ONLINE SUPPLEMENT

Incidence of brain infarcts, cognitive change and risk of dementia in the general population: The AGES –Reykjavik Study

Supplemental Methods

Rating of Cerebral Microbleeds

For cerebral miscrobleed (CMB) detection, we used a 2-dimensional T2*-weighted gradient echo-type echo planar sequence (echo time 50 milliseconds (msec), repetition time 3,050 msec, flip angle 90°, field of view (FOV) 220 mm, matrix 256 x 256, slice thickness 3 mm) and a proton density/T2-weighted fast spin echo sequence (first echo time 22 msec, second echo time 90 msec, repetition time 3,220 msec, echo train length 8, flip angle 90°, FOV 220 mm, matrix 256 x 256, slice thickness 3 mm).[1] Imaging at both time-points used identical acquisition parameters. The CMBs from both time-points were rated semi-quantitatively by two trained radiographers on the MRI scans in terms of size and anatomic location with good intrarater and interrater reliabilities for CMB detection.[2] CMBs were defined as a focal area of signal void within the brain parenchyma that is observable on T2*-weighted gradient echo-type echo planar sequence scans and smaller or unobservable on T2-weighted fast spin echo scans.[1] We counted up to 30 CMBs in lobar regions (frontal, parietal, temporal, and occipital) and in deep (basal ganglia and thalamus, corpus callosum, and brainstem) or cerebellar regions. If there were >30 CMBs, they were coded as 30.[3]

Quantification of white matter hyperintensity volume

The quantification of white matter hyperintensity (WMH) volume was computed automatically with an algorithm based on the Montreal Neurological Institute pipeline.[4] The AGES-Reykjavik/Montreal Neurological Institute pipeline has been modified to accommodate full brain coverage including cerebellum and brainstem, multispectral images (T1-weighted 3D spoiled-gradient recalled sequence, FLAIR and proton density/T2-weighted fast spin echo sequences), high throughput and minimal editing. The segmentation pipeline, its components and accuracy have been described in detail elsewhere.[5] In brief, the pipeline segments 4-tissue classes separately using the multispectral images. In addition to WMH volume, the pipeline generates volumes for grey matter (GM), white matter (WM) and cerebral-spinal fluid (CSF). The key processing stages were as follows: stereotaxic registration was achieved after signal non-uniformity correction by an affine transformation of the T1-weighted images to the ICBM152 template. Intersequence registration was performed by registering images from the individual (T2/proton density, fluid-attenuated inversion recovery) sequences to the T1-weighted images in order to accurately align all image volumes acquired during an acquisition session. Linear signal intensity normalization was then applied to correct for signal intensity variations across images in the different sequences. Finally, tissue classification was achieved with an artificial neural network classifier. The absolute volumes of the four tissue types were subsequently calculated and converted to native space volumes using the scale factor obtained from the stereotaxic registration transformation.

Supplemental Tables

Supplemental Table I. Infarcts overall: Mean change in cognitive function from baseline to follow-up by prevalence and incidence of infarcts and sex

	Men					Women				
		Mean change in cognitive function					Mean change in cognitive function			
Cognitive domains and groups of infarcts	n	Mean	95%CI Lower	95%CI Upper	p-value	n	Mean	95%CI Lower	95%CI Upper	p-value
Memory										
No prevalent & no incident	559	-0.25	-0.31	-0.19	Reference	967	-0.24	-0.28	-0.19	Reference
One or more prevalent & no incident	211	-0.24	-0.33	-0.15	0.79	284	-0.24	-0.32	-0.15	0.98
No prevalent & one or more incident	112	-0.32	-0.45	-0.20	0.29	134	-0.34	-0.46	-0.22	0.10
One or more prevalent & one or more incident	167	-0.43	-0.53	-0.33	0.003	117	-0.39	-0.51	-0.26	0.03
Executive function										
No prevalent & no incident	559	-0.31	-0.37	-0.25	Reference	967	-0.16	-0.20	-0.11	Reference
One or more prevalent & no incident	211	-0.27	-0.37	-0.18	0.56	284	-0.17	-0.25	-0.09	0.82
No prevalent & one or more incident	112	-0.28	-0.42	-0.16	0.76	134	-0.25	-0.36	-0.14	0.14
One or more prevalent & one or more incident	167	-0.39	-0.49	-0.29	0.16	117	-0.29	-0.41	-0.17	0.04
Processing speed										
No prevalent & no incident	559	-0.32	-0.38	-0.27	Reference	967	-0.32	-0.36	-0.28	Reference
One or more prevalent & no incident	211	-0.35	-0.43	-0.27	0.60	284	-0.31	-0.38	-0.25	0.90
No prevalent & one or more incident	112	-0.52	-0.63	-0.40	0.002	134	-0.31	-0.40	-0.21	0.87
One or more prevalent & one or more incident	167	-0.66	-0.75	-0.57	<0.0001	117	-0.40	-0.51	-0.30	0.12

