ANCOVA analysis on brain region-wise cortical thickness measures, after controlling age, gender, education level, showed significant differences in the thickness at the left pars orbitalis (F=3.277, p=0.003) and the volume of left thalamus (F=4.279, p<0.001) among three groups. Post hoc analysis indicated that the HAP group had thinner cortex in the left pars orbitalis compared to the NAP group. Ordinal logistic regression

analysis revealed that NPI (p=0.014) and cortical thickness at the left pars orbitalis (p=0.037) were independent predictors of antipsychotic drug dosage. Further association analysis between cortical thickness of the left pars orbitalis and DDDs revealed a significant negative correlation (r=-0.229, p=0.04) even after adjusting for gender, age, education level, MMSE and NPI score. **Conclusions:** This study provides first-ever evidence that brain anatomical changes may serve as valuable biomarkers in prediction of antipsychotic drug dosage for patients with BPSD. The result has significant implications for optimizing clinical management strategies and offers insights into the intricate neuropathological mechanisms of BPSD.

P61- RESEARCH PROGRESS ON THE PATHOGENESIS BETWEEN ALZHEIMER'S DISEASE AND SARCOPENIA.

M. Yao[1], Z. Wei[2] (1. Department of Neurology, Beijing Tiantan Hospital, Capital Medical University - Beijing (China), 2. Center for Cognitive Neurology, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University - Beijing (China))

Objective: Alzheimer's disease (AD) is the most common type of cognitive impairment, and its association with sarcopenia has received increasing attention in recent years. Both AD and sarcopenia are closely related to aging, and their pathogeneses are complex and diverse. This article reviews the bidirectional relationship between AD and sarcopenia, underlying biological mechanisms, as well as pharmacological and non-pharmacological interventions, intending to provide new perspectives on the common pathological basis and offer ideas for future therapeutic strategies, to improve the life quality of patients. **Methods:** We searched PubMed, CNKI, Wanfang and other databases, entered the keywords "Alzheimer's disease" and "Sarcopenia", searched Chinese and English literature in the past 3-5 years, and summarized the latest research progress. **Results:** 1. Epidemiological Association: Epidemiological studies reveal a strong correlation between these conditions: AD patients exhibit higher sarcopenia prevalence correlated with disease severity, while sarcopenia independently accelerates cognitive decline and increases AD risk by 2.97-fold. 2. Mechanisms of AD-Induced Sarcopenia: (1) Peripheral Amyloid Pathology: Accumulation of amyloid precursor protein (APP) and β amyloid (Aβ) in peripheral tissues disrupts neuromuscular junction (NMJ) integrity, reduces cholinergic innervation, as well as activates the transforming growth factor- β/Smad/muscle RING-finger protein 1 pathway, leading to muscle atrophy. (2) Neuroendocrine Dysregulation: Elevated brain angiotensin II levels in AD models induce systemic inflammation and oxidative stress, exacerbating skeletal muscle damage. (3) Autonomic Dysfunction: Hypoperfusion in key regions of the central autonomic network, then may disrupt sympathetic regulation of muscle reinnervation (cortical central autonomic network (CAN) involvement), hypothalamic-pituitary-somatotropic axis impairment (neuroendocrine decline in females), and limbic dysfunction (amygdala-hippocampus), driving sarcopenia through direct autonomic, neuromuscular and systemic endocrine-inflammatory pathway. (4) Gut-Brain-Muscle Axis: Elevated intestinal mucosal permeability in AD

