Participants will be classified into four clinico-pathological groups: two concordant groups – (1) true AD (both clinically and pathologically confirmed AD) and (2) true healthy (no clinical or pathological evidence of AD); and two discordant groups – (3) resilient (pathologically confirmed AD without clinical symptoms) and (4) symptomatic without pathology (clinical AD with absent or minimal pathological confirmation). Multinomial logistic regression will be used to examine associations between educational attainment and group classification. RESULTS/ANTICIPATED RESULTS: We hypothesize that higher educational attainment will be associated with an increased likelihood of clinico-pathological discordance. Specifically, individuals with higher education are expected to be overrepresented in the resilient group (high pathology, no clinical AD) compared to the true AD group (both clinical and pathological AD). Conversely, lower education levels may be more common in the true AD and symptomatic without pathology groups, reflecting reduced cognitive reserve or potential diagnostic misclassification. We further anticipate that within the discordant groups, higher education will correlate with better baseline and follow-up cognitive performance despite comparable levels of neuropathological burden. DISCUSSION/SIGNIFICANCE OF IMPACT: Findings would suggest that education enhances cognitive reserve, mitigating the clinical effects of AD pathology and helping explain why some individuals remain cognitively intact despite significant disease. Recognizing this role highlights the need to integrate neuropathological and reserve-related factors in AD research and diagnosis.

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A Positive Lens on Perinatal Health: Dimensions of Well-Being as Protective Factors Against Preterm Birth

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OBJECTIVES/GOALS: The objectives of this project were to (1) develop a multidimensional well-being index, reflecting personal capacities and environmental conditions, and (2) evaluate its association with preterm birth. The goal of this investigation was to illustrate the value of multidimensional well-being for understanding health outcomes. METHODS/STUDY POPULATION: The LIFE study was a retrospective cohort of postpartum US-born Black women (ages 18+) recruited 2009–2011 from a suburban Detroit hospital. Eligible participants self-identified as African American, had singleton births, and spoke English; exclusions included incarceration, cognitive impairment, or serious mental health conditions. Trained interviewers collected survey and medical data during postpartum stays. Of 1,410 recruits (71% response), 1,177 had complete data. Key variables were binarized; logistic regression models assessed associations with preterm birth. RESULTS/ANTICIPATED RESULTS: Few of the 21 binarized variables showed individual statistical significance. Significant predictors included having someone to offer advice about a crisis or to listen when needing to talk about oneself or one's problems, and self-rated physical and mental health satisfaction. Of the dimension scales, only the physical health scale (physical health rating, mental health rating, and mental health satisfaction) was significant. The overall well-being index was borderline significant for lower odds of preterm birth (OR=0.934, 95% CI: 0.887–1.002, p=0.0593), reaching significance when adjusted for maternal age (OR=0.938 95% CI: 0.883-0.998, p=0.0414). DISCUSSION/SIGNIFICANCE OF IMPACT: This study's findings underscore that well-being is best understood as a holistic interconnected construct. By centering context, this approach advances health equity, encourages systemic accountability and change, and inspires innovative public health research.

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Amyloid-associated ligamentum flavum remodeling in lumbar stenosis: Unraveling inflammatory and fibrotic pathways

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OBJECTIVES/GOALS: Amyloid deposition in the ligamentum flavum (LF) is associated with LF hypertrophy and resulting lumbar stenosis (LS) in some patients. Whether amyloid causes inflammation and subsequent fibrosis in the LF is unclear. An association between amyloid and markers of inflammation may present an opportunity to treat early stenosis with medical therapy. METHODS/STUDY POPULATION: LF specimens from 66 patients with lumbar stenosis (LS) were analyzed, including 33 amyloid-positive and 33 amyloid-negative patients matched by age and diagnosis. We performed immunohistochemistry on 7 tissue sections per specimen for biomarkers of inflammation (IL-6, C9) and fibrosis (Collagen, Elastin, TGF-β1, α-SMA, ROCK1). All biomarkers were quantified using a validated random forest classifier in QuPath. In Aim 1, we compared the collagen-to-elastin ratio between groups as an indicator of fibrosis, with secondary comparison of the collagen and elastin percent (α=0.025 each, Bonferroni corrected). In Aim 2, we will compare expression of IL-6, C9, TGF-β1, α-SMA, and ROCK1 using a multivariate mixed-effects regression model to identify inflammatory and fibrotic patterns linked to amyloid deposition. RESULTS/ANTICIPATED RESULTS: This study tests the hypothesis that amyloid deposition in the ligamentum flavum (LF) drives fibrosis, and the resulting LF hypertrophy and lumbar stenosis (LS), via an inflammatory pathway. Aim 1 analyses are complete, and amyloid-positive LF demonstrated a higher collagen-to-elastin ratio, with a mean difference of 0.31 (0.07–0.55, p = 0.014). This difference is driven by elastin, which covers 7.5% less tissue area in amyloid-positive LF (p = 0.008). This is the first histological evidence that amyloid is associated with altered extracellular matrix composition in the LF. We hypothesize that amyloid-positive LF will show elevated expression of IL-6 and C9, comparable TGF-β1 and α-SMA, and lower ROCK1, supporting an inflammatory pathway to LF hypertrophy distinct from pathways triggered by mechanical stress. DISCUSSION/SIGNIFICANCE OF

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IMPACT: This work will provide evidence on a possible role of amyloid in the pathophysiology of LS in a subset of patients. Our results will guide more robust quantitative analyses, including proteomics and transcriptomics, and for the first time, may support trial of anti-amyloid medical therapies to slow the progression of this primarily surgical disorder.