Values are mean longitudinal change in the various cognitive domains with 95% confidence interval (CI) by groups of any type of infarcts (overall) and sex after adjusting for age and time interval between MRI scans. P-values indicate if change in cognition in persons with prevalent and/or incident infarcts was significantly different from the change in persons without infarcts (reference).
In men the interaction between the change in cognition and infarct groups was statistically significant for memory (p=0.01) and processing speed (p<0.0001) but not for executive function (p=0.38). In women the interaction was not statistically significant for any of the cognitive domains (memory; p=0.07, executive function; p=0.13, processing speed; p=0.44).

Supplemental Table II. Cortical infarcts: Mean change in cognitive function by prevalence and incidence of infarcts and sex

	Men					Women				
		Mean change in cognitive function					Mean change in cognitive function			
Cognitive domains and groups of cortical infarcts	n	Mean	95%CI Lower	95%CI Upper	p-value	n	Mean	95%CI Lower	95%CI Upper	p-value
Memory										
No prevalent & no incident	804	-0.27	-0.32	-0.22	Reference	1343	-0.24	-0.29	-0.20	Reference
One or more prevalent & no incident	120	-0.21	-0.33	-0.09	0.36	85	-0.37	-0.52	-0.22	0.11
No prevalent & one or more incident	77	-0.37	-0.51	-0.22	0.23	49	-0.33	-0.53	-0.14	0.38
One or more prevalent & one or more incident	48	-0.58	-0.76	-0.40	0.002	25	-0.39	-0.67	-0.12	0.29
Executive function										
No prevalent & no incident	804	-0.29	-0.35	-0.24	Reference	1343	-0.18	-0.22	-0.14	Reference
One or more prevalent & no incident	120	-0.31	-0.43	-0.19	0.81	85	-0.06	-0.21	0.08	0.12
No prevalent & one or more incident	77	-0.35	-0.50	-0.20	0.48	49	-0.23	-0.42	-0.05	0.57
One or more prevalent & one or more incident	48	-0.50	-0.69	-0.31	0.04	25	-0.46	-0.72	-0.20	0.04
Processing speed										
No prevalent & no incident	804	-0.37	-0.42	-0.33	Reference	1343	-0.32	-0.35	-0.28	Reference
One or more prevalent & no incident	120	-0.35	-0.46	-0.24	0.74	85	-0.39	-0.51	-0.27	0.27
No prevalent & one or more incident	77	-0.60	-0.73	-0.46	0.002	49	-0.33	-0.49	-0.17	0.89
One or more prevalent & one or more incident	48	-0.84	-1.01	-0.67	<0.0001	25	-0.36	-0.58	-0.14	0.68

Values are mean longitudinal change in the various cognitive domains with 95% confidence interval (CI) by groups of cortical infarcts and sex after adjusting for age and time interval between MRI scans. P-values indicate if change in cognition in persons with prevalent and/or incident cortical infarcts was significantly different from the change in persons without cortical infarcts (reference).

In men the interaction between the change in cognition and cortical infarct groups was statistically significant for memory (p=0.005) and processing speed (p<0.0001) but not for executive function (p=0.20). In women the interaction was not statistically significant for any of the cognitive domains (memory; p=0.25, executive function; p=0.06, processing speed; p=0.72).

