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The frequency and influence of dementia risk factors in prodromal Alzheimer's disease.

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ABSTRACT

We investigated whether dementia risk factors were associated with prodromal Alzheimer's disease (AD) according to the International Working Group-2 and National Institute of Aging-Alzheimer's Association criteria, and with cognitive decline. 1394 subjects from with Mild Cognitive Impairment (MCI) from 14 different studies were classified according to these research criteria, based on cognitive performance and biomarkers. We compared the frequency of ten risk factors between the subgroups and used Cox-regression to examine the effect of risk factors on cognitive decline. Depression, obesity and hypercholesterolemia occurred more often in individuals with low-AD-likelihood, compared to those with a high-AD-likelihood. Only alcohol use increased the risk of cognitive decline, regardless of AD pathology. These results suggest that traditional risk factors for AD are not associated with prodromal AD or with progression to dementia, among subjects with MCI. Future studies should validate these findings and determine whether risk factors might be of influence at an earlier stage (i.e. preclinical) of AD.

Keywords: Alzheimer's disease, risk factors, IWG-2 criteria, NIA-AA criteria, biomarkers, prognosis.

1. Introduction

Various risk factors have been associated with an increased risk for Alzheimer's disease (AD) (Breteler, 2000; de Bruijn and Ikram, 2014). Recently, research criteria have been proposed to identify AD in subjects with mild cognitive impairment (MCI) by their biomarker status, referred to as prodromal AD by international working group-2 (IWG-2) (Dubois, et al., 2014) and MCI due to AD by the National Institute of Aging-Alzheimer Association (NIA-AA) (Albert, et al., 2011). It remains uncertain whether risk factors are associated with prodromal AD/ MCI due to AD, and whether they influence the rate of cognitive decline. This information could improve early diagnosis and lead to new targets for secondary prevention strategies.

Among the best-validated risk factors for AD are atherosclerosis, depression, diabetes mellitus, hypercholesterolemia, hypertension, lacunar infarcts, stroke, obesity, smoking, and alcohol consumption (Breteler, 2000; de Bruijn and Ikram, 2014; Deckers, et al., 2015). Diabetes mellitus, depression, hypertension, stroke and cardiovascular diseases have also been associated with an increased risk of progressing from cognitively normal to MCI (Pankratz, et al., 2015; Roberts, et al., 2015). Moreover, an association with cognitive decline has been found in both cognitively normal and MCI subjects (Jefferson, et al., 2015; Kaffashian, et al., 2013). Therefore, we hypothesize that risk factors will occur more frequently in individuals with prodromal AD/MCI due to AD. We also expect that risk factors will increase the risk of progression to dementia.

We aim to investigate the frequency of several risk factors in individuals with prodromal AD/MCI due to AD, classified according to the IWG-2 and NIA-AA criteria, relative to subjects who do not meet these criteria. Secondly, we aim to examine whether risk factors influence the rate of cognitive decline.

2. Methods

2.1 Subjects

Subjects were recruited from five multicenter memory-clinic based studies: DESCRIPA (Visser, et al., 2008), German Dementia Competence Network (DCN) (Kornhuber, et al., 2009), EDAR (www.edarstudy.eu), the European Alzheimer's Disease Consortium (EADC)-PET study (Morbelli, et al., 2012) and American Alzheimer's Disease Neuroimaging Initiative (ADNI-1) study (Mueller, et al., 2005); and nine centers of the EADC and/or European Medical Information Framework (EMIF)-AD: Amsterdam (van der Flier, et al., 2014), Antwerp (Somers C., In press), Barcelona (Alcolea, et al., 2014), Brescia (Frisoni, et al., 2009), Coimbra (Baldeiras, et al., 2008), Gothenburg (Wallin, et al., 2016), Kuopio (Seppala, et al., 2011), Liège (Bastin, et al., 2010) and Lisbon (Maroco, et al., 2011). For subjects who participated in more than one study, we used data from the study with the longest follow-up.

