apolipoprotein ε4 status and a number of midlife health and lifestyle indicators, including blood pressure, cholesterol and marital status. Results: Depressive signs in midlife, as measured in this study, were significantly related to general cognitive impairment in later life, but also separately to both mild cognitive impairment and Alzheimer’s disease. When dichotomized into high versus low levels of depressive signs the odds ratios were 2.19 (1.1 to 4.3) for mild cognitive impairment and 3.81 (1.3 to 11.5) for Alzheimer’s disease. Significant associations were also found between the separate measures of hopelessness and loneliness on the one hand and the separate outcomes of mild cognitive impairment and Alzheimer’s disease on the other. Conclusions: The results support a causal relation between depressive signs relatively early in life and cognitive function in later life. Clinical relevance includes the long-term health implications of depressive signs in midlife also for the risk of dementia.

EFFECTS OF HYPERTENSION ON COGNITIVE DECLINE: MEDIATION BY EXPOSURE DURATION, ANTIHYPERTENSIVE TREATMENT AND APOE-Ε4 GENOTYPE

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Background: Presence of vascular risk factors and the emergence of cognitive decline are both common in older people. A deterioration of cognitive functions may be the first sign of dementia. It is therefore important to identify vascular risk factors for cognitive decline and to treat vascular symptoms in order to minimize effects on cognition. Aim: The aim of this study was to investigate the effects of hypertension, diabetes and APOE-Ε4 genotype on cognitive decline over a 12-year episode, in a normal aging population. Methods: Method: 1,823 healthy participants in the Maastricht Aging Study completed baseline assessment between 1993 and 1995. Twelve-year follow-up results at three different time points with six-year intervals were available for seventy-five percent of the baseline group (n = 903). Neuropsychological assessment was performed in three cognitive domains: verbal memory (delayed recall), psychomotor speed (letter-digit copying) and executive functioning (set shifting). Results: Participants with evidence of exposure to high blood pressure for at least six years showed a larger cognitive decline in all three cognitive domains, compared to participants without hypertension or who had high blood pressure on only one occasion. Diabetes was negatively associated with cognitive performance at baseline; however, effects of diabetes on cognitive decline were not mediated by exposure time. Presence of at least one Apolipoprotein E-ε4 (APOE-ε4) allele increased the effect of hypertension on the three cognitive measures for individuals with hypertension and at least six years exposure years. Effects of APOE-ε4 genotype and exposure were only present in individuals with untreated hypertension. Conclusions: Hypertension-related cognitive decline is mediated by exposure duration, antihypertensive treatment, and APOE-ε4 genotype. Effects of type-2 diabetes on cognitive decline are not mediated by exposure-time. Implications of these findings are discussed.

SEVERITY OF DIABETES AND SHORT TERM RISK OF DEMENTIA IN MIDDLE AGED MEN: THE CALIFORNIA MEN'S HEALTH STUDY

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Background: Although elderly individuals with diabetes are at a greater risk of dementia, less is known about the control and/or management of diabetes and the short term risk of dementia in middle aged individuals. The goal of this study was to evaluate diabetes severity and short term risk of dementia in a large cohort of middle aged men. Methods: We evaluated the association between diabetes severity (type of treatment and glycosylated hemoglobin [HbA1c]) and risk of dementia among 31,631 participants in the California Men’s Health Study, a prospective cohort of Northern California Kaiser Permanente (KP) members, ages 45-69 (mean age 58), initiated in 2002. Socio-demographic variables were collected via questionnaire, while diabetes information was gathered from the KP Diabetes Registry. Initial diagnoses of dementia were collected from medical records in primary care, neurology, and neuropsychology from 2003-2007. Cox proportional hazard models adjusted for age, race, education, marital status, body mass index, smoking, heart disease and stroke were used to investigate the association between diabetes severity and four year risk of dementia. Results: Fourteen percent of the participants had diabetes (4544) and 332 were diagnosed with dementia during the follow-up. Those with diabetes had a 72% greater risk of dementia (adjusted hazards ratio [aHR] = 1.72, 95% confidence intervals [CI], 1.33,2.19) versus those without diabetes. Those with diabetes and insulin treated had nearly a 300% greater risk of dementia (aHR = 3.99, 95% CI 2.21, 7.21); those with diabetes and using oral medications a non-significant 36% greater risk (aHR = 1.36, 95% CI 0.93, 2.1) and those being treated for diabetes with behavioral changes a 40% non-significant risk increase (aHR = 1.40, 95% CI 0.89, 2.1) versus those without diabetes. Those with evidence of glycemic control (HbA1c < 7) had a 50% greater risk (aHR = 1.53, 95% CI 1.03, 2.28) versus those without diabetes; while those with evidence of poor glycemic control (HbA1c ≥ 9) a 86% greater risk (aHR = 1.86, 95% CI 1.1, 3.46). Conclusions: Even in middle-age, diabetes severity is associated with increased short term risk of dementia. Future studies should evaluate the role of diabetes control on brain health.