Supplemental Table III. Cerebellar infarcts: Mean change in cognitive function by prevalence and incidence of infarcts and sex

	Men					Women				
		Mean change in cognitive function					Mean change in cognitive function			
Cognitive domains and groups of cerebellar infarcts	n	Mean	95%CI Lower	95%CI Upper	p-value	n	Mean	95%CI Lower	95%CI Upper	p-value
Memory										
No prevalent & no incident	723	-0.26	-0.31	-0.21	Reference	1116	-0.25	-0.30	-0.21	Reference
One or more prevalent & no incident	166	-0.32	-0.42	-0.22	0.26	218	-0.20	-0.30	-0.11	0.33
No prevalent & one or more incident	84	-0.31	-0.45	-0.17	0.50	102	-0.36	-0.49	-0.22	0.15
One or more prevalent & one or more incident	76	-0.44	-0.59	-0.29	0.02	66	-0.37	-0.54	-0.20	0.18
Executive function										
No prevalent & no incident	723	-0.32	-0.37	-0.26	Reference	1116	-0.16	-0.21	-0.12	Reference
One or more prevalent & no incident	166	-0.29	-0.40	-0.19	0.71	218	-0.21	-0.30	-0.12	0.33
No prevalent & one or more incident	84	-0.28	-0.43	-0.14	0.69	102	-0.25	-0.38	-0.12	0.20
One or more prevalent & one or more incident	76	-0.37	-0.52	-0.22	0.51	66	-0.25	-0.41	-0.09	0.29
Processing speed										
