Neurovascular imaging markers of brain aging

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6

Incidence of Brain Infarcts, Cognitive Change, and Risk of Dementia in the General Population

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ABSTRACT

Objectives

The differentiation of brain infarcts by region is important since their etiology and clinical implications may differ. Information on the incidence of these lesions and association with cognition and dementia from longitudinal population studies is scarce. We investigated the incidence of infarcts in cortical-, subcortical-, cerebellar- and overall brain regions and how prevalent and incident infarcts associate with cognitive change and incident dementia.

Methods

Participants (n=2,612, 41% men, mean age 74.6±4.8) underwent brain MRI for assessment of infarcts and cognitive testing at baseline and on average 5.2 years later. Incident dementia was assessed according to international guidelines.

Results

Twenty-one percent of the study participants developed new infarcts. The risk of incident infarcts in men was higher than the risk in women (1.8 (95%CI, 1.5-2.3)). Persons with both incident and prevalent infarcts showed steeper cognitive decline and had almost double relative risk of incident dementia (1.7 (95%CI, 1.3-2.2)) compared to those without infarcts. Persons with new subcortical infarcts had highest risk of incident dementia compared to those without infarcts (2.6 (95%CI, 1.9-3.4)).

Conclusions

Men are at greater risk of developing incident brain infarcts than women. Persons with incident brain infarcts decline faster in cognition and have an increased risk of dementia compared to those free of infarcts. Incident subcortical infarcts contribute more than cortical and cerebellar infarcts to incident dementia which may indicate that infarcts of small vessel disease origin contribute more to the development of dementia than infarcts of embolic origin in larger vessels.

INTRODUCTION

Brain infarcts are common findings on magnetic resonance (MR) images in older adults and have been associated with cognitive decline and dementia. Their prevalence has been well documented in several population-based studies.[1-4] Imaging studies generally agree that the prevalence of brain infarcts increases steeply with increasing age and it is over 20% in the 70 to 79 age group and 35% in those older than 85.[4, 5] Most studies with data on prevalence of brain infarcts show no sex disparity in infarct risk.[5] Information on the incidence of brain infarcts from population based longitudinal studies is however scarce.

Previous studies suggest that cerebro-vascular abnormalities contribute to cognitive decline and the development of vascular dementia and Alzheimer's disease (AD).[6, 7] There is however limited information from imaging studies on whether this differs by brain region. The assessment of brain infarcts by region or type is important since the etiology and clinical implications of cerebellar-, cortical- and subcortical infarcts may differ. A distal branch middle cerebral artery occlusion resulting in a cortical stroke usually results from an embolus from either the heart, aortic arch or carotid artery, whereas a small infarct in the subcortical white matter is usually due to a blockage of small penetrating artery (lacunar infarct). The most common etiologies of cerebellar infarcts are however thought to be atherosclerosis, cardiac embolism and migraine.[8, 9]

At least three longitudinal population studies have shown an association of prevalent brain infarcts with increased risk of incident dementia.[10-12] These studies had a relatively small number of incident dementia events and only one of them had MRI observations at two time points and none evaluated the association of infarcts with dementia by infarct location.

The objectives of this study were to investigate the incidence and risk of incident infarcts in cortical-, subcortical-, cerebellar- and overall brain regions by sex. Further, to investigate cognitive change and the risk of incident overall dementia in relation to prevalent and incident infarcts in those brain regions.

METHODS

Study population

The longitudinal data in the present study are from a population-based cohort of men and women, who participated in the Age Gene/Environment Susceptibility-Reykjavik

Study (AGES-Reykjavik Study). Briefly, from 2002 to 2006, 5,764 surviving participants of the Reykjavik Study were examined. From 2007 to 2011 a follow-up visit was conducted comprising of 3,316 surviving participants who agreed to participate. Reasons for not attending the follow-up examination included: death (n=1039), refusal (n=1198), and could not be contacted (n=211). The AGES-Reykjavik Study has been approved by the Icelandic National Bioethics Committee and by the Institutional Review Board for the Intramural Research Program of the National Institute on Aging, National Institutes of Health, USA. Written informed consent was obtained from all participants.

MRI acquisition

MR images were acquired on a single research-dedicated 1.5T Signa system (General Electric Medical Systems, Waukesha, WI). The image protocol used for the analysis of brain infarcts and described in detail elsewhere[13] included a proton density (PD)/T2-w fast spin-echo (FSE) sequence, a fluid attenuated inversion recovery (FLAIR) sequence and a T2*-w gradient echo-planar-imaging (GRE-EPI) sequence. Imaging at both time-points used identical acquisition parameters.