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patients, which resulted in the entry of bacterial endotoxins into circulation, and hence caused damage to skeletal muscle directly or through increasing inflammatory response and oxidative stress indirectly. 3. Mechanisms of Sarcopenia-Induced AD Progression: (1) Myokine Dysregulation: Exercise-induced muscle contraction promotes myokine secretion. Sarcopenia-induced muscle decline reduces secretion, disrupting myokine regulation and contributing to Alzheimer's pathology through stimulatory pathways. (2) Pro-Inflammatory Myokines: Elevated hemopexin levels in sarcopenia promote neuroinflammation. 4. Co-pathogenesis: (1) Genetic Susceptibility: Polymorphisms in APOE, brain-derived neurotrophic factor (BDNF), angiotensin-converting enzyme (ACE), fat mass and obesity-associated protein (FTO) and Fibronectin type III Domain Containing 5 (FNDC5) genes increase vulnerability to both disorders. (2) Mitochondrial dysfunction and oxidative stress: Mitochondrial dysfunction disrupts energy/calcium balance, triggers oxidative stress, exacerbating Alzheimer's pathology, synaptic dysfunction and cognitive decline. Simultaneously activating ubiquitin-proteasome degradation reduces myosin levels, inducing sarcopenia. (3) Chronic Inflammation: Chronic inflammation can lead to neuronal damage and death, and can also increase the catabolism of skeletal muscle fibers and proteins, accordingly, causing the occurrence of AD and sarcopenia. (4) Peripheral APP Deposition: APPswe in muscle could increase senescence-associated secretory phenotype (SASPs) and pro-inflammatory cytokines levels, and decrease growth factors levels, inducing muscle cellular senescence, speeding up neurodegeneration in hippocampus. It can directly lead to sarcopenia, and it can also indirectly promote AD-related brain pathology through systemic inflammation (hippocampal inflammation, blood-brain barrier damage, neurogenesis defects). 5. Intervention Strategies: (1) Non-Pharmacological Approaches: ① Exercise: Combined aerobic and resistance training enhances BDNF, irisin, and mitochondrial biogenesis, improving cognitive function and muscle strength. ② Nutrition: Oral administration of B vitamins, probiotics, Vitamin D, n-3 fatty acids, proteins and essential amino acids and other nutrients, and higher Mediterranean diets adherence suppresses systemic inflammatory markers, strengthens muscle-brain communication, and maintains neuromuscular metabolic homeostasis. ③ Cognitive Training: Dual-task gait training (e.g., walking while performing cognitive tasks) enhances motor coordination and cognitive-multitasking abilities, reducing fall risks and functional decline rates in comorbid populations. (2) Pharmacological Advances: ① selective androgen receptor modulators (SARMs): Selective androgen receptor modulators increase lean mass and upregulate neprilysin for Aβ clearance. ② ACE Inhibitors and Ang1-7: Counteract Ang II-induced neuroinflammation and muscle damage. ③ Acetylcholinesterase inhibitors (AChEIs) improve central cholinergic transmission and promote muscle fiber regeneration via satellite cell activation, though their neuromuscular excitatory side effects require careful management. ④ Emerging Therapies: Compounds like RJx-01 (galantamine-metformin) enhance NMJ stability and mitochondrial function. **Conclusions:** AD and sarcopenia are commonly observed comorbidities in aging populations, imposing substantial socioeconomic and healthcare burdens. Epidemiological studies demonstrate a bidirectional association: AD progression correlates with sarcopenia prevalence (positively associated with cognitive decline severity), while sarcopenic patients exhibit accelerated cognitive deterioration. Mechanistically, AD pathogenesis promotes sarcopenia via peripheral Aβ accumulation, cerebral angiotensin II elevation, autonomic network hypoperfusion, and gut-barrier disruption; conversely, sarcopenia exacerbates AD pathology through myokine dysregulation and hemopexin-mediated neuroinflammatory cascades. Shared etiological factors include genetic/epigenetic alterations, mitochondrial oxidative stress, chronic inflammation, and ectopic APP deposition. Non-pharmacological interventions (resistance exercise, Mediterranean diet, cognitive training) and pharmacological agents (e.g., SARMs, AChEIs) have shown efficacy in dual-pathology management. Future research priorities include elucidating molecular crosstalk mechanisms and developing precision therapeutics through interdisciplinary collaboration.

P62- EFFICACY AND SAFETY ASSESSMENT OF NON-PHARMACOLOGICAL INTERVENTIONS FOR AGITATED BEHAVIOR IN ALZHEIMER'S DISEASE: A RANDOMIZED CONTROLLED TRIAL. H. Xiao[1] *(1. Professor - Jiangsu (China))*

Background: Agitated behavior in Alzheimer's Disease (AD) (NPI score ≥ 4) significantly reduces patients' quality of life and increases caregiver burden. Existing pharmacological treatments have limited efficacy and safety risks, making evidence-based support for non-pharmacological interventions urgent. **Methods:** This study employed a prospective three-arm randomized controlled design (single-blind assessment), enrolling a total of 120 patients with mild to moderate AD (MMSE 10-24), randomly divided into three groups: Cognitive Behavioral Therapy (CBT) group (n=40): Modified STAR-C program (focused on behavior-triggered cognitive restructuring), 60 minutes per session, three times a week for 8 weeks. Music Therapy group (n=40): Individualized music stimulation (ISO principle), 30 minutes per session, five times a week for 8 weeks. Control group (n=40): Routine care. The primary endpoint was the change in NPI agitation subscale scores (baseline, 4 weeks, 8 weeks); secondary endpoints included quality of life (QoL-AD), cognition (ADAS-cog), and caregiver burden (Zarit scale). Safety was monitored throughout according to CTCAE v5.0. **Results:** Improvement in Agitated Behavior. CBT group: 8-week score decreased from 6.8±1.2 to 4.1±0.9 (Δ=-40.2%; 95% CI: -43.5 to -36.8; p<0.01), with a 19.1% decrease at 4 weeks, showing a sustained downward trend. Music group: 8-week score decreased from 7.0±1.1 to 5.3±1.1 (Δ=-25.0%; 95% CI: -28.1 to -22.0; p<0.05), with accelerated improvement in the later phase (8-week decrease of 24.3% vs. 11.4% at 4 weeks). Inter-group differences: The improvement in the CBT group was significantly better than that in the music group (8-week p=0.013), and both intervention groups were significantly better than the control group (Δ=-2.3%; p<0.001). Secondary Outcomes. Quality of Life: The CBT group improved by 3.5 points (95% CI: 2.8-4.1), significantly higher than the music group's 2.1 points (1.5-2.7) (p=0.021). Caregiver Burden: The CBT group reduced by 7.2 points (-8.0 to -6.4), significantly better than the music group's 4.5 points (-5.2 to -3.8) (p=0.002). Cognitive Function: No significant inter-group differences (p=0.108). Safety. The adverse event rate in the intervention groups (2.5%) was significantly lower than that in the control group (15%): CBT group: 1 case of transient exacerbation of agitation (resolved within 24 hours). Music group: 1 case of fall. Control group: 3 cases of exacerbated agitation (requiring pharmacological intervention) and 2 cases of fall. No treatment-related serious adverse events. **Conclusions:** Cognitive Behavioral Therapy significantly outperformed music therapy in improving agitated behavior in Alzheimer's Disease (40.2%) and safety. Its structured behavioral intervention model not only alleviates caregiver burden but also enhances quality of