No prevalent & no incident	723	-0.36	-0.41	-0.31	Reference	1116	-0.33	-0.37	-0.30	Reference
One or more prevalent & no incident	166	-0.47	-0.56	-0.37	0.04	218	-0.27	-0.35	-0.20	0.15
No prevalent & one or more incident	84	-0.58	-0.71	-0.45	0.002	102	-0.28	-0.39	-0.17	0.35
One or more prevalent & one or more incident	76	-0.55	-0.68	-0.41	0.01	66	-0.40	-0.54	-0.26	0.35

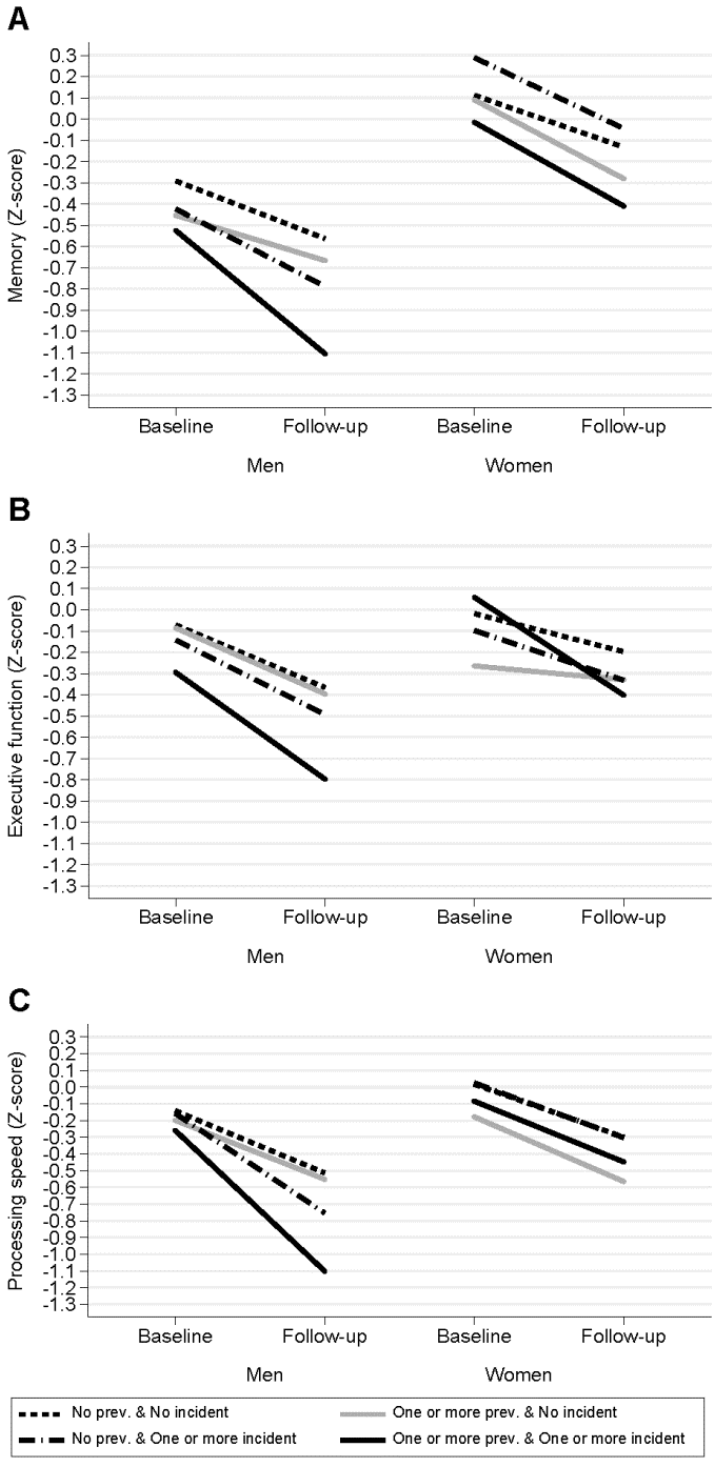
Values are mean longitudinal change in the various cognitive domains with 95% confidence interval (CI) by groups of cerebellar infarcts and sex after adjusting for age and time interval between MRI scans. P-values indicate if change in cognition in persons with prevalent and/or incident cerebellar infarcts was significantly different from the change in persons without cerebellar infarcts (reference). In men the interaction between the change in cognition and cerebellar infarct groups was statistically significant for speed (p=0.001) but not for memory (p=0.12) nor executive function (p=0.84). In women the interaction was not statistically significant for any of the cognitive domains (memory; p=0.15, executive function; p=0.37, speed; p=0.27).