MRI semi-quantitative rating

Brain infarcts from both time-points were rated semi-quantitatively by two trained radiographers who recorded the presence, number, and location of the lesions. An infarct was defined as a defect of the brain parenchyma with a signal intensity isointense to that of cerebrospinal fluid on all sequences used for the rating (FLAIR, PD/T2/T2*-w).[14] All infarcts were included regardless of whether they were clinically apparent or not. Cortical infarcts were defined as defects involving or limited to the cortical ribbon and surrounded by an area of high signal intensity on FLAIR images (Figure 1A). Subcortical infarcts were defined as parenchymal defects not extending into the cortex, surrounded by an area of high signal intensity on FLAIR with a minimal size diameter of 4-mm (Figure 1B). This minimal size was used, because for smaller parenchymal defects it is harder to assess reliably whether they are based on perivascular spaces or lacunar infarcts. Defects surrounded by a rim of hemosiderin were excluded since it is not possible to distinguish parenchymal hematomas from hemorrhagic infarcts. The presence of hemosiderin was defined as an area of signal loss on T2*-w scans that was invisible or smaller on T2- and PD-w images. Cerebellar infarcts were defined as parenchymal defects in the cerebellum. They were not required to have a surrounding rim of high signal intensity on FLAIR or T2-w images since cerebellar infarcts often lack such rims (Figures 1C&D). There were no size criteria for cortical- nor cerebellar infarcts. Infarcts that spanned two different anatomical areas were assigned to the location with the largest diameter of the defect. Defects in the subcortical area without a rim or area of high signal intensity on

FLAIR, with a minimal size diameter of 4-mm and without evidence of hemosiderin were regarded as enlarged perivascular-spaces and excluded.

Intra- and inter-observer reliability was assessed for the two observers every 6 months and shown to be good. The intra-observer reliability (Kappa statistics) was 0.90 and 0.85 for cortical-; 0.85 and 0.87 for cerebellar- and 0.89 and 0.93 for subcortical infarcts. The inter-observer reliability for cortical-, cerebellar- and subcortical infarcts was 0.82, 0.70 and 0.76 respectively.

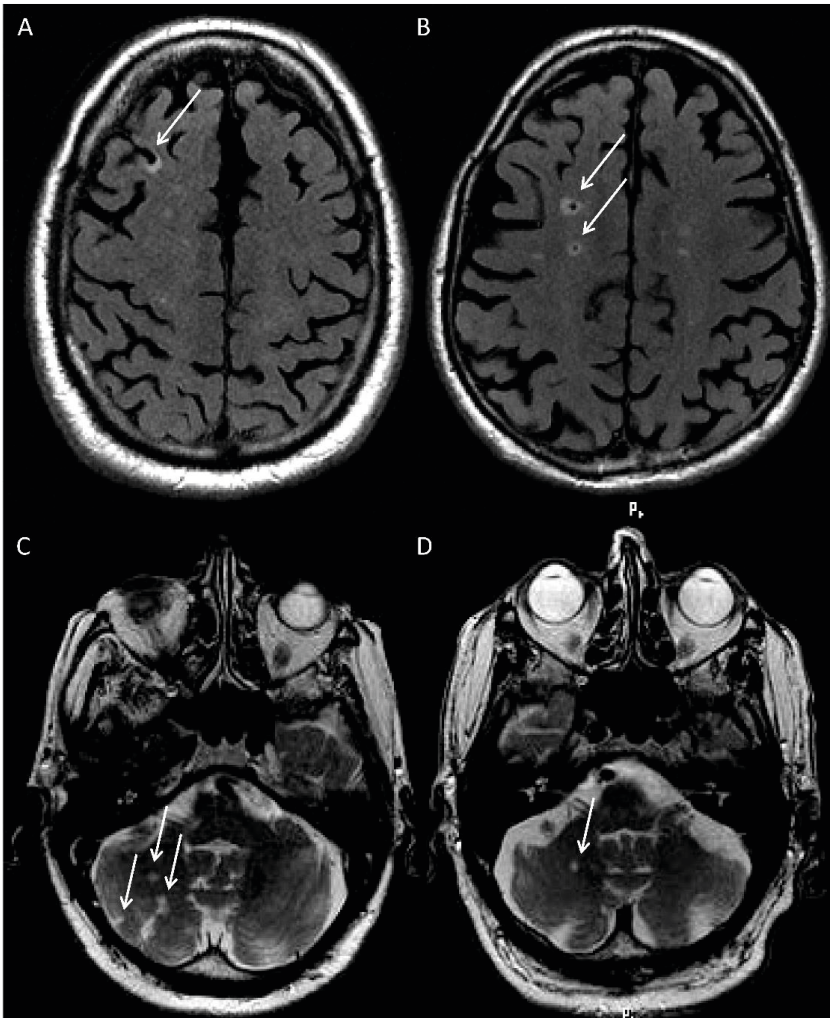

Figure 1. Example images of infarcts in subregions. A, Cortical infarct in the right frontal lobe on a fluid-attenuated inversion recovery (FLAIR) image. B, Subcortical infarcts on a FLAIR image in the right frontal lobe. C and D, Cerebellar infarcts on a T2-weighted image.

Cognition and dementia

The assessments of cognition and dementia have been described in detail elsewhere.[15] In brief, a battery of cognitive tests was administered to all participants and 3 cognitive domain scores calculated: Memory, processing speed and executive function. We computed sex specific composite measures by averaging the standardized Z-scores across the tests in each domain. A change in cognition was calculated separately by domain by subtracting the follow-up from baseline scores.

