among the elderly might be a novel early marker of future dementia risk.

O1-11-04 HEARING LOSS IN OLDER MEN AND RISK OF DEMENTIA

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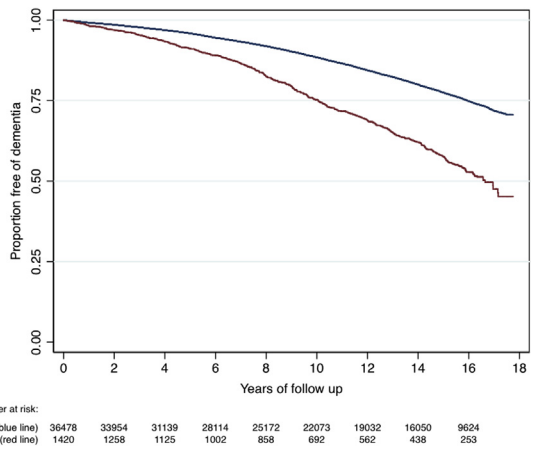
Background: Hearing impairment is a significant health issue worldwide. The risk of hearing loss increases with age and is estimated to affect up to 40% of those over the age of 65, and in as many as 75% in those older than 80 years. Hearing loss may be associated with increased risk of dementia in later life. **Methods:** We investigated this association through a prospective, cohort study of 37898 older men. The Health in Men Study (HIMS) recruited a community-representative sample of men aged 65 to 85, free of dementia living in Perth, Western Australia, between April 1996 and November 1998. The follow-up of participants for the current study closed on 31 December 2013. We used the Western Australian Data Linkage System (WADLS), that included inpatient and outpatient health services, and death registries to retrieve relevant clinical information. WADLS was used to define the presence of dementia and hearing impairment. As both hearing loss and dementia increase the risk of death, we used competing risk regression (with death as the competing outcome) to investigate the longitudinal association between hearing loss and dementia. **Results:** Mean age of the men included was 72.5 years (SD=4.6) with a mean follow up period of 11.1 (SD 5.4) years. There were 1420 men with hearing loss at baseline and 6948 men (18.3%) developed dementia during follow-up. Men with hearing loss were more likely to develop dementia than men free of significant hearing impairment – adjusted sub-hazard ratio 1.69, 95%CI=1.54-1.85. Figure 1 shows the proportion of participants who remained free of dementia during follow-up according to the presence of a recorded diagnosis of hearing loss. **Conclusions:** We found an increased risk of incident dementia with hearing impairment. This is an important finding, particularly in light of recent suggestions that mid-life hearing loss may account for up to 9.1% of dementia cases world-wide, and efforts to reduce its impact should continue to be explored.



O1-11-05 MULTISENSORY IMPAIRMENT AND RISK OF DEMENTIA IN BLACK AND WHITE OLDER ADULTS

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Background: There is growing interest in the link between sensory function and cognition. No study has examined impairment in multiple senses (multisensory impairment) and risk of dementia incorporating measures of hearing, vision, smell, and touch. Our objective was to evaluate whether presence of multisensory impairment was associated with higher risk of dementia compared with having a single or no sensory impairment. **Methods:** We studied 1,810 black and white older adults from the Health, Aging, and Body Composition Study, a prospective cohort study of older adults who were aged 70-79 and dementia-free at enrollment. Sensory abilities (hearing, vision, smell, touch) were assessed at study years 3-5, and sensory impairment in each modality was determined based on the following established cut-offs: visual impairment: visual acuity $\leq$20/40 or log contrast sensitivity $<$1.55; moderate-severe hearing loss: $>$40 decibels pure tone average at 500, 1,000, 2,000, and 4,000 Hz; poor smell: lowest tertitle of 12-item Cross Cultural Smell Identification Test; and impaired touch: peripheral nerve function insensitivity based on monofilament-10g or vibration detection threshold. Incident dementia over the following 10 years was determined based on a combination of hospitalization records, dementia medications, or clinically significant cognitive decline ($\geq$1.5 SD decline in Modified Mini-Mental State Exam scores, race-specific). Using Cox proportional hazard models, we investigated the association between number of sensory impairments (0-4) and risk of dementia, adjusted for demographics, comorbid cardiovascular and metabolic conditions, smoking, alcohol use, and exercise. **Results:** Sensory impairments were common: 36% had visual impairment, 35% had hearing loss, 22% had poor smell, and 12% had peripheral nerve insensitivity and 522 (29%) had multisensory impairment. Increasing number of sensory impairments was associated with risk of dementia in a graded fashion ($p<0.001$). Compared to no sensory impairments, the adjusted Hazard Ratio (HR) was 1.5 (95% CI:1.1, 2.0) for 1 sensory impairment, 1.9 (95% CI:1.4, 2.6) for 2 sensory impairments, and 2.9 (95% CI:1.9, 4.3) for 3+ sensory impairments. **Conclusions:** Multisensory impairment was strongly associated with increased risk of dementia. Although, the nature of this relationship needs further investigation, sensory function assessment in clinical visits may help identify patients at high risk of dementia.