life. Music therapy is suitable for patients needing to avoid the risk of exacerbated agitation. Both non-pharmacological interventions are clinically practical and can be individually selected based on patient characteristics. **Keywords:** Alzheimer's disease, agitated behavior, cognitive behavioral therapy, music therapy, randomized controlled trial. **Conflict of Interest Statement:** The authors declare no conflicts of interest.

P63- POTENTIAL ROLE OF SHORT-TERM BLOOD PRESSURE VARIABILITY ACROSS THE ALZHEIMER'S DISEASE CONTINUUM.

Q. Ren[1], J. Jiang[1], X. Zou[1], W. Li[1], S. Jiang[1], M. Zhao[1], T. Jiang[1], H. Zhang[1], J. Xu[1] *(1. Beijing Tiantan Hospital, Capital Medical University - Beijing (China))*

Background: Emerging evidence indicates that blood pressure variability (BPV) is a modifiable vascular risk factor for Alzheimer's disease (AD). Herein, we aimed to systematically evaluate the potential role of short-term BPV across the AD continuum. **Methods:** This study included 263 patients on the AD continuum from the Chinese Imaging, Biomarkers, and Lifestyle study between January 1, 2023, and December 31, 2023. Partial Spearman's correlation and restricted cubic spline analysis were performed to assess the associations between BPV and neuropsychological tests, cerebrospinal fluid biomarkers, and multimodal neuroimaging measures, respectively. The mediating effects of multimodal neuroimaging measures on the association between BPV and neuropsychiatric symptoms (NPS) were analyzed. **Results:** Elevated standard deviation (SD) of nightly diastolic blood pressure (DBP) was correlated with higher Neuropsychiatric Inventory (NPI) scores ($r = 0.19$, $P = 0.034$). The increased SD of nightly systolic blood pressure (SBP) was correlated with increased Hamilton Anxiety Scale (HAMA) scores and total tau levels ($r = 0.20$, $P = 0.026$; $r = 0.17$, $P = 0.027$), and elevated coefficient of variation (CV) of nightly SBP was correlated with higher HAMA scores, but lower Aβ42/40 levels ($r = 0.20$, $P = 0.026$; $r = -0.18$, $P = 0.021$). The nightly variability of SBP showed an inverted U-shaped relationship with Montreal Cognitive Assessment scores (P for nonlinear = 0.015; P for nonlinear = 0.021). The left cuneus volume mediated 29.41% of the association between the CV of nightly SBP and HAMA scores, while the right medial orbitofrontal thickness mediated 35.44% of the association between the CV of nightly DBP and NPI scores. **Conclusions:** This study confirmed the potential role of short-term BPV in the AD continuum. These findings provide evidence of a vascular pathway to AD, as well as a potential and accessible intervention target for patients on the AD continuum.

NEW THERAPIES AND CLINICAL TRIALS

P64- THE USE OF DYNAMIC NECK LYMPHATICOVENOUS ANASTOMOSIS (LVA) IN THE ADJUNCTIVE TREATMENT OF ALZHEIMER DISEASE: A RETROSPECTIVE CASE SERIES.