Inclusion criteria consisted of baseline diagnosis of MCI according to the criteria of Petersen (Petersen, 2004), and at least one of the following biomarkers available at baseline: amyloid-beta (A β) 1-42 and tau (total tau and/or phosphorylated tau) in CSF, hippocampal volume on magnetic resonance imaging (MRI) or cerebral glucose metabolism on [18F]FDG-PET of the brain. Moreover, baseline data had to be available on at least one of the selected risk factors, as well as information on

educational level and at least one clinical follow-up assessment. Exclusion criteria were diagnosis of dementia at baseline.

2.2 Clinical assessment

The clinical assessment is described in detail by Vos et al. (Vos, et al., 2015). In short, clinical assessment was performed at each site according to local routine protocol.

Cognitive impairment was defined as Z-score < -1.5 SD on at least one neuropsychological test, which could be a memory or non-memory test.

2.3 Outcome at follow-up

Cognitive decline was defined as progression to dementia according to the Diagnostic and Statistical Manual of Mental Disorders (APA, 1994), or a decline on the Mini-Mental State Examination (MMSE) of at least 3 points at follow-up. We used a combination of these two measures, as for a subgroup (n=17) no clinical diagnosis at follow-up was available. For sub analyses, diagnosis of AD-type dementia at follow-up was made according to the National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer’s Disease and Related Disorders Association criteria (NINCDS-ADRDA) (McKhann, et al., 1984).

The medical ethics committee at each site approved the study. All subjects provided informed consent.

2.4 Biomarker assessment

Biomarker assessment was performed according to the routine protocol at each site and center-specific cut-offs were used to define abnormality, as described elsewhere

(Vos, et al., 2015). Examination of medial temporal lobe atrophy on MRI and cerebral glucose metabolism on FDG-PET were performed through visual assessment.

2.5 Subject classification

Subjects were classified as having prodromal AD according to the IWG-2 criteria using CSF A β 1-42 and tau biomarkers (Table 1). The NIA-AA criteria distinguish between six groups that indicate the likelihood that MCI is due to AD, based on combinations of amyloid and neuronal injury markers. We used CSF A β 1-42 as amyloid marker and CSF total tau, CSF phosphorylated tau, cerebral glucose metabolism on FDG-PET, hippocampal volume or medial temporal lobe atrophy on MRI as neuronal injury markers (Table 1).

2.6 Risk factors

We assessed the following risk factors at baseline: atherosclerotic disease, depression, diabetes, hypercholesterolemia, hypertension, lacunar infarct, obesity, stroke, current smoking, and current alcohol use. Not all risk factors were available for each subject. Supplemental Table 1 provides an overview of the available risk factors for each center. The risk factor definitions are described by center in Supplemental Table 2. For all risk factors occurrence in medical history was used as a standard. For some risk factors, we used additional definitions based on rating scales, physical measurements or medication use, based on availability (Supplemental Table 2).

2.7 Statistical analyses

Baseline differences between the biomarker profile groups were analyzed using ANOVA for continuous variables and Chi-Square test for categorical variables. The

relation of risk factors with prodromal AD/MCI due to AD was tested with logistic regression (IWG-2 criteria) or multinomial regression (NIA-AA criteria). Cox proportional hazards models were used to test the effect of each risk factor on the rate of cognitive decline in the total sample, and for the IWG-2 and NIA-AA biomarker subgroups. All analyses were adjusted for age, sex, education and center. Statistical analyses were performed using SPSS version 22.0 with the significance level set at $p < 0.05$. We corrected for multiple comparisons, using the false discovery rate (FDR) adjustment (Benjamini and Hochberg, 1995), taking into account the testing of ten risk factors. In tables, we reported uncorrected p-values and we indicated which associations were significant after correction for multiple comparisons in tables and the text.

