P2-301 THE ALZRISK PROJECT: THE WEB-BASED CATALOGUE AND META-ANALYSIS OF FINDINGS FROM EPIDEMIOLOGIC STUDIES OF NON-GENETIC RISK FACTORS FOR ALZHEIMER'S DISEASE

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Background: The AlzGene database documents putative genetic risk factors for AD, but there is no centralized source of summary information for non-genetic risk factors. The volume of reports has expanded substantially in recent years, and studies vary considerably, making tools to organize and summarize relevant findings increasingly valuable. Modeled on AlzGene, but modified to accommodate the greater complexity of exposure definition and timing in this setting, the AlzRisk database (www.alzrisk.org) aims to provide a comprehensive, unbiased, publicly available and regularly updated summary of epidemiologic reports on non-genetic risk factors for AD. **Methods:** We identify eligible publications through systematic review of peer-reviewed papers, and require prospective data from large, well-defined cohorts; sufficient details on design and findings; and adjustment-at a minimum-for age and sex. We report the findings in detailed tables grouped on exposure definition, and provide documentation of our search strategy and a discussion summarizing critical issues in interpreting the results. Where comparable data are available in at least four populations, we conduct meta-analyses. **Results:** Currently, AlzRisk includes 122 papers on 12 risk factors from 47 po pulations. We were able to meta-analyze data for five risk factors, which indicated an overall adverse association of diabetes with AD risk, a weakly protective association of aspirin use with AD risk, and no consistent association corresponding to history of hypertension, systolic blood pressure, diastolic blood pressure, hormone therapy, non-aspirin NSAID use, vitamin C supplement use, vitamin E supplement use, and the combination of these vitamin supplement intakes. Among risk factors where we could not perform meta-analyses, physical and mental activity and moderate alcohol consumption were associated with reduced AD risk; history of severe head injury, elevated homocysteine, and midlife obesity were associated with increased AD risk; and inflammatory biomarkers showed no clear associations with risk. Work on lipid profile, statin use, and dietary patterns is underway, and additional risk factors are planned. **Conclusions:** With its detailed assessments of high-quality evidence, the AlzRisk Project clearly shows where evidence is plentiful or lacking, and provides a clear view of the strength and limitations of that evidence and what questions remain to be explored.

P2-302 VASCULAR RISK FACTORS, APOE GENE ABNORMALITIES IN WHITE-MATTER MICROSTRUCTURE, AND COGNITIVE DECLINE IN OLD AGE: A POPULATION-BASED STUDY

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Background: Cognitive aging can be accelerated by vascular risk factors (VRFs) and genetic susceptibility. We investigated the associations of VRFs and APOE ε4 with abnormalities in white-matter microstructure and cognitive decline among older people. **Methods:** This study included 241 participants (age 60+ years; 63% women) in the Swedish National study on Aging and Care in central Stockholm, who were free of dementia and stroke at baseline and were re-examined at three years, six years or both. At baseline, data on demographics, VRFs, and APOE genotype were collected through interviews, clinical examinations, laboratory tests, and inpatient register system. Fractional anisotropy (FA) and mean diffusivity (MD) of seven regions of interests were assessed using diffusion-tensor imaging, and global scores for FA and MD were derived from factor analysis. Volume of white-matter hyperintensities (WMH) was measured through automatic segmentation. Global cognitive function was assessed with the Mini-Mental State Examination (MMSE) at baseline and follow-ups. Data were analyzed with multivariate linear regression and linear mixed models. **Results:** Current smoking, heavy alcohol drinking, hypertension, and diabetes were marginally or significantly associated with a lower FA score or a higher MD score. Having multiple ($\geq$2) VRFs, compared to having none of these four VRFs, was significantly associated with a lower FA score and a higher MD score, independent of WMH volume. There were statistical interactions between VRFs and APOE ε4 on FA and MD scores, such that having multiple VRFs was significantly associated with a lower FA score or a higher MD score only among APOE ε4 carriers. A low FA score or a high MD score at baseline was significantly associated with a faster decline in MMSE score. Compared with having neither VRFs nor APOE ε4, having any of those four VRFs or having both VRFs and APOE ε4 allele was significantly associated with a faster decline in MMSE score during the follow-up period. **Conclusions:** This study suggests that VRFs are associated with abnormalities in white-matter microstructure and cognitive decline. The detrimental effects of VRFs on brain microstructure and cognitive function appear to be reinforced by carrying APOE ε4 allele.