X. Chen[1], C. Ding[1] *(1. Peking University Shenzhen Hospital - Shenzhen (China))*

Background: Despite decades of extensive studies into Alzheimer's disease, a definitive cure remains elusive [1]. There has been a growing interest in cervical lymphaticovenous anastomosis (LVA) as a new therapeutic method. This study aimed to assess the safety and potential clinical advantages of the dynamic neck LVA technique in patients with AD. **Methods:** Five patients with AD underwent bilateral MC-dLVA at Peking University Shenzhen Hospital between November 2024 to January 2025. The clinical outcome was evaluated based on PET-CT imaging, cerebrospinal fluid (CSF) biomarker analysis, and cognitive assessment, including mini-mental state examination (MMSE) and Montreal Cognitive Assessment (MoCA), taken at baseline and perioperative stages [2]. Our surgical procedure utilized vein grafts from the distal lower limb to connect deep cervical lymphatic vessels to the external jugular vein. **Results:** All subjects demonstrated vessel patency, with no intraoperative or postoperative complications observed. PET-CT scans indicated enhanced glucose metabolism and diminished accumulation of amyloid and tau proteins. All patients exhibited improvements in MMSE and MoCA scores, and caregivers noted advancements in cognitive function and emotional well-being. **Conclusions:** Dynamic neck LVA appears to be a safe, minimally invasive procedure with potential cognitive and metabolic benefits in AD. Further studies with larger cohorts and longer follow-up are warranted to confirm these preliminary findings. **Keywords:** Alzheimer's disease, cognitive impairment, cervical lymphaticovenous anastomosis. **Disclosures:** VVWs employer received a grant from Pharmatown. The authors declared no competing interests. **References:** 1. Scheltens P, et al. Lancet 2021; 397(10284):1577-1590. doi:10.1016/S0140-6736(20)32205-4. 2. Graff-Radford J, et al. Lancet Neurol 2021; 20(3):222-234. doi:10.1016/S1474-4422(20)30440-3.

P66- KC-150 IMPROVES THE COGNITIVE FUNCTION OF AD PATIENTS AND RELATED TO THE ACTIVATION OF THE LEFT FRONTAL AND PARIETAL LOBE RELATED TO FNIRS TASK.

X. Li[1], T. Ma[1], Y. Li[1], Q. Zhang[2], G. Wen[1], Y. Lv[1] *(1. Neurology department of Hainan Provincial People's Hospital - Haikou (China), 2. Neurology department of Shandong Provincial Public Health Clinical Centre - JInan (China))*

Background: With the process of an ageing society in China, the incidence of cognitively impaired dementia patients are increasing year by year. Among them, Alzheimer's disease (AD) brings a heavy burden to families and society. Non-drug intervention may prevent and curb the development and deterioration of the disease. **Objective:** This study aims to explore the possible effects and mechanisms of KC-150 (rice bran extract valeric acid and white astragalus extract quamate) on the cognitive function of AD patients. **Methods:** 50 patients diagnosed with AD were in the neurology outpatient clinic of our hospital from February 2024 to February 2025 were selected and included in this study. They were diagnosed by neuropsychological assessments, serum or cerebrospinal fluid dementia marker detection, neuroimage and other regular routines. KC-150 were orally given to those patients for 8 weeks. Besides, near-infrared functional imaging (fNIRS) of language fluency task (VFT), MMSE and MoCA assessments were performed before and after the KC-150. The Blockage means of HBO level and distribution were compared, the paired T test was employed to evaluate the difference before and after the intervention as KC-150. Also the correlation analysis was carried out on the MMSE, MoCA and fNIRS VFT blockage results before and after the intervention as KC-150. **Results:** The average time of first fixation in AD patients was significantly shortened by KC150 ($P < 0.05$). AD After taking KC-150, VFT task-related HbO increased significantly ($P < 0.05$), and increased in frontal lobe activation among which CH43, CH44, CH45, CH46, CH47 and CH48 on the left frontal lobe have significant differences($P < 0.05$). Pearson correlation analysis indicated that MoCA is correlated with the increase of HbO related to VFT task. **Conclusions:** KC-150 can significantly improve the cognitive function of patients with AD. This effect is probably related to enhancement of the activation of the left and parietal

lobe of the fNIRS task. **Keywords:** AD, KC-150, MoCA, fNIRS, VFT.

P67- THERAPEUTIC TARGETING OF BRD4 IN A HIGH-FAT DIET-INDUCED COGNITIVE IMPAIRMENT.

L. Sun[1], W. Zhai[1] (1. The First Hospital of Jilin University - Chang Chun (China))

Previous studies have demonstrated a strong association between obesity, metabolic disorders, and cognitive impairment in the elderly. However, the mechanisms underlying the onset and progression of these conditions remain poorly understood. To investigate this, we employed 8-month-old C57BL/6J mice fed a high-fat diet (HFD) to establish a model of age-related obesity and cognitive decline. In vitro, HT22 neuronal cells were treated with high glucose (HG) and palmitic acid (PA) to simulate a high-glucose, high-lipid environment. Using these models, we examined changes in Brd4 expression and associated pathological alterations both in vivo and in vitro. Furthermore, we evaluated the therapeutic potential of targeting Brd4 in HFD-induced cognitive impairment through stereotactic intracerebral injection of AAV vectors. Transcriptomic analysis was performed to identify the involved molecular pathways. Our findings revealed that HFD-induced dementia mice exhibit pronounced inflammatory responses both in the peripheral and central nervous systems, accompanied by neuronal damage and apoptosis. In vitro experiments also confirmed increased neuronal injury, apoptosis, and oxidative stress. Notably, these pathological features were alleviated by stereotactic AAV-mediated Brd4 targeting in vivo or by pharmacological inhibition of Brd4 in vitro.

P68- MULTICENTER CASE REGISTRY STUDY OF LECANEMAB IN EARLY ALZHEIMER'S DISEASE IN NORTHWEST CHINA.