3. Results

3.1 Subject characteristics

We included 1394 individuals (mean age = 69.7, SD 8.3; 51% female). Seven hundred and fifty-eight subjects had data available on both amyloid and neuronal injury markers, while 636 subjects only had data on a neuronal injury marker (medial temporal lobe atrophy $n=528$, FDG-PET $n=108$). Five hundred and eighty individuals (42%) showed cognitive decline after an average follow-up time of 2.3 (SD 1.2) years. Table 2 shows the characteristics of the subjects classified according to the IWG-2 and the NIA-AA criteria.

3.2 Analyses in subjects with both amyloid and neuronal injury markers

Based on the IWG-2 criteria, 302 subjects (40%) were classified as prodromal AD. Individuals with prodromal AD were older ($p < 0.001$), showed a lower score on the

MMSE at follow-up ($p < 0.001$) and were more likely to progress to AD-type dementia at follow-up ($p < 0.001$) compared to subjects without prodromal AD. According to the NIA-AA criteria, 142 individuals (10%) were classified in the low-AD-likelihood group, 356 (26%) in the high-AD-likelihood group, 54 (4%) in the Isolated Amyloid Pathology (IAP) group, and 206 (15%) in the Suspected Non-AD Pathophysiology (SNAP) group. Subjects in the high-AD-likelihood group were older and most likely to progress to AD-type dementia, compared to all other groups (Table 2).

3.2.1. Frequency of risk factors

Table 3 shows the frequency of AD risk factors for the NIA-AA groups with both amyloid and neuronal injury data. Compared to the high-AD-likelihood group, subjects in the low-AD-likelihood group had a higher frequency of depression (46% vs. 17%, $p = 0.004$, FDR $p = 0.020$), obesity (21% vs. 8%, $p = 0.004$, FDR $p = 0.020$) and hypercholesterolemia (43% vs. 27%, $p = 0.009$, FDR $p = 0.030$). No differences were found between the groups for the other risk factors (Table 3).

Supplemental Table 3 shows the frequency of risk factors for the groups according to the IWG-2 criteria. In the group without prodromal AD we found higher frequencies of depression (34% vs. 16%, $p = 0.009$, FDR $p = 0.045$) and obesity (17% vs. 8%, $p = 0.007$, FDR $p = 0.045$) compared to the group with prodromal AD (Supplemental Table 3).

3.2.2. Effect of risk factors on cognitive decline

In the total group of subjects with both amyloid and neuronal injury markers, alcohol use was associated with a higher risk of cognitive decline (HR=1.5, $p = 0.003$, FDR

p=0.030, Table 4). There were no significant interactions between risk factors and NIA-AA group classification, indicating that the effect of risk factors was similar for all groups. Using the IWG-2 classification, the effects of depression, hypercholesterolemia, and smoking were different between the two groups, but these differences were no longer statistically significant after adjusting for multiple testing (Table 4).

3.3 Analyses in subjects with only neuronal injury markers

Table 2 shows the characteristics of the 258 (21%) subjects classified as uninformative/inconclusive and the 350 (25%) included in the intermediate-AD-likelihood group according to the NIA-AA criteria. The subjects in the intermediate-AD-likelihood differed on all characteristics from the uninformative/inconclusive group.

The frequency of risk factors for the subjects who had only neuronal injury markers available is described in Supplemental Table 4. In the intermediate-AD-likelihood-group lacunar infarcts occurred more frequently (40%), compared to the uninformative/inconclusive group (16%, $p<0.001$). There were no differences for the other risk factors (Supplemental Table 4).

In the subjects with only neuronal injury markers available, none of the risk factors increased the risk of cognitive decline. Also, there was no difference between the two NIA-AA groups in the rate of cognitive decline (Supplemental Table 5).

3.4 Post-hoc analyses – progression to AD-type dementia

When we repeated the analyses with only progression to AD-type dementia as an outcome in subjects with both amyloid and neuronal injury markers available (n=725), alcohol use was no longer associated with an increased risk of progression (HR=1.3, 95% CI: 0.9 – 1.8, p=0.164).