Participants with dementia were identified in a 3-step procedure described previously.[14] Briefly the Mini-Mental-State-Examination and the Digit-Symbol-Substitution-Test were administered to all participants. Screen-positives were administered a diagnostic battery of neuropsychological tests, and among them, screen positives were examined by a neurologist and a proxy interview was administered. A consensus diagnosis, according to international guidelines, was made by a panel of experts. In addition to case identification at the baseline and follow-up exams, all participants that attended the baseline exam were tracked for dementia diagnosis through vital statistics and hospital records, and the nursing and home based Resident Assessment Instrument (RAI)[16], allowing for a more complete follow-up and less misclassification of cases as controls.

Analytic sample

Of the 3,316 participants who attended the follow-up study, 2,612 participants (1,070 men and 1,542 women) were included in the final sample. Compared to these participants, the 704 excluded persons were more often men, more likely to be older, to have hypertension, diabetes and atrial fibrillation. The reasons for exclusions were: MRI contraindications and claustrophobia (n=595), disability or refusals preventing a visit to the MRI facility (n=59). Additional 50 persons were excluded due to the diagnosis of dementia at baseline (n=31) or missing dementia assessment (n=19). Of the 5,764 participants in the baseline study, 4,766 had baseline MRI. Participants with MRI at baseline and not included in the final sample with follow-up MRI had higher prevalence of brain infarcts, more WMH volume and lower relative brain volume relative to intracranial volume.

Symptomatic infarcts

Prevalent strokes were obtained from medical records (69 of 2612 participants (3%)), 14% (11 of 69 participants) of which were adjudicated by a dementia neurologist, a stroke neurologist and a neuroradialogist. This same adjudication process was used to diagnose all incident strokes, which included strokes that occurred between the 1st and 2nd MRI (average 5.2 years between).

Statistical analysis

All analyses were performed with SAS/STAT®9.2 (SAS Institute Inc). For each infarct region (cortical-, cerebellar-, subcortical- and infarcts overall), subjects in the study sample were divided into four groups based on the absence/presence of infarcts: 1] No prevalent and no incident; 2] One or more prevalent and no incident; 3] No prevalent and one or more incident and 4] One or more prevalent and one or more incident. Baseline characteristics of the study sample between infarct groups were compared using a general linear model after adjusting for age.

Modelling the association between infarct groups with longitudinal change in the different cognitive domains was performed using a random effects model (PROC-MIXED) for men and women separately. The longitudinal change in cognition was presented in Z-scores with 95% confidence interval (95%CI) using time between MR scans as the time variable and adjusting for age at baseline. Multiplicative terms between time and infarct group, and time and baseline age was tested, to allow for the different estimates of change over time among the four brain infarct groups and to test if change between brain infarct groups was statistically significant or not.

The relative risks (risk-ratios, RRs) were estimated using a Poisson regression model with a robust variance estimator within PROC-GENMOD. The risk-ratios of incident infarcts in relation to sex were estimated after adjusting for age and the time interval between MR scans. The analysis of the effect of sex was repeated after additionally adjusting for brain volume and vascular risk-factors including smoking (current and former), total serum cholesterol, high-density lipoprotein cholesterol, use of cholesterol-lowering medication, hypertension (use of anti-hypertensive medication, systolic blood-pressure>140 mmHg and/or diastolic blood pressure>90 mmHg), C-reactive protein and coronary artery calcium-score.

Finally, the risk-ratios of incident dementia were estimated in relation to the four groups of infarcts after adjusting for age, sex and time interval between MR scans where the reference group was the group of persons without infarcts (model 1). These analyses were repeated after additionally adjusting for potential confounders: First by adding baseline vascular risk-factors and level of education (model 2), second, by additionally adding history of symptomatic brain infarcts (model 3) and third by additionally adding baseline presence of brain microbleeds and baseline white matter hyperintensity volume (model 4), both MRI markers of manifest cerebral small vessel disease.[17] Definitions of microbleeds and WMH are provided in supplementary material.

Results

Overall, 803 of the 2612 participants (31%) had prevalent infarcts on MRI of whom 43 (5.4%) had clinical stroke events. Both men and women with one or more prevalent or incident infarct compared to men and women without infarcts were more likely to be older and to have higher coronary calcium (Table 1). For the same groups, men but not women were significantly more likely to have diabetes, atrial fibrillation, lower relative brain volumes and cognitive scores for all domains (age adjusted p-value for all <0.05). The average time between baseline and follow-up assessments was 5.2±0.2 (mean±SD) years.

Incidence and risk estimates of brain infarcts

Overall, 545 of 2612 individuals had1240 new brain infarcts in total with an average size of 8.5±6.0 mm and n=87 (7%) being larger than 15 mm. The cumulative incidence of new MRI detected infarcts over a mean period of 5.2 years was 20.9% (26.4% in men vs. 17.0% in women). Of those with a new infarct on MRI, 37 (6.8%) had clinically recorded events. For cortical-, cerebellar- and subcortical infarcts detected with MRI, the incidence was 7.8%, 13.0% and 4.4% respectively. The incidence in all regions was higher in men compared to women and the age adjusted risk was significantly higher in men compared to women in all regions ($p<0.05$) with cortical infarcts having the strongest sex difference. After adjusting additionally for vascular risk-factors and brain volume, the increased risk in men compared to women remained significant for all infarct regions except cerebellar (Table 2).