ACCELERATED PROGRESSION FROM MILD COGNITIVE IMPAIRMENT TO DEMENTIA IN PEOPLE WITH DIABETES

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Background: Although the influence of diabetes on cognitive aging is well established, the effect of diabetes on the progression from mild cognitive impairment (MCI) to dementia is still debated. We examined whether people with diabetes or prediabetes have a higher risk for cognitive decline and an accelerated progression from MCI to dementia. Methods: Within the Kungsholmen Project, 963 cognitively intact participants and 302 subjects with MCI (120 amnestic MCI or aMCI and 182 other cognitive impairment no dementia or oCIND) aged ≥75 were assessed at baseline. The two cohorts were followed for 9 years to detect incident dementia (DSM-III-R criteria) and incident MCI (Petersen’s criteria). Diabetes was ascertained...
The lack of association between diabetes and the risk of MCI in our study also participated in MCI progression by more than two years in people with MCI. Diabetes and prediabetes triple the risk of progression to dementia and an additional association between diabetes and MCI was observed. Diabetes led to a multi-adjusted hazard ratio of 3.64 (95% CI, 2.05-6.45) for dementia in subjects with MCI, and accelerated the progression of diabetes-free participants. Data were analyzed using standard and time-dependent Cox models. Results: During the 9-year follow-up, in the cognitively intact cohort, 182 people developed MCI (42 aMCI and 140 CIND), and 212 developed dementia in the MCI cohort. 155 persons progressed to dementia. Diabetes and prediabetes led to a multi-adjusted hazard ratio of 3.64 (95% CI, 2.05-6.45) for the risk of dementia in subjects with MCI, and accelerated the progression from MCI to dementia by 2.33 years. Neither cross-sectional nor longitudinal association between diabetes and MCI was observed. Conclusions: Diabetes and prediabetes triple the risk of progression to dementia and anticipate dementia occurrence by more than two years in people with MCI. The lack of association between diabetes and the risk of MCI in our study suggests that diabetes might lead to dementia bypassing MCI or shortening the MCI phase in old people.

**THE OBESEITY RELATED GENE, FTO, INCREASES THE RISK FOR INCIDENT ALZHEIMER’S DISEASE IN A PROSPECTIVE POPULATION BASED STUDY**

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**Background:** The FTO gene has been shown to affect body mass index (BMI), the risk for diabetes and leptin levels. These vascular risk factors seem to play a role in the development of Alzheimer disease (AD) and dementia. Methods: Therefore the study aimed to explore the direct role of the FTO gene on AD and dementia risk in old age. Secondarily, vascular risk factors, such as BMI, diabetes, cardiovascular diseases (CVD) and physical inactivity were taken into account to explore possible modifiers to the association. A possible interaction with APOE, the only confirmed genetic risk factor for AD in addition to a role for vascular risks, was assessed. Data was gathered from the Kungsholmen project, a prospective population based study. A dementia free cohort (n=1003) of 75+ old people originating from Sweden was followed for 9 years to detect incident AD and dementia cases (DSM-III-R criteria). The FTO polymorphism (rs9939609) and APOE ε4 (rs429358) were genotyped at baseline. Cox regression models were used to assess the relative risk of developing AD and dementia according to FTO genotypes, taking into account diabetes, BMI, CVD and physical inactivity. Results: Compared to carriers of the TT-genotype, AA-carriers had a higher risk for AD (RR 1.58, 95% CI: 1.11-2.24) and for dementia (RR 1.48, 95% CI: 1.09-2.02) after adjustment for age, gender, education, and APOE genotype. An interaction between FTO and APOE was found, with increased risk for dementia for those carrying FTO-AA and APOE ε4. The effect of the AA-genotype on AD and dementia risk remained after additional adjustment for diabetes, BMI, CVD and physical inactivity. Conclusions: To conclude, the FTO A-allele increases the risk for dementia, and in particular AD, independently of diabetes, BMI, CVD and physical inactivity measured at baseline. Further, the A-allele interacts with APOE ε4 and thereby doubles the dementia risk. This finding sheds light of a role of the FTO gene in the central nervous system, and gives further support for the importance of metabolic dysregulation on the development of AD and dementia.