Since the ADNI cohort excluded subjects with depressive symptoms (GDS>6), we repeated the analyses concerning depression without ADNI subjects. This did not influence the results.

4. Discussion

We examined the frequency of vascular and lifestyle risk factors in prodromal AD/MCI due to AD, and the influence of these factors on cognitive decline, in subjects with MCI. We found that the frequencies of depression, hypercholesterolemia and obesity were higher in the group without AD pathology compared to the group with AD pathology. Only alcohol increased the risk of cognitive decline, regardless of AD-pathology.

4.1 Frequency of risk factors

Contrary to our hypothesis we found higher frequencies of depression, hypercholesterolemia and obesity, in the group without prodromal AD and in the low-AD-likelihood group. This suggests that subjects without prodromal AD or low-AD-likelihood had cognitive impairment due to other causes than AD, such as depression or vascular disorders (DeCarli, 2003; Gorelick, et al., 2011). It is also possible that low cholesterol or low body mass index are risk factors for prodromal AD in this elderly sample. While obesity and hypercholesterolemia in middle age have been

shown to be predictive for AD (Deckers, et al., 2015; Kivipelto, et al., 2005), other studies showed that this association is reversed at older age, such that low body mass index and low cholesterol increase the risk for AD (Anstey, et al., 2008; Johnson, et al., 2006). When we compared the frequencies observed in the current study to the prevalence of risk factors reported in meta-analyses and population-based cohort studies (Supplemental Table 6), we found that the frequencies of obesity and hypercholesterolemia in the high-AD-likelihood group were decreased, while frequencies were similar in subjects with a low-AD-likelihood. On the contrary, the frequency of depression in the high-AD-likelihood group was similar to that in the general population while it was higher in the low-AD-likelihood group compared to the population-based studies. This would suggest that the difference in frequencies of obesity and hypercholesterolemia between the low and high-AD-likelihood in our study results from a decrease of obesity and hypercholesterolemia in the high-AD-likelihood, rather than from an increase in the low-AD-likelihood. Conversely, the difference in frequency in depression between groups could result from an increase in frequency of depression in the low-AD-likelihood. This indicates that depression can be a possible cause of MCI in the studied population (DeCarli, 2003; DeFrancesco, et al., 2009). Clearly there are methodological differences in the inclusion of subjects, definition and method of ascertainment of risk factors and age range between the current study and the population based studies. Studies that directly compare frequency of risk factors in prodromal AD to cognitively normal subjects are needed to further clarify this.

4.2 Influence of risk factors on cognitive decline

Alcohol consumption was associated with an increased risk of cognitive decline, independent of AD-pathology. Although this finding is in line with several previous studies (Deckers, et al., 2015; Jauhar, et al., 2014) that identified alcohol as a risk factor for cognitive decline, other studies have reported a protective or no relation to alcohol consumption with incident AD (Anstey, et al., 2009; Ruitenberg, et al., 2002). These conflicting results could be explained by differences in study population (MCI versus cognitively normal), definitions of alcohol consumption (dichotomous versus categories based on the amount of alcohol use) and the type of alcohol. When conversion to AD-type dementia was used as outcome instead of conversion to dementia or a decline on the MMSE, we found that the effect of alcohol was no longer significant. This suggests that alcohol consumption mainly has an effect on progression to non-AD types of dementia or cognitive decline in general.

4.3 IWG-2 vs. NIA-AA criteria

The results on frequency of risk factors were comparable for the IWG-2 and NIA-AA criteria. Also, when comparing the effect of risk factors on cognitive decline we found similar outcomes when using the two sets of criteria. This shows that although the IWG-2 criteria only classify neuronal injury based on tau in CSF and the NIA-AA criteria also include other neuronal injury markers, this did not influence the results. Although the outcomes were similar for the two sets of criteria, the NIA-AA criteria provided more insight into which specific biomarker profile was associated with a higher frequency of a certain risk factor, which could be useful to give a more refined diagnosis and prognosis of early AD and age-related comorbidities.