Prevalence and incidence of brain infarcts and cognitive change

Individuals, especially men, with both prevalent and incident infarcts overall showed steeper cognitive decline in all domains compared to persons without infarcts (Figure 2). In men, this association was significant for all infarct regions and domains except overall- and cerebellar infarcts which were not significantly associated with performance in executive function (Tables 1-4 and Figures 1-3 in the supplementary material). In women this association was significant for infarcts overall and performance in memory and executive function but not speed (Figure 1 and Table 1 in the supplementary material). Further, in women this association was only significant for cortical infarcts and performance in executive function (Tables 2-4 and Figures 1-3 in the supplementary material).

The risk of incident dementia

Dementia was diagnosed in 120 (4.6%) at the study consensus meeting (including 86 with AD, 21 with VaD, 9 with other subtype and 4 with mixed dementia) and 238 were identified later through vital statistics, hospital records and the RAI. Therefore, a total of 358 (13.7%) became demented during 9-year average follow-up. Persons with new brain

Table 1. Baseline characteristics of participants by infarcts overall and sex

Characteristics	No prevalent & no incident		One or more prevalent & no incident		No prevalent & one or more incident		One or more prevalent & one or more incident	
	Men n=567	Women n=990	Men n=220	Women n=290	Men n=113	Women n=139	Men n=170	Women n=123
Age,mean±SD	74.1±4.4	74.0±4.7	74.8±4.6	75.3±5.0	75.0±4.4	75.5±5.4	76.4±4.9	76.1±4.7
BMI,mean±SD	26.8±3.6	27.6±4.6	27.2±3.5	27.3±4.2	26.6±3.3	27.5±4.3	26.8±3.5	27.7±4.3
Hypertension %	74.4	75.6	80.5	83.5	75.2	80.6	81.8	82.9
Diabetes %	9.7	6.7	16.9	8.3	9.7	8.6	15.9	8.9
Smoking status %								
Never	28.9	52.6	25.5	51.7	32.7	53.6	32.4	57.7
Former	60.9	32.5	61.8	38.3	59.3	32.6	58.2	32.5
Current	10.2	15.0	12.7	10.0	8.0	13.8	9.4	9.8
Total cholesterol (mmol/L), mean±SD	5.3±1.1	6.0±1.1	5.0±1.0	5.9±1.1	5.4±1.1	5.9±1.2	5.1±1.0	6.0±1.0
Atrial Fibrillation %	6.6	2.4	12.3	4.2	7.2	2.9	13.6	1.6
Coronary calcium, mean±SD	735±919	294±568	1061±1291	442±758	877±1112	416±607	1057±1168	521±743
Education level %								
Primary	14.1	25.0	12.8	23.8	10.8	23.2	11.2	29.5
Secondary	51.1	51.6	58.0	51.0	67.6	50.0	51.2	43.4
College	14.3	17.3	12.3	19.7	10.8	15.2	12.9	21.3
University	20.4	6.2	16.9	5.5	10.8	11.6	24.7	5.7
Cognition Z-score, mean±SD								
Memory	-0.12±0.82	0.28±0.89	-0.21±0.86	0.26±0.84	-0.29±0.77	0.18±1.0	-0.44±0.76	0.03±0.82
Executive function	0.08±0.80	0.09±0.75	0.01±0.75	0.05±0.78	0.06±0.75	0.03±0.70	-0.25±0.78	-0.04±0.79
Processing Speed	0.03±0.70	0.16±0.77	-0.02±0.74	0.16±0.73	-0.09±0.73	0.08±0.70	-0.20±0.79	-0.07±0.75
Relative Brain Volume %	72.2±3.4	74.3±3.6	71.1±3.2	73.3±3.4	71.7±3.3	73.8±3.5	70.9±3.6	73.1±3.2
Relative WMH Volume %	0.94±0.84	0.97±1.04	1.34±1.26	1.27±1.17	1.11±1.10	1.43±1.51	1.65±1.33	1.70±1.65
Cerebral microbleeds %	25.2	13.1	44.7	23.4	22.8	14.9	31.8	19.4

Abbreviations: SD=Standard deviation, ml=milliliters, BMI=Body Mass Index, BP=Blood pressure, mmHg=millimeter of Mercury, WMH=White Matter Hyperintensity.

Table 2. Incidence and risk of brain infarcts by sex

	Overall (n=2612)	Men (n=1070)	Women (n=1542)	Men vs. Women	
Infarct region	Incidence, n (%)	Incidence, n (%)	Incidence, n (%)	Model 1 Risk-ratio (95%CI)	Model 2 Risk-ratio (95%CI)
Overall	545 (20.9)	283 (26.4)	262 (17.0)	1.8 (1.5-2.3)	1.5 (1.1-1.9)
Cortical	203 (7.8)	126 (11.8)	77 (5.0)	2.9 (2.1-4.0)	2.4 (1.6-3.7)
Cerebellar	340 (13.0)	162 (15.1)	178 (11.5)	1.3 (1.0-1.7)	1.0 (0.7-1.5)
Subcortical	116 (4.4)	68 (6.4)	48 (3.1)	2.3 (1.6-3.4)	1.9 (1.0-3.4)

Values in first three columns are number and percent of incident brain infarcts, overall and by sex. Values in last two columns
are risk-ratios with 95% confidence intervals (95%CI). Model 1: Adjusted for age and time interval between MR scans. Model 2: Additionally adjusted for brain volume and vascular risk-factors.