Supplemental Table IV. Subcortical infarcts: Mean change in cognitive function by prevalence and incidence of infarcts and sex

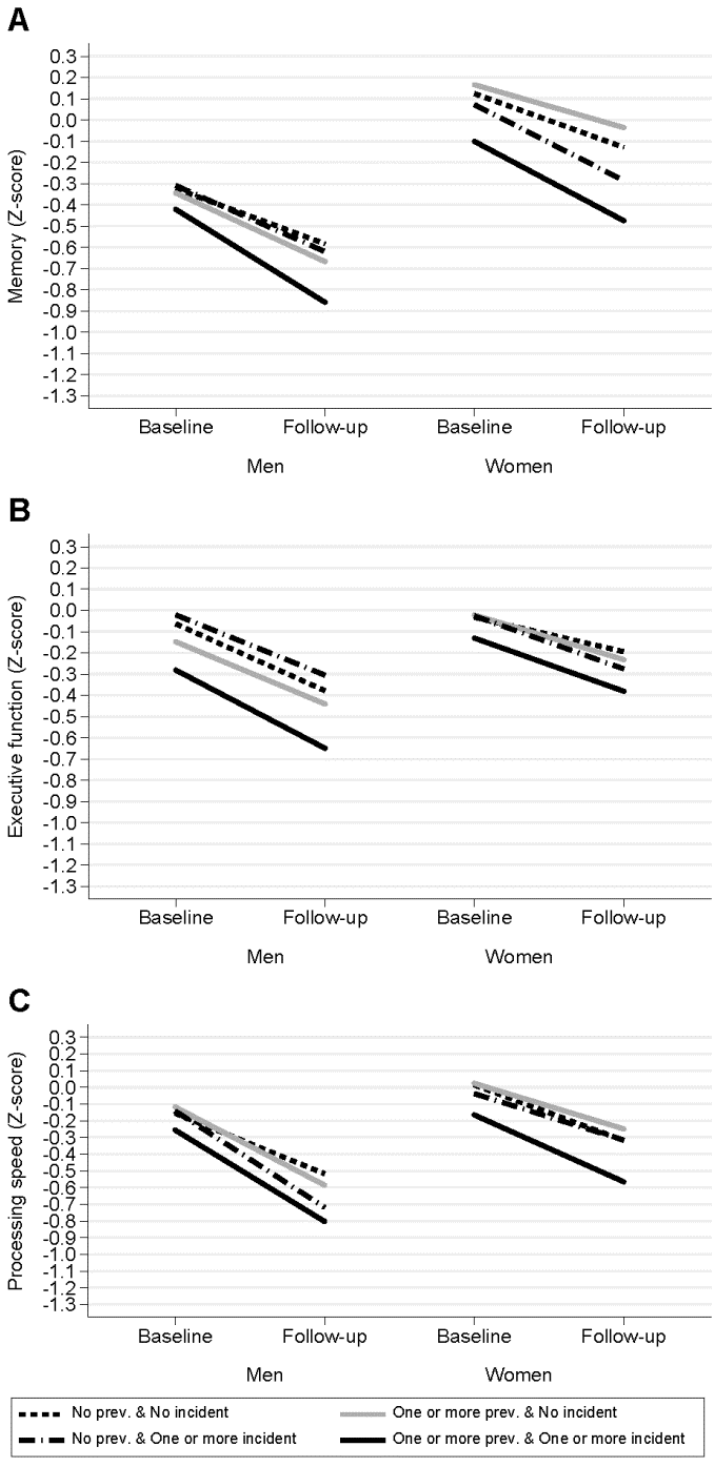
	Men					Women				
		Mean change in cognitive function					Mean change in cognitive function			
Caognitive domains and groups of subcortical infarcts	n	Mean	95%CI Lower	95%CI Upper	p-value	n	Mean	95%CI Lower	95%CI Upper	p-value
Memory										
No prevalent & no incident	912	-0.27	-0.32	-0.23	Reference	1375	-0.20	-0.24	-0.17	Reference
One or more prevalent & no incident	70	-0.24	-0.39	-0.09	0.66	80	-0.39	-0.54	-0.24	0.02
No prevalent & one or more incident	41	-0.53	-0.73	-0.33	0.01	37	-0.28	-0.51	-0.06	0.49
One or more prevalent & one or more incident	26	-0.55	-0.80	-0.30	0.03	10	-0.54	-0.97	-0.11	0.12
Executive function										
No prevalent & no incident	912	-0.31	-0.36	-0.26	Reference	1375	-0.18	-0.22	-0.14	Reference
One or more prevalent & no incident	70	-0.29	-0.45	-0.14	0.87	80	-0.17	-0.31	-0.02	0.48
No prevalent & one or more incident	41	-0.29	-0.50	-0.09	0.88	37	-0.36	-0.57	-0.15	0.41
One or more prevalent/ one or more incident	26	-0.56	-0.82	-0.31	0.04	10	0.09	-0.32	0.49	0.32
Processing speed										
No prevalent & no incident	912	-0.37	-0.42	-0.33	Reference	1375	-0.31	-0.35	-0.28	Reference
One or more prevalent & no incident	70	-0.53	-0.67	-0.39	0.03	80	-0.39	-0.52	-0.27	0.21
No prevalent & one or more incident	41	-0.72	-0.91	-0.54	0.0003	37	-0.51	-0.69	-0.33	0.04
One or more prevalent & one or more incident	26	-0.95	-1.18	-0.72	<0.0001	10	-0.41	-0.75	-0.06	0.60

Values are mean longitudinal change in the various cognitive domains with 95% confidence interval (CI) by groups of subcortical infarcts and sex after adjusting for age and time interval between MRI scans. P-values indicate if change in cognition in persons with prevalent and/or incident subcortical infarcts was significantly different from the change in persons without subcortical infarcts (reference). In men the interaction between the change in cognition and subcortical infarct groups was statistically significant for memory (p=0.01) and speed (p<0.0001) but not for executive function (p=0.28). In women the interaction was not statistically significant for any of the cognitive domains (memory; p=0.99, executive function; p=0.21, speed; p=0.11).