P. Liu[1], S. Cui[1], S. Wei[1], L. Gao[1], Q. Qu[1], J. Wang[1] (1. The First Affiliated Hospital of Xi'an Jiaotong University - Xi'an (China))

Background: Background: Lecanemab (Leqembi®) is the first drug approved by FDA for the treatment of early Alzheimer's disease (AD) (mild cognitive impairment due to AD or mild AD dementia) with confirmed brain amyloid pathology. However, the efficacy and safety of Lecanemab in China had not been reported. **Methods:** This is a multicenter case registry study conducted at 30 hospitals in Northwest China. All AD patients treated with Lecanemab were enrolled. The efficacy of Lecanemab were evaluated using Clinical Dementia Rating-Sum of Boxes (CDR-SB), Alzheimer's Disease Assessment Scale (ADAS-cog), Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL) and Minimal-Mental State Examination (MMSE) every 3 months. Amyloid-related imaging abnormalities (ARIA) were monitored via MRI-T2-FLAIR and MRI-SWI sequences. Blood samples were collected to evaluate the changes of plasma biomarkers (including Aβ42, Aβ40, Aβ42/40 and p-tau181). **Results:** There were 136 participants received Lecanemab treatment until July 1, 2025, all of whom were confirmed Aβ-positive by CSF or PET scans. The mean age was 67.8 years (range 37-88), with 90 (66.2%) female participants. The mean years of education was 11.9 years. Among the participants, 11 (8.1%) were homozygous for the ApoE ε4 allele, and 51 (37.5%) were heterozygous. At baseline, the CDR-SB score was 4.2±2.3, the MMSE score was 18.0±6.4, the ADAS-cog score was 18.4±10.5, and the ADCS-ADL score was 54.4±20.5. There were 67 participants completed

the 3-month follow-up, 36 participants completed the 6-month follow-up, 11 participants completed the 9-month follow-up. The longest follow-up duration was 52 weeks. There were no significant changes in cognitive scales among the 36 participants completed 6-month follow-up. The change in CDR-SB at 6 months compare to baseline was -0.31 (95% CI -2.29 to 1.66, P=0.740), for the MMSE score was -0.77 (95% CI -3.08 to 1.55, P=0.494), for the ADAS-cog score was -0.02 (95% CI -4.40 to 4.37, P=0.994), and for the ADCS-ADL score was -1.89 (95% CI -5.95 to 2.17, P=0.314). The plasma Aβ42/40 was increased 0.016 (95% CI 0.003- 0.030, P=0.039), while plasma p-Tau 181 was decreased 0.83 (95% CI 0.199 to 1.461, P=0.014) compare to baseline. Only 1 ARIA has been reported. Approximately 26% of patients reported treatment-related adverse events primarily involved infusion-related reactions, such as fever and chills, typically occurring within 24 hours post-infusion, which were alleviated with symptomatic treatment. **Conclusions:** This real-world study suggests that Lecanemab is well-tolerated in clinical use in Northwest China, with manageable adverse effects and no severe adverse events such as ARIA reported to date. The neuropsychological scales keep stable during the 6-month follow-up, but plasma biomarkers showed significant improvement after treatment. A long time follow-up and large sample are needed. **Keywords:** Alzheimer's disease, lecanemab.

PRE-CLINICAL TRIALS/TRANSLATIONAL RESEARCH FOR ALZHEIMER DRUG DEVELOPMENT INTERVENTIONS

P69- THE EFFECTS OF LECANEMAB ON COGNITIVE FUNCTION AND HIPPOCAMPAL NERVE REGENERATION IN HYPERTENSIVE AD MICE.

C. Zhao[1], X. Zhang[1], M. Zhang[1], C. Lv[1] (1. The first hospital of China Medical University - Shenyang (China))

Background: Alzheimer's disease (AD) is a neurodegenerative disorder of the central nervous system. Its hallmark pathological features include extracellular deposition of amyloid-beta (Aβ) plaques and intracellular accumulation of neurofibrillary tangles formed by hyperphosphorylated tau (p-tau). Hypertension is an important comorbidity of AD. Lecanemab is a humanized monoclonal antibody, which can selectively neutralize and clear amyloid-beta (Aβ) protein aggregates that cause AD neuropathy. At present, the efficacy of lecanemab in AD patients with hypertension remains uncertain. We explored the effects of lecanemab on cognitive function and hippocampal neurogenesis in hypertensive AD mice. **Method:** Research subjects included male 10-month-old APP/PS1 transgenic the AD mice and AngII mice, which were randomly divided into four groups: APP/PS1+PBS group, APP/PS1+Lecanemab group, APP/PS1+AngII+PBS group, and APP/PS1+AngII+Lecanemab group, with 6 mice in each group. Lecanemab (30 mg/kg) or PBS were administered intravenously via the tail vein once a week. After four weeks of continuous treatment, cognitive function was evaluated using the water maze test and the Y-maze test. The deposition of amyloid-beta (Aβ) protein in mouse brains was detected using immunofluorescence staining, while dendritic spine density and synaptic length were quantified through Golgi staining. **Result:** We found that Lecanemab intervention significantly improved cognitive performance in both APP/PS1 and APP/PS1+AngII mice. This was demonstrated in the Y-maze test by an increased number of novel arm entries, longer exploration time, and greater exploration distance compared to the APP/PS1+PBS