Table 3. Relationship between the presence of infarcts overall and incident dementia

	Infarcts vs. no infarcts (n)		Model 1	Model 2	Model 3	Model 4
Overall infarcts	Incident dementia (n=358)	Without dementia (n=2254)	Risk-ratio (95%CI)	Risk-ratio (95%CI)	Risk-ratio (95%CI)	Risk-ratio (95%CI)
No prevalent & no incident	169	1388	Reference	Reference	Reference	Reference
One or more prevalent & no incident	65	445	1.0 (0.8-1.3)	1.1 (0.8-1.4)	1.0 (0.8-1.4)	1.0 (0.7-1.3)
One or more incident & no prevalent	52	200	1.5 (1.2-2.00)	1.6 (1.2-2.1)	1.6 (1.2-2.1)	1.6 (1.2-2.1)
One or more prevalent & one or more incident	72	221	1.7 (1.3-2.2)	1.7 (1.3-2.2)	1.6 (1.2-2.1)	1.4 (1.1-1.9)

Values show number of persons with infarcts overall versus those without infarcts in groups of persons with and without incident dementia together with the risk-ratios of incident dementia by infarct group. Risk-ratios are with 95% confidence intervals (95%CI). Model1: Adjusted for baseline age, sex, time interval between MRI scans. Model 2: Additionally adjusted for vascular risk-factors and education. Model 3: Additionally adjusted for symptomatic infarcts. Model 4: Additionally adjusted for brain microbleeds and white matter hyperintensity volume.

infarcts showed an increased risk of incident dementia compared to persons without infarcts or persons with prevalent infarcts. The risk of incident dementia after adjusting for age, sex and time interval between MRI scans, was almost double for persons with both prevalent and incident infarcts (Table 3, model 1). This relationship was independent of vascular risk-factors and level of education (model 2). This estimate remained statistically strong (p=0.009) after additionally adjusting for history of symptomatic infarcts (model 3), which attenuated risk estimate by 6% and by 18% after additionally adjusting for brain microbleeds and white matter hyperintensity volume (model 4). There was no significant interaction with sex in the relationship between overall infarcts and incident dementia (p=0.42). Compared to those without infarcts or with prevalent infarcts only, the risk of dementia was higher in persons with incident infarcts only or both prevalent and incident infarcts in all sub-regions (Table 4). Of the three sub-regions, the risk for persons with

new cortical infarcts was similar to the risk of having new infarcts in any brain region; 1.7 (95%CI, 1.3 to 2.2). The risk of developing a new infarct was lowest for persons with cerebellar infarcts; 1.5 (95%CI, 1.1 to 2.1) and highest for persons with subcortical infarcts; 2.6 (95%CI, 1.9 to 3.4) (Table 4). The relationship of dementia with infarcts by sub-region was independent of vascular risk-factors and level of education, but similar to the results on all infarcts, estimates were attenuated by 5-15% after additionally adjusting for symptomatic infarcts, brain microbleeds and WMH volume. There were no significant interactions with sex in the relationship between infarcts in the sub-regions and dementia (data not shown).

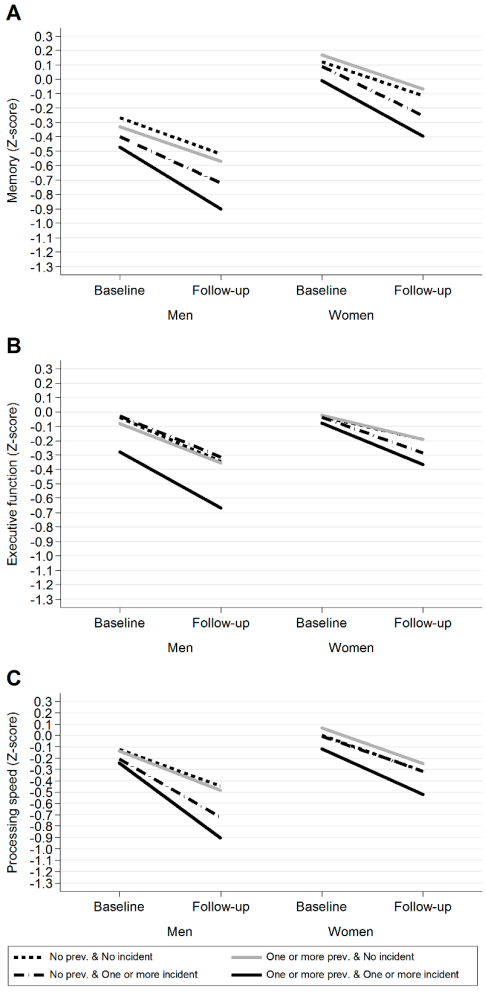

Figure 2. Infarcts overall: Mean change in cognition by prevalence and incidence of infarcts and sex. The graphs show mean change in A) memory, B) executive function and C) speed respectively for men and women by groups of prevalent- and incident infarcts overall after adjusting for age and time interval between MRI scans.

