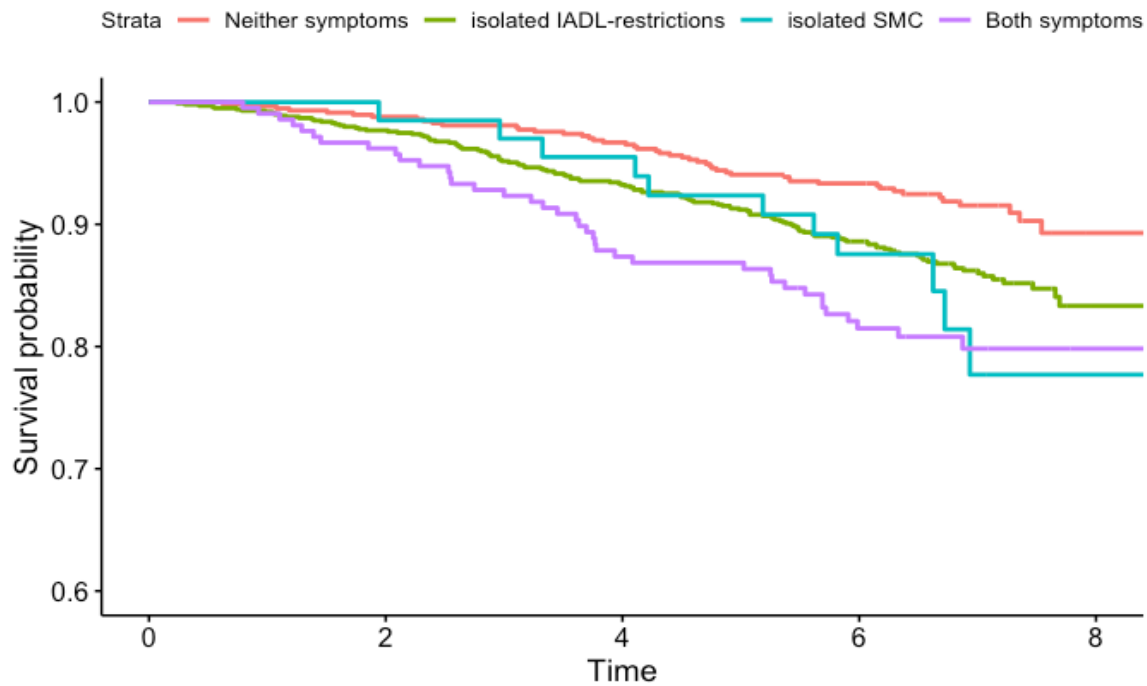


Supplementary Material

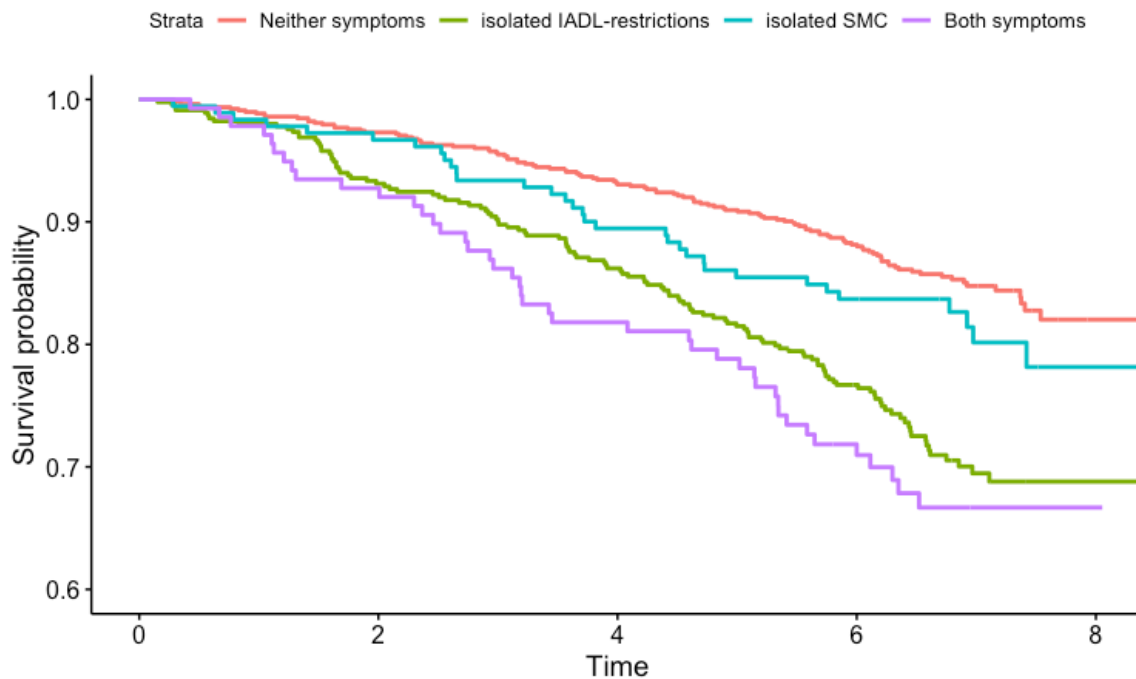
Sex Differences in the Relation Between Subjective Memory Complaints, Impairments in Instrumental Activities of Daily Living, and Risk of Dementia