P2-303 DEMOGRAPHIC VARIATIONS IN MID-LIFE COGNITIVE FUNCTION: THE CARDIA STUDY

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Background: Although dementia prevalence may vary by sex, race, education, and age, less is known about demographic differences in mid-life cognition. Objective: To determine demographic differences in mid-life cognitive function and whether differences in clinical factors or behaviors explain any observed demographic differences in cognitive function. **Methods:** We studied 3,319 participants enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) study who were aged 18-30 years at baseline (1985-1986). Enrollees were balanced on sex, race (black or white), education ($\leq$high school or >high school), and age (18-24 or 25-30 years) at four urban U.S. sites. Cognitive function, measured at the 25 year follow-up exam, was assessed with the Rey auditory verbal learning test (RAVLT) for memory, the Digit Symbol Substitution Test (DSST) test of processing speed and attention, and the Stroop interference test of attention and executive function. We examined sex, race, education (year 25), and age differences in cognitive function, before and after adjusting for clinical factors (depressive symptoms, systolic and diastolic blood pressure, fasting glucose, diabetes status, height, APOE e4 status) and behavioral factors (physical activity, waist circumference, smoking) at year 10, using multivariable linear regression models.

Table
Adjusted cognitive function tests scores at year 25: the CARDIA study, 1985-2010

	Rey auditory verbal learning test (words)		Digit symbol substitution test (symbols)		Stroop interference test	
	Adjusted for demographics[a] (n=3,319)	Fully adjusted[b] (n=2,823)	Adjusted for demographics[a] (n=3,319)	Fully adjusted[b] (n=2,823)	Adjusted for demographics[a] (n=3,319)	Fully adjusted[b] (n=2,823)
Characteristic	Estimates (Standard Errors)					
Intercept	6.59 (0.42)[c]	6.47 (1.74)[c]	58.50 (2.00)[c]	47.60 (8.19)[c]	25.57 (1.45)[c]	33.50 (5.76)[c]
Black race	-1.61 (0.16)[c]	-1.45 (0.17)[c]	-8.72 (0.75)[c]	-8.18 (0.81)[c]	6.32 (0.54)[c]	6.03 (0.57)[c]
Female sex	1.93 (0.14)[c]	1.94 (0.19)[c]	7.75 (0.64)[c]	8.02 (0.87)[c]	-0.57 (0.47)	-0.54 (0.61)
Offset for Black women	-0.53 (0.20)[c]	-0.62 (0.22)[c]	NA	NA	NA	NA
Age at year 25						
≥52 years	-0.37 (0.15)[d]	-0.26 (0.17)	-5.64 (0.73)[c]	-5.25 (0.80)[c]	3.25 (0.53)[c]	2.66 (0.56)[c]
49-51 years	-0.24 (0.17)	-0.15 (0.18)	-3.40 (0.79)[c]	-3.41 (0.86)[c]	1.97 (0.58)[c]	1.67 (0.61)[c]
46-48 years	-0.05 (0.17)	-0.05 (0.19)	-1.24 (0.83)	-1.49 (0.90)	1.74 (0.60)[c]	1.61 (0.63)[c]
≤45 years	Referent	Referent	Referent	Referent	Referent	Referent
Education at year 25						
>College	2.52 (0.38)[c]	2.17 (0.44)[c]	21.90 (1.82)[c]	19.31 (2.09)[c]	-10.59 (1.32)[c]	-8.68 (1.47)[c]
College graduate	2.16 (0.38)[c]	1.85 (0.44)[c]	18.18 (1.83)[c]	16.30 (2.09)[c]	-9.95 (1.32)[c]	-8.22 (1.47)[c]
Some college	1.43 (0.38)[c]	1.30 (0.44)[c]	14.26 (1.80)[c]	13.47 (2.05)[c]	-7.49 (1.31)[c]	-6.47 (1.44)[c]
High school	0.56 (0.39)	0.52 (0.45)	8.65 (1.87)[c]	9.04 (2.11)[c]	-4.68 (1.36)[c]	-3.90 (1.48)[c]
<High school	Referent	Referent	Referent	Referent	Referent	Referent
Center at year 25						
Birmingham	0.60 (0.14)[c]	0.62 (0.15)[c]	-4.82 (0.67)[c]	-4.92 (0.73)[c]	1.85 (0.48)[c]	1.93 (0.51)[c]
Chicago	-0.31 (0.14)[d]	-0.25 (0.15)	-0.97 (0.66)	-0.95 (0.73)	0.53 (0.48)	0.08 (0.51)
Minneapolis	-0.37 (0.14)[c]	-0.49 (0.15)[c]	-2.80 (0.66)[c]	-2.79 (0.73)[c]	1.13 (0.48)	1.13 (0.51)[d]
Oakland	Referent	Referent	Referent	Referent	Referent	Referent