Table 4. Relationship between the presence of cortical, cerebellar, and subcortical infarcts and incident dementia

	Infarcts vs. no infarcts		
Infarct region/infarct groups:	Incident dementia (n=358)	Without dementia (n=2254)	Risk-ratio (95%CI)
Cortical			
No prevalent & no incident	267	1928	Reference
One or more prevalent & no incident	39	175	1.3 (1.0-1.7)
No prevalent & one or more incident	32	97	1.7 (1.3-2.2)
One or more prevalent & one or more incident	20	54	1.5 (1.00-2.2)
Cerebellar			
No prevalent & no incident	234	1643	Reference
One or more prevalent & no incident	50	345	0.9 (0.7-1.2)
No prevalent & one or more incident	39	155	1.2 (0.9-1.6)
One or more prevalent & one or more incident	35	111	1.5 (1.1-2.1)
Subcortical			
No prevalent & no incident	290	2050	Reference
One or more prevalent & no incident	27	129	1.2 (0.8-1.6)
No prevalent & one or more incident	32	48	2.6 (1.9-3.4)
One or more prevalent & one or more incident	9	27	1.9 (1.1-3.3)

Values show number of subjects with infarcts in the various regions versus those with no infarcts in corresponding regions in the groups of subjects with and without incident dementia together with the risk-ratios of incident dementia by infarct group. Risk-ratios are with 95% confidence intervals (95%CI) adjusted for baseline age, sex, time interval between MRI scans.

DISCUSSION

We found the incidence of brain infarcts to be almost double in men compared to women. Persons, especially men with both incident and prevalent infarcts showed steeper cognitive decline than people without infarcts. The risk of incident dementia was 1.7-fold in those with both prevalent and incident infarcts compared to those without infarcts and was not significantly different in men compared to women. Of the brain sub-regions, incident subcortical infarcts contributed most to the development of dementia with 2.6-fold risk of incident dementia compared to persons without infarcts.

Three population based imaging studies determined brain infarct incidence.[18-20] The overall incidence in these studies ranged from 9.5% to 18.5% in a 5-year follow-up period, which is consistent with the incidence in this study (20.9%) when considering age differences between these studies and an estimated 40% increase in relative-risk of new infarcts for every 5-years of increasing age.[20]

The age adjusted risk of incident infarcts overall in men compared to women was 1.8-fold higher and 2.9-fold higher in the cortical region. Conversely, two other studies of the older general population found no significant difference in brain infarct incidence between men and women[19, 20] and most studies examining brain infarct prevalence do not support a sex disparity in infarct risk.[5] In our study, men were at greater risk than women of developing new brain infarcts in all sub-regions. However, after adjusting additionally for vascular risk-factors and brain volume, the risk remained significant for cortical- and subcortical infarcts only, suggesting that the sex difference is driven by disease in both large and small vessels.

We found a trend of greater decline in cognitive function with increased overall infarct load. Persons with both prevalent and incident infarcts showed a steeper decline in cognition compared to persons without infarcts or persons with only prevalent- or only incident infarcts. This relationship was stronger and more often significant in men than in women for all infarct regions and cognitive domains. Men with prevalent and incident cortical- and subcortical infarcts showed significantly more cognitive decline than men without infarcts in all cognitive domains.

This study showed a significant increase in the risk of dementia in persons with new brain infarcts. Several clinical MRI studies have revealed increased odds of dementia in subjects with brain infarcts[21-23] but others not.[24] Four population based studies assessed this relationship, one using a cross-sectional design[25] and three using a longitudinal design.[10-12] Results from the Chicago Health and Aging Project [25] showed no significant relationship between overall infarcts and dementia but did find that persons with cortical infarcts were fourfold more likely to have dementia. Our results are similar to the three longitudinal cohort studies where the presence of overall brain infarcts was shown to increase the risk of dementia. However, two of these studies did not have information on incident infarcts from a follow-up MRI[10, 12] so there was no information on how those new infarcts may contribute to developing dementia. As we have shown, additional new infarcts are associated with more cognitive decline and an even higher risk for dementia than just having prevalent infarcts. Together our findings may well indicate a pattern of stepwise decline after first infarct and that new infarcts trigger steeper cognitive decline and increase the risk of dementia. There was also no assessment of the specific sub-regions we investigated [10-12] which provides information about the location of the vascular damage, which has clinical implications.

Although evidence has accumulated that vascular abnormalities and brain infarcts contribute to the development of dementia, limited information exists on whether this contribution differs by brain regions. Alzheimer's disease and small vessel disease share

risk factors that lead to cognitive decline and dementia.[26] In clinical pathological studies it has been demonstrated that individuals with subcortical infarcts are more likely to have dementia or require fewer plaques and tangles for a clinical diagnosis of AD.[27, 28] Subcortical infarcts found by MRI are a measure of small vessel disease.[17] Our results showed that persons with new subcortical infarcts on MRI were more than two-fold more likely to have incident dementia, even after adjusting for microbleeds and WMH volume that are other MRI markers of manifest small vessel disease. The association of cortical- and cerebellar infarcts with incident dementia was not as strong as for subcortical infarcts. This may indicate that infarcts of small vessel disease origin contribute more to the development of dementia than infarcts of embolic origin in larger vessels.

