Prevalence of vascular and lifestyle risk factors in different stages of prodromal Alzheimer's disease and its influence on cognitive decline.

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Background: Vascular and lifestyle risk factors may increase the risk for Alzheimer's disease (AD). Recently, criteria have been prosed for diagnosis of AD in subjects with MCI by an International Working Group-2 (IWG-2) and National Institute of Aging-Alzheimer (NIA-AA). Aim of this study was to investigate whether vascular risk factors are associated with prodromal AD and with cognitive decline at follow-up.
Methods: We selected subjects from multicenter studies (DESCRIPA, DCN, EDAR, EADC-PET, and ADNI) and from 7 centers from the EADC or EMIF-AD. Inclusion criteria were baseline MCI diagnosis, availability of minimally one AD-biomarker (aβ1-42 and tau in CSF, HCV on MRI, glucose metabolism on FDG-PET) and at least one clinical follow-up. Cognitive tests and biomarkers were used to classify subjects with or without prodromal AD according to IWG-2 and in six groups according to NIA-AA. Prevalence of risk factors was calculated for each prodromal AD group (Table 1). We compared prevalence using logistic regression (IWG-2 groups) or multinomial regression (NIA-AA criteria subgroups). The interplay of risk factors and prodromal AD stage was examined using Cox regression with decline on the MMSE or progression to AD dementia as outcome, all corrected for demographics and center.
Results: We included 1391 subjects with a mean follow-up of 2.3 years and an average age of 69.7 years. Subjects with prodromal AD according to IWG-2 criteria had a lower prevalence for depression (p=0.015), hypertension (p=0.023) and obesity (p=0.014) compared to the no-prodromal AD group. A longitudinal interaction of smoking and prodromal AD was found (HR= 2.00, p=0.018), with higher cognitive decline among non-

smokers compared to smokers without prodromal AD. Using the NIA-AA criteria we found a lower prevalence for depression, hypertension, obesity and smoking and a higher prevalence for atherosclerotic disease in the high-likelihood-AD group (Table 1). Longitudinal analyses revealed a trend towards an interaction of hypertension and NIA-AA group (HR=0.93, p=0.056), in which hypertension increased the risk of cognitive decline in groups with a normal amyloid marker.
Conclusion: We showed that vascular and lifestyle risk factors have an impact on prodromal AD stages and influence cognitive decline. These findings have implications for clinical practice and intervention strategies.

Table 1: Prevalence of vascular risk factors in NIA-AA groups.

	Low likelihood (n=157) Amyloid- Injury-	**High likelihood (n=364)** Amyloid+ Injury+		**SNAP (n=208)** Amyloid- Injury+		**IAP (n=66)** Amyloid+ Injury-		**Intermediate likelihood (n=319)** Amyloid? Injury+		**Inconclusive (n=277)** Amyloid? Injury-	
Risk factors	Prevalence	Prevalence	P-value	Prevalence	P-value	Prevalence	P-value	Prevalence	P-value	Prevalence	P-value
Atherosclerotic disease (n=998)	1%	9%	**0.038**	9%	**0.043**	7%	0.223	11%	0.070	9%	**0.044**
Current depression (n=680)	50%	31%	**0.026**	40%	0.302	27%	**0.056**	33%	0.070	42%	0.372
Diabetes (n=988)	9%	8%	0.929	13%	0.286	15%	0.180	12%	0.631	14%	0.237
Hypercholesterolemia (n=966)	37%	29%	0.126	39%	0.858	38%	0.881	44%	0.794	51%	0.143
Hypertension (n=1331)	60%	50%	**0.030**	54%	0.098	60%	0.767	54%	0.166	54%	0.152
Lacunar infarct (n=497)	29%	23%	0.107	30%	0.443	18%	0.394	40%	0.496	16%	**0.010**
Stroke (n=707)	4%	3%	0.854	4%	0.847	6%	0.299	4%	0.281	4%	0.437
Obesity (n=971)	20%	9%	**0.016**	19%	0.629	11%	0.195	12%	0.127	13%	0.092
Current or former smoker (n=1216)	54%	37%	**0.039**	42%	0.266	45%	0.139	38%	0.177	32%	**0.014**
Current alcohol use (n=1006)	45%	54%	0.317	44%	0.927	51%	0.494	49%	0.880	40%	0.726

P-values are corrected for age, gender, years of education and center and indicate a difference in prevalence compared to the low likelihood group. SNAP = suspected non-Alzheimer pathophysiology, IAP = Isolated amyloid pathology.