Interpretative Key: For the Rey auditory verbal learning test, the range of scores is 0-15, with increasing scores indicating better performance. For the Digit Symbol Substitution Test, the range of scores is 0-133, with increasing scores indicating better performance. For the Stroop interference test, a higher score indicates worse performance on the task. NA = not applicable.

[a] Model adjusted for race, sex, age, educational attainment at year 25, and center at year 25.

[b] Model adjusted for race, sex, age, educational attainment at year 25, clinical center at year 25, and year 10 values of depressive symptoms, systolic and diastolic blood pressure, fasting glucose, diabetes status, height, physical activity, waist circumference, and cigarette smoking.

[c] P≤0.01

[d] P≤0.05

Results: Cognitive scores varied by sex, race, education, and age. For all tests, cognitive scores were lower in blacks than whites, after adjusting for demographics (Table). Compared to men, w omen scored (mean ± standard error, SE) 7.75 ± 0.64 symbols higher on the DSST (P<0.001), but similarly on the Stroop (P=0.22). A small race-by-sex interaction (P=0.01) was seen for the RAVLT, but not for the other 2 tests. Adjusted mean RAVLT scores (± SE) were 10.08 ± 0.09 for white women, 8.15 ± 0.10 for white men, 7.94 ± 0.10 for black women, and 6.54 ± 0.12 for black men. Cognitive scores tended to be lower in older adults and those with fewer years of education. Most demographic differences persisted after full adjustment, although the magnitude of the age and sex differences reduced slightly (Table). Results were similar in analyses including APOE e4. **Conclusions:** Demographic differences in cognition appear in mid-life and are not fully explained by clinical or lifestyle factors.

P2-304 APPLICATION OF SYSTEMS MEDICINE TO ALZHEIMER'S DISEASE AND DEMENTIA RESEARCH: A SYSTEMATIC REVIEW

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Background: Systems medicine offers a novel paradigm that is well established in the study of complex chronic diseases that arise as the result of multiple interacting factors such as cancer and diabetes. Systems medicine models may help to account for the dynamic interactions between biological, clinical and environmental factors in Alzheimer's disease (AD) and dementia. Our aim was to examine the extent to which systems medicine has been applied to dementia research. **Methods:** We conducted a systematic review using EMBASE, Medline and PsycInfo from inception to January 2014 plus backward and forward citation searches of included publications following a pre-defined protocol (see Figure). Experts in the field were contacted to identify any additional relevant publications. We searched for publications applying a computational or mathematical model of AD or dementia and integrating dynamically interacting factors on multiple levels (biological, clinical and/or environmental). No date or language restrictions were used. Two reviewers independently screened titles and abstracts, and conducted full text reviews. Discrepancies were resolved by discussion with involvement of two additional reviewers. **Results:** We selected 24 studies for full-text review. Two studies met all inclusion criteria and provide useful examples to illustrate the potential of the systems medicine paradigm. The first study incorporated a multifactorial computational model of AD pathogenesis, and was subsequently extended in the second study to incorporate the hypothesized role of estrogen in