O1-11-06 IMPAIRED OLFACTORY FUNCTION IS ASSOCIATED WITH ACCELERATED COGNITIVE DECLINE AND NEURODEGENERATION IN THE BRAIN

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Background: Poor olfactory function has been linked to an increased risk of dementia. However, the association of olfactory function with cognitive decline, and its underlying mechanisms remains unclear. We aimed to verify the hypothesis that impaired olfaction is associated with accelerated cognitive decline and neurodegenerative markers on MRI. **Methods:** Within the Rush Memory and Aging Project, 1501 dementia-free older adults (mean age 79) were identified at study entry and followed for up to 15 years. Olfactory function was assessed using the Brief Smell Identification Test (B-SIT) at baseline, and categorized as: anosmia (B-SIT <6), hyposmia (B-SIT: 6-10 in men and 6-10.25 in women), and normal (B-SIT: 10.25-12 in men and 10.5-12 in women). Global cognitive function was assessed annually with a battery of 19 tests, from which a composite score was derived. In a cross-sectional sub-study, 380 participants underwent magnetic resonance imaging (MRI) to assess whole-brain gray and white matter, and regions of interest. Data were analyzed using linear mixed-effects models and linear regression models. **Results:** At study entry, 190 (12.7%) had anosmia, 893 (59.5%) had hyposmia and 418 (27.9%) had normal olfactory function. In multi-adjusted models, B-SIT score was positively associated with cognitive function over time (β: 0.02, 95% CI: 0.01 to 0.02). Compared to normal olfaction, hyposmia (β: -0.04, 95% CI: -0.05 to -0.02) and anosmia (β: -0.11, 95% CI: -0.14 to -0.09) were associated steeper cognitive decline. In the MRI analysis, impaired olfaction (hyposmia and anosmia) was related to lower volumes of the hippocampus (β: -0.19, 95% CI: -0.32 to -0.05), entorhinal cortex (β: -0.16, 95% CI: -0.24 to -0.08), fusiform (β: -0.45, 95% CI: -0.78 to -0.14), precentral (β: -0.43, 95% CI: -0.84 to -0.03) and total middle temporal cortex (β: -0.38, 95% CI: -0.73 to -0.03). **Conclusions:** Impaired olfaction predicts accelerated cognitive decline and indicates neurodegeneration in the brain among dementia-free older adults. Our findings suggest that olfactory impairment may be a cost-effective marker for identifying individuals at risk of accelerated cognitive aging.

ORAL SESSIONS
O1-12
CLINICAL:
NOVEL THERAPEUTIC APPROACHES FOR NEURODEGENERATIVE DISEASE

O1-12-01 PHASE II STUDY DATA ON SAFETY AND EFFICACY OF GM-CSF/LEUKINE® IN MILD-TO-MODERATE ALZHEIMER'S DISEASE

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Background: Rheumatoid arthritis (RA) patients have a reduced risk of developing Alzheimer's disease (AD), which was originally hypothesized as attributable to their usage of non-steroidal anti-inflammatory drugs (NSAIDs). However, clinical trials with NSAIDs were unsuccessful in both AD and MCI subjects. We therefore pursued our hypothesis that intrinsic factors within RA pathogenesis itself may underlie the AD protective effect(s). We focused on the innate immune system, tested several protein cytokines upregulated in RA blood, and found that 20 daily injections of 5 mg GM-CSF reduced AD pathology by greater than 50% and completely reversed the cognitive impairment of transgenic AD mice. Additionally, we found that bone marrow transplant (BMT) patients treated with Leukine® (recombinant human GM-CSF) plus recombinant G-CSF to treat leukopenia showed significantly improved cognitive functioning at six months compared to BMT patients who received G-CSF alone or no treatment. **Methods:** We are conducting two double blind Phase II pilot safety and efficacy trials of Leukine® in mild-to-moderate AD subjects at 250 mg/m^2/day SC for 5 days/week for either three weeks or 24 weeks with follow-up visits at 45 and 90 days. Neurological and neuropsychological assessments, and MRI and amyloid-PET scans are performed to assess the effects of treatment. **Results:** Interim analyses of 15 subjects treated with Leukine® and 15 subjects treated with placebo in our three-week trial showed no drug-related adverse events, including no evidence of amyloid-related imaging abnormalities (ARIAs), which indicate micro-hemorrhage or vasogenic edema. When comparing measures at the end of treatment to baseline, the mean changes of the MMSE score showed improvement in the Leukine® group relative to baseline (p=0.0029) and to the placebo group (p=0.0175) by repeated measures mixed model analysis. Differences were not significant by the follow-up visits. Amyloid PET data are only available for the last 10 subjects and did not reach significance. **Conclusions:** These results, although preliminary and based on a small number of subjects, indicate that completing the three-week trial and continuing our Alzheimer's Association "Part the Cloud"-funded 24-week trial of GM-CSF/Leukine® in subjects with mild-to-moderate AD are warranted. We will report on the progress of both trials.

O1-12-02 EVALUATION OF THE EFFICACY, SAFETY, AND TOLERABILITY OF ORALLY ADMINISTERED BI 409306, A NOVEL PHOSPHODIESTERASE 9 INHIBITOR, IN TWO RANDOMIZED CONTROLLED PHASE II STUDIES IN PATIENTS WITH PRODROMAL AND MILD ALZHEIMER'S DISEASE

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Background: There are currently no approved treatments for the prodromal stage of Alzheimer's disease (AD) and approved treatments for AD dementia have limited efficacy. Novel treatments for early stages of AD would allow a targeted approach to address early cognitive deficits, delaying onset of more severe symptoms. BI 409306, a potent and selective phosphodiesterase-9A inhibitor, is hypothesized to improve cognitive function and memory. These two, proof-of-concept, double-blind, parallel-group, randomized controlled phase II studies aimed to assess the efficacy and safety of BI 409306 over a 12-week treatment period in prodromal and mild AD. **Methods:** Studies 1 and 2 assessed patients with prodromal AD and mild AD, respectively. Following a single-blind run-in period, patients were randomized to receive one of four doses of