**O2-06-07 CHANGE IN LEUKOCYTE TELOMERE LENGTH AND RISK OF DEMENTIA**

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**Background:** Telomeres cap and protect chromosome ends. Their attrition, resulting from progressive rounds of cell division, is linked to replicative senescence of human somatic cells. While Leukocyte telomere length (LTL) has been found to be associated with mortality and diseases of aging, most studies involved LTL measured at one point in time. We examined change in LTL over five years in the Cardiovascular Health Study (CHS), an observational cohort of adults age 65 and older, and evaluated associations between longitudinal change in LTL and risk of dementia over that time period. Methods: A total of 550 participants of the CHS Cognition Study provided DNA which allowed measurement of LTL in 1992 and 1997 by Southern blots of the terminal restriction fragments. Dementia was classified over an average of 6.0 years of follow-up by a committee of neurologists and psychiatrists utilizing data from clinic visits, neuropsychiatric tests, medical records and physician questionnaires. Subtype was determined utilizing MRI images. Dementia status at the end of the CHS Cognition Study (2000) was the outcome for these analyses. Unconditional logistic regression was used to determine associations with risk of dementia and change in LTL. Results: Participants were an average of 74.2 (standard deviation-SD 4.6) years old, 58% were women and 10.1% were African-American. Mean LTL length at baseline was 6.30 kilobase (kb) pairs (SD 0.55). An average of -0.14 kb (SD 0.24) were lost over the next five years. While LTL at baseline was not related to subsequent dementia onset (Odds Ratio - OR: 1.07, 95% Confidence Interval - CI: 0.82 -1.39), change in LTL was significantly associated with risk of dementia (OR: 1.17, 95% CI: 1.05-1.31, p = .002). Adjusted for age, gender and race, those in the quartile of greatest LTL loss (greater than 0.29 kb LTL) were three times more likely to be classified with dementia than those in the lowest quartile of LTL loss (less than 0.008 kb LTL): HR: 2.96, 95% CI: 1.17-7.54, p = .02). Results were similar for both Alzheimer’s disease and vascular dementia. Conclusions: Longitudinal telomere dynamics may help explain parameters of aging including determination of dementia risk in older adults.

**O2-06-08 BIOAVAILABLE TESTOSTERONE DECREASES THE RISK OF ALZHEIMER’S DISEASE IN NON-DEMENTED CHINESE OLDER MEN: A ONE-YEAR COHORT STUDY**

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**Background:** The association of testosterone with dementia risk has been largely explored in men with androgen insufficiency or hypogonadism, with inconsistent findings. We hypothesized that bioavailable testosterone may have a role in the prevention of cognitive decline in non-demented Chinese older men. Methods: A total of 173 non-demented Chinese older men (mean age 76.6 ± 6.9 years) were recruited from a community based study. Cognitive status was assessed using the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog). Testosterone levels were measured using liquid chromatography tandem mass spectrometry (LC-MS/MS). Results: At baseline, total testosterone levels were lower in the dementia onset group compared to the non-dementia group (p = .02). After adjustment for age, gender, education, and BMI, a 10% increase in free testosterone levels was associated with a 14% reduction in the risk of dementia (OR: 0.86, 95% CI: 0.76-0.98). Conclusions: Higher bioavailable testosterone levels may be associated with a lower risk of dementia in non-demented Chinese older men.