4.4 Strengths and limitations of the study

Strengths of the study are the large sample size, the broad spectrum of assessed risk factors and longitudinal data on clinical outcome. There are also limitations to this study that should be mentioned. Some of the biomarker subgroups were small and some risk factors were only available in a subgroup or had a low frequency, which limited statistical power. The data used in this study was contributed by different centers and data was not collected using the same protocol. This might have led to variability, although it does reflect current clinical practice. Furthermore, the use of indirect measures (e.g. medical history) of risk factors could have introduced heterogeneity in classification. We were unable to study the potential interactions between risk factors, as not all centers contributed data on all risk factors. We had only limited data available on medication use, which did not allow us to control for this. Also, we could not correct for the duration and the severity of a risk factor, as we had no information on this. Although the mean follow-up was 2.3 years, some individuals likely would have shown cognitive decline at a later stage. Since these findings are based on clinical research populations, they may not be generalizable to other settings.

4.5 Conclusion

In summary, we found that dementia risk factors were not associated with prodromal AD/MCI due to AD in subjects with MCI, and only alcohol increased the risk of cognitive decline, regardless of underlying pathology. Moreover, we found that a lower frequency of hypercholesterolemia or obesity may be indicative of early AD in an elderly population. Although our findings should be validated in future studies, they could have implications for clinical practice, future scientific studies, as well as for selection of individuals for participation in clinical trials. Different risk factor

profiles in subjects with MCI could be related to distinct etiologies of cognitive dysfunction, and therefore may have different prognostic values. Management of alcohol habits could possibly lessen or prevent further cognitive decline. Future studies should focus on the role of risk factors in even earlier stages of AD (e.g. preclinical AD), examine longitudinal biomarkers values, and consider the duration and severity of risk factors. Also, co-occurrence of risk factors and possible synergistic effects on biomarkers should be a topic for future research as we were unable to study this in the current sample.

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Author contributions

Study concept and design: IB, SV, & PJV. Acquisition and/or interpretation of data: all authors. Statistical analysis and drafting the manuscript: IB, SV, & PJV. Critical revision of final draft of manuscript: all authors.

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Table 1: Classification of subjects according to IWG-2 and NIA-AA criteria

	Amyloid marker	Neuronal injury marker
IWG-2 groups	CSF A β 1-42	CSF t-tau or p-tau
No prodromal AD	Abnormal	Normal
	Normal	Abnormal
	Normal	Normal
Prodromal AD	Abnormal	Abnormal
	Amyloid Marker	Neuronal injury markers
NIA-AA groups	CSF A β 1-42	CSF t-tau or p-tau / Medial temporal lobe atrophy on MRI / FDG-PET
Low-AD-likelihood	Normal	All normal
High-AD-likelihood	Abnormal	At least one abnormal
IAP	Abnormal	All normal
SNAP	Normal	At least one abnormal
Intermediate-AD-likelihood	Unknown	At least one abnormal
Inconclusive/uninformative	Unknown	All normal

A β = amyloid-beta, AD = Alzheimer's disease, CSF = cerebrospinal fluid, FDG-PET = fluorodeoxyglucose-positron emission tomography, IAP = Isolated Amyloid Pathology, IWG = International Working Group, MRI = magnetic resonance imaging, NIA-AA = National Institute of Aging-Alzheimer's Association, p-tau = phosphorylated tau, SNAP = non-Alzheimer Pathophysiology, t-tau = total tau.