and APP/PS1+AngII+PBS groups. Lecanemab intervention can significantly enhanced cognitive performance in both APP/PS1 and APP/PS1+AngII mice in water mazes test, both the APP/PS1+Lecanemab and APP/PS1+AngII+Lecanemab groups showed a significant decrease in the time required to find the platform compared with their respective PBS-treated control groups (APP/PS1+PBS and APP/PS1+AngII+PBS). Additionally, the APP/PS1+AngII+Lecanemab group showed a slightly shorter time to find the platform compared to the APP/PS1+Lecanemab group. Immunofluorescence staining revealed that Lecanemab intervention reduces hippocampal Aβ protein expression in APP/PS1 mice. Golgi staining demonstrated that Lecanemab significantly increased the density and length of hippocampal dendritic spines in mice, particularly in the APP/PS1+AngII+Lecanemab group. **Conclusions:** Lecanemab significantly ameliorated cognitive deficits in hypertensive AD model mice and significantly increased dendritic spine density and length. **Keywords:** Alzheimer's disease, lecanemab, cognitive, hypertensive. **Clinical Trial Registry:** KT20242121. **Data Deposition:** None. **Disclosures:** The authors declared no competing interests.

P70- PLASMA PROTEOMICS REVEALS NOVEL PROTEIN SIGNATURES ASSOCIATED WITH DEMENTIA IN CHRONIC PAIN PATIENTS: A PROSPECTIVE COHORT STUDY. P.Y. Gao[1], O. Chen[1], Y. Tang[1] *(1. Xuanwu Hospital Capital Medical University - Beijing (China))*

Background: The relationship between chronic pain and Alzheimer's disease (AD) remains poorly understood, despite growing evidence suggesting shared molecular pathways. Mass spectrometry-based proteomics enables simultaneous analysis of thousands of proteins with high precision, providing advantages over traditional targeted methods. This study aimed to identify distinct plasma protein profiles that may link chronic pain to AD pathogenesis and potentially serve as early biomarkers. **Method:** We analyzed 2,920 plasma proteins from the UK Biobank. Chronic pain participants were identified through self-reported pain lasting over three months at baseline. Cox proportional hazards models assessed longitudinal associations between proteins and risk of all-cause dementia (ACD), AD, and vascular dementia (VaD) in chronic pain individuals. Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) enrichment analyses were performed to identify relevant biological pathways and processes. **Result:** A total of 20,932 chronic pain individuals (mean age: 57.51; 55.60% female), including 695 ACD, 332 AD, and 144 VaD cases, were followed for a median of 13.54 (SD 2.45) years. Among 2,920 analyzed proteins, after false discovery rate correction, GFAP showed the strongest association with all dementia types (ACD: HR=2.26; AD: HR=2.62; VD: HR=2.93). For ACD, NEFL (HR=1.94), GDF15 (HR=1.69) showed increased risk, while HPGDS (HR=0.50) and ITGAV (HR=0.29) showed protective effects. For AD, NEFL (HR=1.78), SYT1 (HR=1.63), and GDF15 (HR=1.57) were risk factors, while BCAN (HR=0.51) was protective. For VD, SPON2 (HR=2.26), GDF15 (HR=1.96), NEFL (HR=1.85), and FABP1 (HR=1.36) showed significant associations. Pathway analyses revealed shared enrichment in cytokine-cytokine receptor interaction and Pi3k-akt signaling across all dementia types. ACD showed specific enrichment in viral protein interaction and MAPK signaling pathways. AD was distinctly enriched in glycosaminoglycan and growth factor binding, while VD showed unique enrichment in ECM-receptor interaction and regulation of actin cytoskeleton. **Conclusions:** Our study revealed distinct protein signatures linking chronic pain to dementia risk, with GFAP as a key marker across all dementia types. The enriched cytokine-cytokine receptor interaction and Pi3k-akt signaling pathways suggest chronic pain may accelerate neurodegeneration through neuroinflammation. These findings highlight potential mechanisms connecting chronic pain to cognitive decline and identify promising biomarkers for early dementia detection in chronic pain patients.