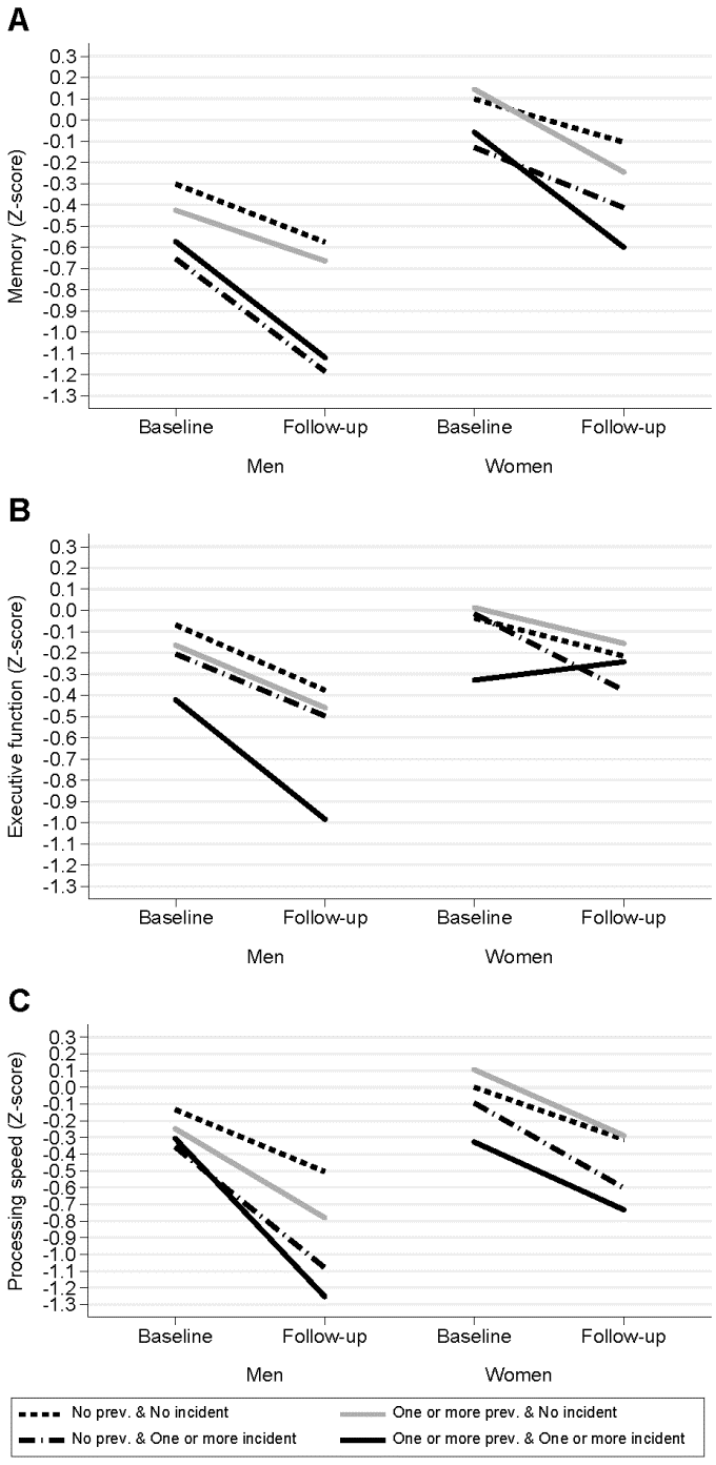
Supplemental Figures



Supplemental Figure I. Cortical infarcts: Mean change in cognition by prevalence and incidence of infarcts and sex. The graphs show mean change in A) memory, B) executive function and C) processing speed respectively for men and women by groups of prevalent- and incident cortical infarcts after adjusting for age and time interval between MRI scans.



Supplemental Figure II. Cerebellar infarcts: Mean change in cognition by prevalence and incidence of infarcts and sex. The graphs show mean change in A) memory, B) executive function and C) processing speed respectively for men and women by groups of prevalent- and incident cerebellar infarcts after adjusting for age and time interval between MRI scans.



Supplemental Figure III. Subcortical infarcts: Mean change in cognition by prevalence and incidence of infarcts and sex. The graphs show mean change in A) memory, B) executive function and C) processing speed respectively for men and women by groups of prevalent- and incident subcortical infarcts after adjusting for age and time interval between MRI scans.

Supplemental References

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