Strengths of this study include the very large well-characterized longitudinal cohort of older persons from the general population with a high number of incident dementia events. To the best of our knowledge this is the first imaging study of a population based cohort to report the incidence of infarcts and their associations with dementia in the subregions included in this study. However, persons with higher prevalence and incidence of brain infarcts may have been underrepresented as those not included in the sample were more often men, more likely to be older, to have hypertension, to have diabetes and to have atrial fibrillation.

CONCLUSIONS

The cumulated 5.2-year incidence of brain infarcts in the elderly general population is over 20%. Men are at greater risk of developing incident brain infarcts than women, particularly in the cortical region. Persons with incident brain infarcts decline faster in cognition and have an increased risk of dementia compared to those free of such lesions. The risk is higher in those with both prevalent and incident infarcts compared to those with either alone, suggesting a cascade where additional infarcts dispose people towards clinical dementia. Incident subcortical infarcts contribute more than cortical and cerebellar infarcts to incident dementia which may indicate that infarcts of small vessel disease origin contribute more to the development of dementia than infarcts of embolic origin in larger vessels.

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SUPPLEMENTARY MATERIAL

Supplementary 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.

SUPPLEMENTARY TABLES

Supplementary table 1. Infarcts overall: Mean change in cognitive function from baseline to follow-up by prevalence and incidence of infarcts and sex

	Men Mean change in cognitive function					Women 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. 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).

Supplementary table 2. Cortical infarcts: Mean change in cognitive function by prevalence and incidence of infarcts and sex

	Men Mean change in cognitive function					Women 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).

Supplementary table 3. Cerebellar infarcts: Mean change in cognitive function by prevalence and incidence of infarcts and sex

	Men Mean change in cognitive function					Women 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

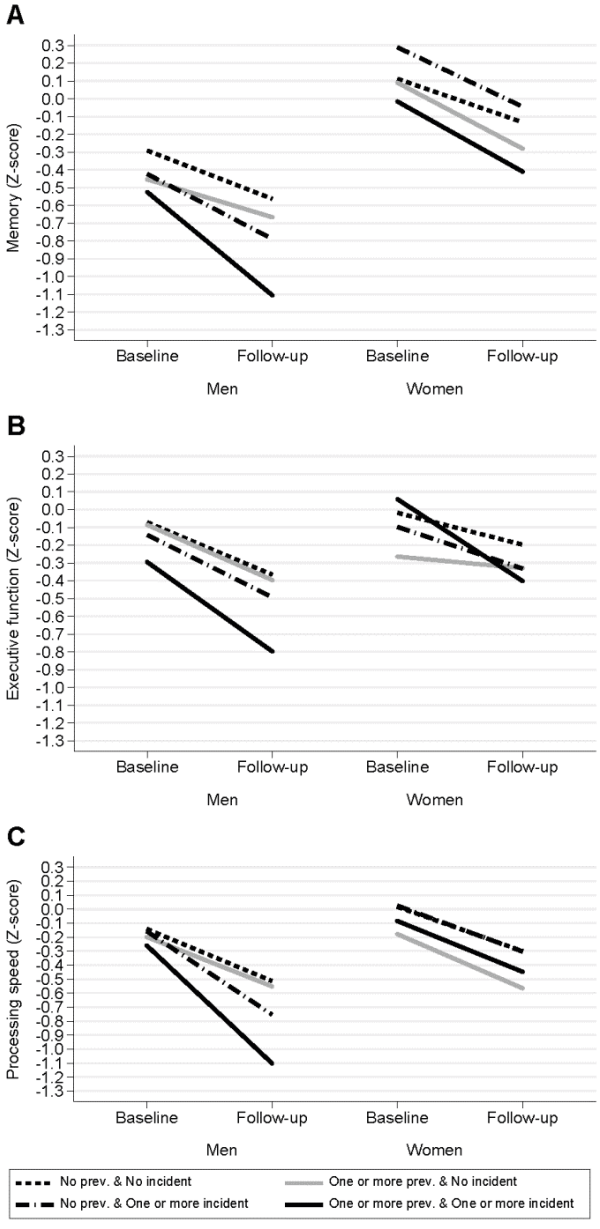
Values are mean longitudinal change in the various cognitive domains with 95% confidence interval (CI) by groups of cerebellar infarcts and sex after adjusting for age and time interval between MRI scans. P-values indicate if change in cognition in persons with prevalent and/or incident cerebellar infarcts 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).