Table 2: Demographics and clinical outcome according to IWG-2 and NIA-AA criteria

	IWG-2 criteria		NIA-AA criteria – Amyloid and neuronal injury markers				NIA-AA criteria- only neuronal injury markers	
	No prodromal AD	Prodromal AD	Group A Low-AD-likelihood	Group B High-AD-likelihood	Group C IAP	Group D SNAP	Uninformative /Inconclusive	Intermediate-AD-likelihood
	N=456	N=302	N=142	N=356	N=54	N=206	N=286	N=350
Age, years	67.3 (8.6)	71.3 (7.5) [¶]	63.4 (8.9) ^{B,D}	71.3 (7.5) ^{A,C,D}	66.2 (7.5) ^B	69.2 (8.0) ^{A,B}	67.8 (8.4)	73.1 (7.2) [#]
Female, n	207 (45%)	148 (49%)	64 (45%)	170 (48%)	25 (46%)	96 (46%)	183 (64%)	177 (50%) [#]
Education, years	10.4 (3.8)	11.7 (4.3) [¶]	10.3 (3.2) ^B	11.6 (4.3) ^{A,D}	11.0 (4.0)	10.2 (3.9) ^B	9.9 (4.6)	10.7 (4.2) [#]
Follow-up, years	2.3 (1.2)	2.3 (1.1)	2.1 (0.9)	2.3 (1.2)	2.3 (1.2)	2.4 (1.3)	2.6 (1.4)	2.3 (1.3) [#]
APOE-ε4*	138 (35%)	184 (68%) [¶]	37 (30%) ^B	205 (65%) ^{A,D}	22 (47%)	58 (32%) ^B	81 (36%)	141 (52%) [#]
MMSE at baseline	27.0 (2.3)	26.1 (2.5) [¶]	27.5 (2.9) ^{B,D}	26.2 (2.5) ^{A,C}	27.3 (2.4) ^B	26.7 (2.3) ^A	27.5 (2.3)	26.6 (2.2) [#]
Decline on MMSE at follow-up [†]	58 (25%)	114 (51%) [¶]	8 (13%) ^B	127 (49%) ^{A,C,D}	6 (16%) ^B	31 (30%) ^B	329 (38%)	106 (45%) [#]
Progression to AD-type dementia at follow-up [‡]	86 (20%)	172 (59%) [¶]	6 (5%) ^{B,D}	193 (56%) ^{A,C,D}	10 (20%) ^{A,B}	49 (24%) ^{A,B}	56 (19%)	167 (47%) [#]

Progression to non-AD dementia at follow-up [§]	38 (9%)	6 (2%) [¶]	12 (9%)	11 (3%)	1 (2%) ^D	20 (10%) ^C	10 (4%)	22 (6%)
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Results are mean (SD) or continuous variables or frequency (%). AD = Alzheimer's disease, APOE = Apolipoprotein E, IAP = Isolated Amyloid Pathology, MMSE = Mini Mental State Examination (range 0-30), IWG = International Working Group, NIA-AA = National Institute of Aging and Alzheimer's Association, SNAP = Suspected non-Alzheimer Pathophysiology. * APOE genotype was only available in a subgroup of the sample: IWG-2 no prodromal AD n=397, prodromal AD n=271; NIA-AA low-AD-likelihood n=123, high-AD-likelihood n=316, IAP n=47, SNAP n=182, uninformative/inconclusive n=226, intermediate-AD-likelihood n=271. † Decline on MMSE at follow-up was defined as a difference of 3 points or more and was available in a subgroup of the samples: IWG-2 no prodromal AD n=237, prodromal AD n=223; NIA-AA low-AD-likelihood n=61, high-AD-likelihood n=259, IAP n=37, SNAP=103, uninformative/inconclusive n=184, intermediate-AD-likelihood n=233. ‡ Progression to AD-type dementia at follow-up was available in a subgroup of the sample: IWG-2 no prodromal AD n=435, prodromal AD n=293, NIA-AA low-AD-likelihood n=134, high-AD-likelihood n=344, IAP n=49, SNAP n=201, uninformative/inconclusive n=286, intermediate-AD-likelihood n=350. § Progression to non-AD dementia at follow-up was available in a subgroup of the samples: IWG-2 no prodromal AD n=433, prodromal AD n=293, NIA-AA low-AD-likelihood n=133, high-AD-likelihood n=343, IAP n=50, SNAP n=200, uninformative/inconclusive n=286, intermediate-AD-likelihood n=350. ¶ p < 0.05 compared to the no prodromal Alzheimer's disease after FDR correction. ^A p < 0.05 compared to low-AD-likelihood after FDR correction. ^B p < 0.05 compared to high-AD-likelihood after FDR correction, ^C p < 0.05 compared to IAP after FDR correction, ^D p < 0.05 compared to SNAP after FDR correction, [#] p < 0.05 compared to the uninformative/inconclusive after FDR correction.