Supplementary Figure 1. Kaplan-Meier curves for probability of mortality in men and women over 8 years of study follow-up with baseline measurements of SMC/IADL-I

Probability of mortality in women

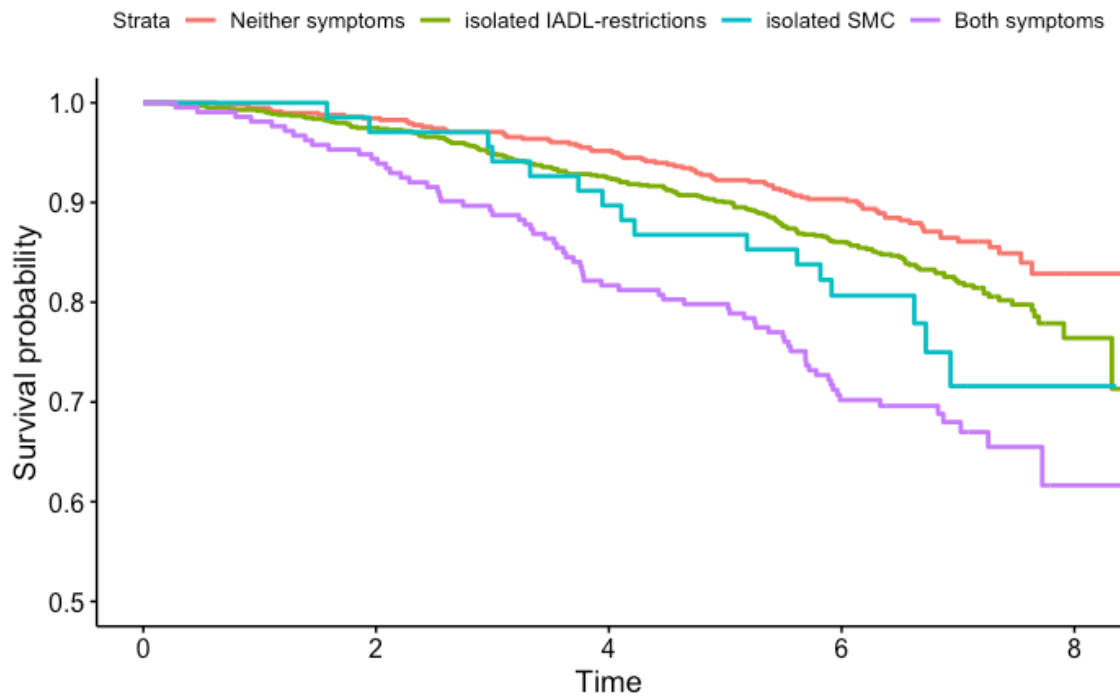


Probability of mortality in men

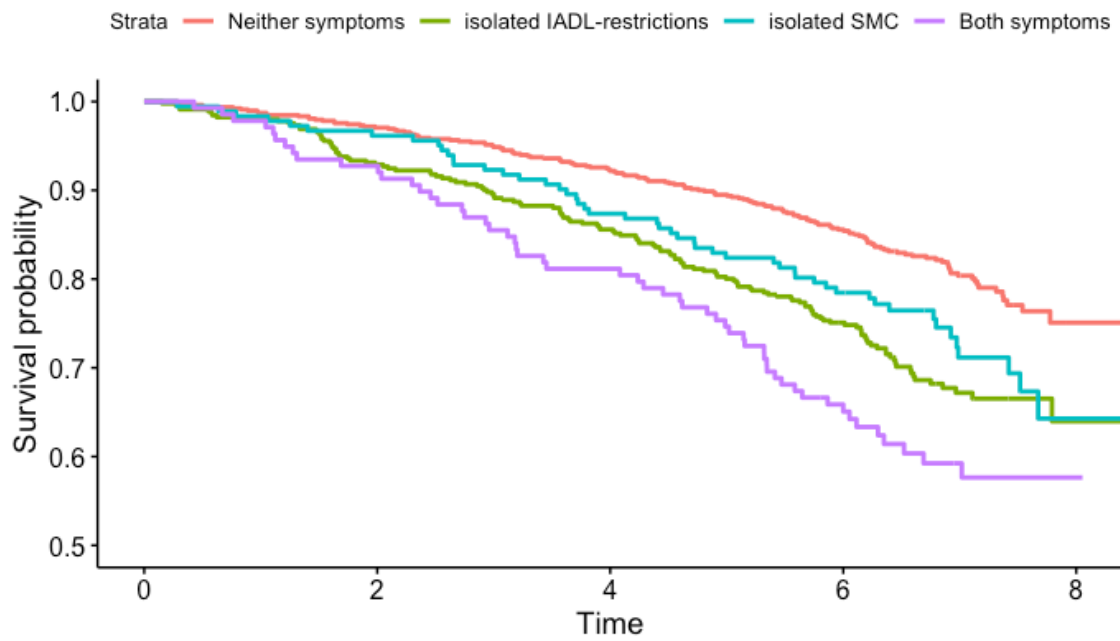


Supplementary Figure 2. Survival analyses of men and women separately with dementia/mortality as outcome.

Probability of dementia/mortality in women



Probability of dementia/mortality in men



Supplementary Table 1. Main analysis with dementia and mortality as outcome

	Model 1			Model 2		
	n events=732, n total=3,407			n events=694, n total=3,261		
Total:	HR	95% CI	p	HR	95% CI	p
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.53	1.17 – 2.02	<0.01	1.35	1.02 – 1.79	0.03
Isolated IADL-I	1.43	1.20 – 1.71	<0.001	1.15	0.95 – 1.39	0.16
SMC + IADL-I	2.43	1.95 – 3.04	<0.001	1.57	1.22 – 2.03	<0.01
Men: *						
	n events=392, n total=1,552			n events=367, n total=1,478		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.46	1.06 – 2.01	0.02	1.35	0.97 – 1.89	0.08
Isolated IADL-I	1.63	1.29 – 2.06	<0.001	1.34	1.04 – 1.72	0.02
SMC + IADL-I	2.25	1.65 – 3.07	<0.001	1.44	1.01 – 2.08	0.05
Women: *						
	n events=340, n total=1,855			n events=327, n total=1,783		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.88	1.11 – 3.18	0.02	1.58	0.92 – 2.69	0.10