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Prevalence of hearing loss and hearing aid use among US older adults: Health and retirement study

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OBJECTIVES/GOALS: Emerging studies demonstrate association of hearing loss with adverse mental and cognitive outcomes, warranting the need for reliable measures of hearing in epidemiological research. This study compared the prevalence of hearing loss among US adults based on objective and self-reported measures, as well as hearing aid use from the HRS. METHODS/STUDY POPULATION: This is a cross-sectional study utilizing data from the 2016/18 Health and Retirement Study (HRS), a nationally representative cohort of US adults aged ≥50 years. Participants who completed both the objective hearing screening using the HearCheck device and hearing-related questionnaires were included (n=13,087). Survey weights were applied to account for the complex sampling design to estimate the prevalence of hearing loss as well as hearing aid use among those with objective hearing loss. Agreement between objective and self-reported hearing status was assessed using Cohen's κ. Multivariable regression analyses examined demographic factors (age, sex, race/ethnicity, income, and education) associated with under-reporting of hearing loss and hearing aid use. RESULTS/ANTICIPATED RESULTS: In this nationally representative sample of US adults aged ≥50 years, the prevalence of objective hearing loss was 52.6% [95% CI: 51.5-53.7] and self-reported hearing loss was 26.9% [25.9-27.9%]. Hearing aid use rate was 9.7% [8.9-10.5] among those with any objective hearing loss (score<6) and 44.9% [41.1-48.9] among those with moderate or worse hearing loss (score<3). Agreement between objective and self-reported hearing was low (Cohen's κ=0.2), with 61.6% [60.1-63.0] under-reporting their hearing loss. In a multivariable model accounting for demographic factors, under-reporting was more likely among females (OR: 1.8 [1.6-2.1]) and individuals with higher education (OR: 2.0 [1.6-2.6]). Hearing aid use was associated with higher education (OR: 2.9 [2.0-4.2]) and higher income (OR: 2.8 [1.9-4.0]). DISCUSSION/SIGNIFICANCE OF IMPACT: Hearing loss is common in older US adults, yet hearing aid use remains low. Frequent under-reporting of hearing loss highlights the need for objective measures in epidemiology studies to elucidate the impact of hearing loss on health outcomes. Addressing costs and awareness may improve access and lessen negative health effects related to hearing loss.

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The impact of BT2-modulated BCAA reduction as a novel therapeutic for Alzheimer's disease

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OBJECTIVES/GOALS: This study evaluates whether BT2-mediated reduction of branched-chain amino acids enhances cognitive performance and alters cortical gene expression in transgenic Alzheimer's disease mouse models, clarifying BCAA's role in AD pathology and assessing BT2's potential as a disease-modifying therapy. METHODS/STUDY POPULATION: Four groups of mice were used: wild-type vehicle, wild-type with 20 mg BT2, AD vehicle, and AD with 20 mg BT2(3,6-dichlorobenzobthiophene2-carboxylic acid). BT2, an inhibitor of branched-chain aminotransferase 2, was administered intraperitoneally to reduce BCAA accumulation implicated in mTOR overactivation and tau hyperphosphorylation. Cortical tissue samples were collected for RT-qPCR analysis of 17 genes linked to neurodegeneration. Y-Maze behavioral assays assessed spatial memory and cognition. ANOVA with post-hoc Tukey's tests ($\alpha = 0.05$) assessed intergroup significance between behavioral and transcriptional outcomes. Additionally, a Random Forest Regressor Model was utilized in order to identify gene expression patterns predictive of cognitive improvement following BT2 treatment. RESULTS/ANTICIPATED RESULTS: BT2 (3,6-dichlorobenzo[b]thiophene-2-carboxylic acid) treatment restored Beclin-1, VPS-26, NRF2, and NF-κB expression to near wild-type levels, correlating with improved Y-Maze performance. These changes enhanced autophagy, reduced inflammation, and improved mitochondrial resilience. Partial recovery of BACE1, MFN2, and PSD-95 indicated moderate restoration of amyloid processing and synaptic plasticity. Enrichr analysis highlighted pathways in autophagy, mitochondrial biogenesis, and miRNA regulation, suggesting BT2 exerts neuroprotective effects by modulating metabolic and inflammatory homeostasis. The Random Forest Regressor Model's Feature importance mapping further revealed that changes in Beclin-1, NRF2, and NF-κB expression most strongly correlated with behavioral recovery. DISCUSSION/SIGNIFICANCE OF IMPACT: BT2 shows strong potential in mitigating Alzheimer's pathology through branched-chain amino acid modulation. It normalizes NRF2, Beclin-1, and NF-κB, promoting neuroprotection and cognitive improvement. This supports BT2 as a promising metabolic therapy warranting further long-term studies.

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Using machine learning models to predict COVID-19 vaccine hesitancy in rural populations during the pandemic: A cross-sectional study

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OBJECTIVES/GOALS: Widespread COVID-19 vaccine hesitancy was a critical barrier to managing the pandemic. Rural populations represent a key demographic in this challenge, yet the specific drivers of their hesitancy remain underexplored. To address this gap, we

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