Supplementary table 4. Subcortical infarcts: Mean change in cognitive function by prevalence and incidence of infarcts and sex

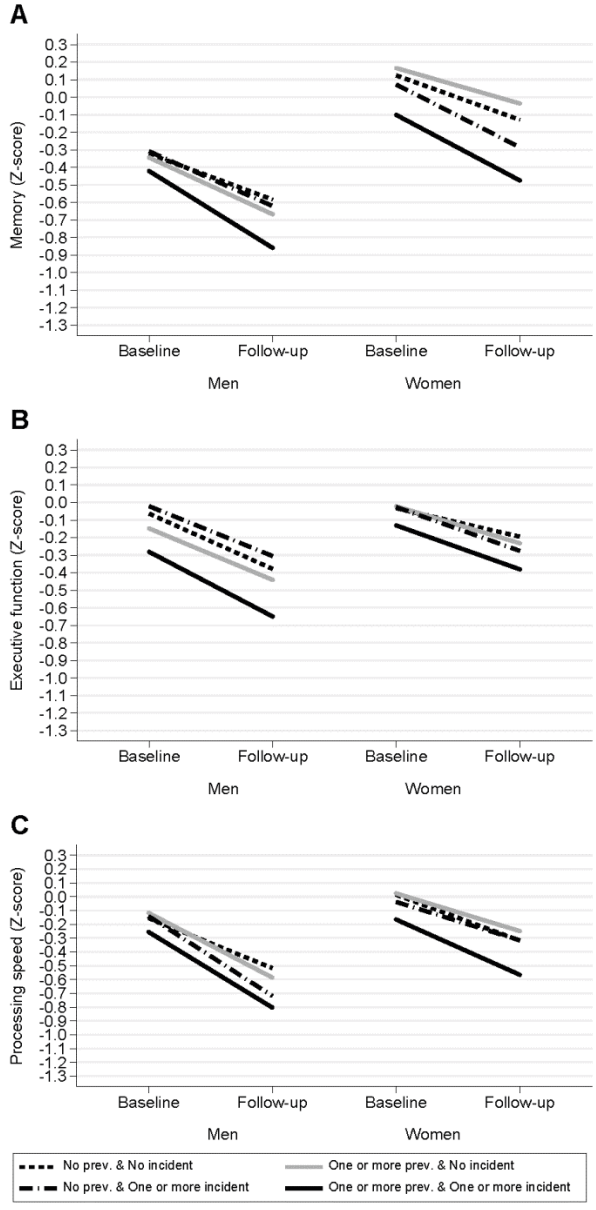
	Men Mean change in cognitive function					Women Mean change in cognitive function				
Cognitive domains and groups of subcortical infarcts	n	Mean	95%CI Lower	95%CI Upper	p-value	n	Mean	95%CI Lower	95%CI Upper	p-value
Memory										
No prevalent & no incident	912	-0.27	-0.32	-0.23	Reference	1375	-0.20	-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).

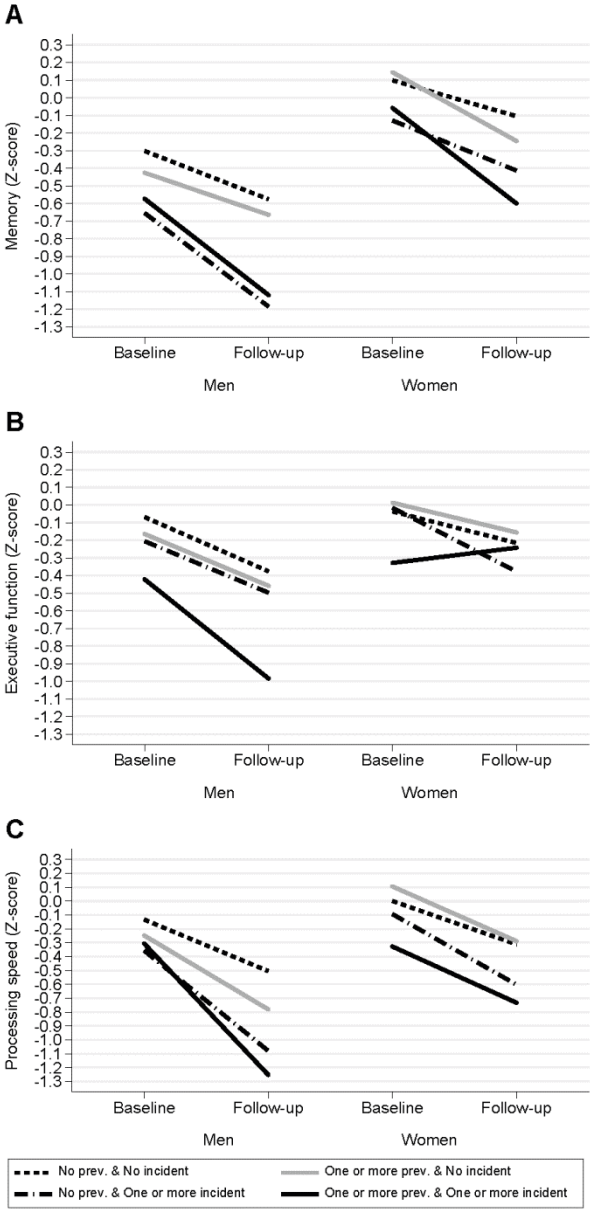
SUPPLEMENTARY FIGURES



Supplementary figure 1. 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.



Supplementary figure 2. 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.



Supplementary figure 3. 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.

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