P71- POLYDOPAMINE MODIFIED WITH BRAIN TARGETING PEPTIDE RVG FOR TREATMENT OF ALZHEIMER'S DISEASE BY INHIBITING OXIDATIVE STRESS AND INFLAMMATORY RESPONSE. C. He[1], H. Chuyi[2], G. Qihao[3] *(1. Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine - Shanghai (China), 2. Renji Hospital, School of Medicine, Shanghai Jiaotong University - Shanghai (China), 3. Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine - Shanghai (China))*

Background: Polydopamine (PDA) has been recognized as an antioxidant and anti-inflammatory agent. However, the difficulty to cross blood-brain barrier (BBB) limits PDA's neuroprotective effects in the brain. Here, we aimed to construct PDA-RVG by modifying the RVG29 polypeptide on PDA nanoparticles (NPs) and investigate whether PDA-RVG improved the cognitive function and pathology of Alzheimer's Disease (AD) by inhibiting oxidative stress and inflammatory response. **Methods:** We first prepared and characterized PDA NPs and tested whether PDA improved AD pathology in APP/PS1 mice. To facilitate PDA's penetration across BBB, we modified RVG29 on PDA and examined its brain-specific targeting ability and biocompatibility. We further tested the effects of PDA-RVG on oxidative stress, inflammatory response and ferroptosis in both in vitro and in vivo AD models. **Results:** PDA demonstrated robust reactive oxygen species (ROS)-scavenging activity and effectively reduced Aβ deposition and the expression of APP and PS1 in APP/PS1 mice. PDA-RVG successfully crossed BBB in an in vitro BBB model. Meanwhile, compared with PDA, PDA-RVG intravenous injection exhibited good brain-specific targeting ability evaluated by fluorescence labeled experiment. Moreover, the hematological analysis revealed no significant differences between the PDA-RVG and control groups. In the in vitro AD experiment, PDA-RVG reduced ROS, inducible nitric oxide synthase, and pro-inflammatory cytokines levels in BV2 cells. Besides, PDA-RVG decreased ROS and apoptosis, while increased glutathione peroxidase4 (GPX4) and the viability of PC12 cells. More importantly, intravenous delivery of PDA-RVG improved cognitive function assessed by Morris water maze, and upregulated the ferroptosis-protective proteins Ferritin Heavy Chain 1 and GPX4 expression. **Conclusions:** PDA improves cognitive function and reduces AD pathology, which is possibly attributed to its ability to scavenge ROS, ameliorate the inflammatory microenvironment and inhibit ferroptosis. Modifying RVG29 grants intravenous delivery of PDA-RVG good brain-specific targeting ability and biocompatibility. This study provides a safe, effective, and promising therapeutic strategy for AD via oxidative stress-associated target. **Keywords:** Alzheimer's disease, polydopamine; PDA-RVG, oxidative stress, neuroinflammation, ferroptosis. **Disclosures:** The authors declared no competing interests.

P72- GUT-BRAIN AXIS CROSSTALK IN ALZHEIMER'S DISEASE WITH OVERWEIGHT: POTENTIAL MECHANISMS INVOLVING DYSBIOSIS OF GUT MICROBIOTA, DISRUPTION OF BLOOD-BRAIN BARRIER AND NEUROINFLAMMATION OF BRAIN. W. Zhang[1] *(1. Beijing Tiantan Hospital, Beijing (China))*

Background: Accumulating evidence has identified that overweight reflected by elevated body mass index (BMI) as a significant risk factor for the development of Alzheimer 's disease (AD). However, the specific mechanisms by which overweight accelerates cognitive decline in AD patients have not yet been elucidated. This study aimed to investigate the impact of overweight on the cognitive function of AD patients and potential mechanisms involving dysbiosis of gut microbiota, disruption of blood-brain barrier (BBB) and neuroinflammation of brain. **Methods:** Total 50 AD patients were recruited and divided into AD with normal BMI (AD-nBMI) and AD with high BMI (AD-hBMI) groups. Demographic data were collected and cognitive function was assessed, the levels of BBB variables, neuroinflammatory factors and AD pathological biomarkers in cerebrospinal fluid (CSF) were measured, gut microbiota and metabolites were analyzed using 16S rRNA gene sequencing and gas chromatography-mass spectrometry analysis, correlations among microbiota and metabolites, BBB variables and neuroinflammatory factors in CSF were analyzed, and the potential mediating effect of gut metabolites on the association between BBB disruption and neuroinflammation in brain was evaluated. **Results:** (1) AD-hBMI group exhibited significantly impaired cognitive function compared to AD-nBMI group, and the severity of cognitive impairment was increased with elevated BMI. (2) AD-hBMI group displayed intensified neuroinflammation in brain, which was associated with exacerbated AD pathology. (3) BBB was apparently disrupted in AD-hBMI group, and evidently correlated with intensified neuroinflammation in brain. (4) BBB disruption led to intensified neuroinflammation in brain. (5) The declined 10-HDAA and elevated indolepyruvic acid in gut mediated the association between disrupted BBB and intensified neuroinflammation in brain. **Conclusions:** Overweight induces dysbiosis of gut microbiota, and disturbed metabolites mediate the association between disrupted BBB and intensified neuroinflammation in brain, which aggravates AD pathology and cognitive impairment. Findings from this investigation provide perspectives on the novel mechanisms and interventional strategies for AD. **Keywords:** Alzheimer's disease, overweight, body mass index, gut microbiota and metabolites-blood-brain barrier, neuroinflammation, Alzheimer's disease pathology, cognitive impairment.