Table 3: Frequency of risk factors for NIA-AA groups

	Low-AD- likelihood	High-AD- likelihood	IAP	SNAP	p-value Low vs. High
Risk factors	N=142	N=356	N=54	N=206	
Atherosclerotic disease (n=1002)	4%	10%	5%	9%	0.277
Depression (n=1129)	46%	17%*	27%	29%	0.004
Diabetes (n=914)	8%	9%	14%	15%	0.960
Hypercholesterolemia (n=1001)	43%	27%*	38%	38%	0.009
Hypertension (n=1346)	50%	47%	54%	47%	0.038
Lacunar infarct (n=497)	29%	23%	18%	30%	0.133
Stroke (n=1013)	3%	4%	6%	5%	0.787
Obesity (n=993)	21%	8%*	8%	18%	0.004
Smoking (n=1195)	53%	36%	40%	42%	0.076
Alcohol use (n=973)	42%	50%	50%	42%	0.352

AD = Alzheimer's disease, IAP = Isolated Amyloid pathology, SNAP = Suspected non-Alzheimer Pathophysiology. Comparisons were corrected for baseline age, gender, years of education and center. *p<0.05 after FDR correction.

Table 4: Effects of risk factors on cognitive decline

Risk factors	Main effect risk factors			Interaction with IWG-2 groups			Interaction with NIA-AA groups		
	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Atherosclerotic disease	1.1	0.7 – 1.7	0.825	0.5	0.2 - 1.3	0.159	0.6	0.4 – 1.1	0.119
Depression	0.7	0.5 – 0.9	0.022	0.5	0.3 – 0.9	0.048	0.8	0.6 – 1.2	0.253
Diabetes	1.0	0.7 – 1.6	0.907	1.1	0.4 - 2.8	0.922	1.2	0.7 – 2.3	0.501
Hypercholesterolemia	0.8	0.6 – 1.0	0.080	2.2	1.2 - 3.9	0.010	1.1	0.8 – 1.5	0.624
Hypertension	0.7	0.4 – 1.1	0.103	0.7	0.5 – 1.1	0.103	0.8	0.6 – 1.1	0.118
Lacunar infarct	0.8	0.3 – 2.1	0.603	0.8	0.3 – 2.1	0.603	0.8	0.4 – 1.6	0.535
Stroke	1.0	0.6 – 1.9	0.899	0.5	0.1 – 1.5	0.201	0.7	0.4 – 1.3	0.263
Obesity	0.7	0.4 – 1.1	0.111	1.0	0.4 - 2.6	0.993	1.1	0.6 – 2.1	0.771
Smoking	1.2	0.9 – 1.5	0.214	1.8	1.1 - 3.0	0.017	1.2	0.9 – 1.7	0.233
Alcohol use	1.5	1.2 – 2.0	0.003*	0.8	0.5 - 1.4	0.478	0.9	0.7 – 1.3	0.624

CI = Confidence Interval, HR = Hazard Ratio, IWG = International Working Group, NIA-AA = National Institute of Ageing Alzheimer’s Association. Cognitive decline is defined as progression to dementia or 3 points decline on MMSE at follow-up. Hazard ratios and 95% CIs were calculated using Cox regression analyses and corrected for baseline age, gender, years of education and center. *p<0.05 after FDR correction.