P73- ALZHEIMER'S DISEASE WITH DEPRESSION: MECHANISMS INVOLVING CYBRD1 GENE, IRON METABOLISM DISTURBANCE AND TEMPORAL CORTEX ATROPHY. W. Zheng[1] *(1. Beijing Tiantan Hospital - BeiJing (China))*

Background: Depression is one of the most common neuropsychiatric symptoms in Alzheimer's disease (AD), affecting approximately 50% of AD patients. Given the known association and similar pathogenesis between AD and depression, it is imperative to uncover the potential mechanisms. **Methods:** Firstly, the differentially expressed genes (DEGs) in the temporal cortex related to depression and AD via bioinformatics method were identified, and the functional enrichment analysis were performed via Metascape

to explore the specific molecular pathways. Secondly, demographic variables of 21 patients of AD with depression (AD-D) and 39 cases of AD with no depression (AD-nD) were collected from Beijing Tiantan Hospital. Demographic variables and cognitive function were recorded. The levels of iron and related proteins, including transferrin, ferritin and lactorferrinin, in cerebrospinal fluid (CSF) were measured by colorimetric method and enzyme-linked immunosorbent assay. The thickness of temporal cortex was evaluated by magnetic resonance imaging. The correlations among depression, the levels of iron and related proteins and iron in CSF and the thickness of temporal cortex were analyzed in AD patients. Finally, Mendelian randomization was conducted to clarify the causality between iron and related proteins and depression. **Results:** We for the first time identified 5 shared differentially expressed genes (AHNAK, VCAN, CYBRD1, WLS and QKI) between depression and AD by integrated analyses of GEO datasets. Among these genes, cytochrome B reductase 1 (CYBRD1), an iron-related gene, was identified as a differentially expressed gene in temporal cortex related to both depression and AD via bioinformatics analysis. The frequency of depression in AD patients was as high as 35%. The proportion of depression in female was higher than that in male AD patients (P<0.05). Compared with AD-nD group, AD-D group had significantly elevated transferrin level in CSF after adjusting for gender (P<0.05).Transferrin level in CSF was positively correlated with Hamilton Depression Scale (HAMD) score in AD patients; Mendelian randomization data indicated that transferrin causally increase the risk of depression (all P<0.05).The thickness of right temporal cortex was negatively correlated with HAMD score (P<0.05). Transferrin level in CSF was negatively correlated with the thickness of bilateral temporal cortex and ferritin level in CSF was negatively correlated with the thickness of left temporal cortex in AD-D group (all P<0.05). **Conclusions:** CYBRD1, an iron-related gene, is identified in the temporal cortex of patients with both AD and depression. Transferrin levels are significantly elevated in the brains of patients with AD and depression, and transferrin causally increases the risk of depression. The disturbed iron metabolism is closely associated with temporal cortex atrophy in patients with AD and depression. This investigation provides clinical evidence for decreasing the elevated transferrin level and iron deposition in CSF and its effect on temporal cortex atrophy, and eventually alleviating depression in AD patients. **Keywords:** AD, depression, CYBRD1, iron metabolism, transferrin, temporal cortex atrophy.

P75- NEXT GENERATION OF AD THERAPEUTICS: THE ASOS TARGETING CIRCAB-A RNA AND ANTIBODIES TARGETING AB175 OLIGOMERS. D. Mo[1] *(1.Beijing Lighting-Brain Therapeutics Co., Ltd - Beijing (China))*

The Mechanisms that trigger Aβ production in sporadic Alzheimer's disease are still obscure. We recently reported the expression of a human circular RNA (circAβ-a) encoded Aβ peptide precursor variant (Aβ175). Here we shown that a specifically developed antibodies detected robust endogenous Aβ175 expression in HEK293 cells and hNSC-derived human neurons, underscoring the potential of Aβ175 as a salient Aβ precursor. Furthermore, we detected high levels of Aβ175 oligomers in young-adult human brains. In intermediate and old-age human brain samples, accumulation of soluble Aβ175 pentamers was reduced and Aβ175 oligomers were components of most insoluble Aβ plaques in older human brain. While it is well established that fl-APP protein is cleaved predominantly

by α-secretase rather than β-secretase, our fl-APP knock-out and Aβ175 knock-down experiments in HEK293 cells substantiated Aβ175, not fl-APP, as the major precursor of Aβ peptides. Moreover, we demonstrated that AAV9 virus-expressed circAβ-a gave rise to Aβ175 oligomers, leading to extensive extracellular Aβ plaque depositions and microglial activation in mouse brain; this recapitulates critical pathogenic hallmarks within a sporadic AD mouse model. We conclude a causal relationship between human circAβ-a RNA expression, dysregulation of Aβ175 oligomer processing/aggregation and Aβ plaque accumulation in sporadic AD. The tested antisense oligonucleotides (ASOs) specifically targeting circAβ-a and the developed humanized Aβ175 oligomer antibodies in this study have the potential to lead the way to next generation disease modifying drugs. Indeed, circAβ-a RNA targeting ASOs specifically reduced the Aβ175 expression and rescued the cognitive impairment in the circAβ-a expressing mice. Such novel weapons will be crucial to combat Alzheimer's disease - one of the greatest health challenges of our time.