Isolated IADL-I	1.26	0.96 – 1.65	0.09	1.02	0.74 – 1.36	0.89
SMC + IADL-I	2.53	1.83 – 3.51	<0.001	1.70	1.17 – 2.46	0.005

Risk of dementia and mortality combined in individuals with isolated SMC (SMC), isolated impairments in IADL (IADL-I), or both (SCM + IADL-I), compared to individuals with neither (No SMC/IADL-I), in the total population and stratified according to sex. Hazard ratio's (HR) and 95% confidence intervals (95%CI) from Cox regression analyses accounting for age and sex (model 1), additionally adjusted for education, living-status, history of stroke, heart disease, diabetes, antihypertensive use, and Mini-Mental Examination, Geriatric Depression Scale, and Visual Association Test scores (model 2).

* p-interactions, compared to reference categories (no SMC/no IADL-Impairments):

Model 1: Isolated SMC*sex, p=0.43; Isolated IADL-I*sex, p=0.16; SMC+IADL-I*sex, p=0.63

Model 2: Isolated SMC*sex, p=0.59; Isolated IADL-I*sex, p=0.13; SMC+IADL-I*sex, p=0.43

* p-values for the overall interaction (models including versus not including sex interaction terms):

Model 1: p<0.01, Model 2: p=0.11.

Supplementary Table 2A. Sensitivity analyses defining IADL-Impairment using separate cut-off scores for men and women based on the sex specific median ALDS score, IADL-I, with dementia as outcome

	Model 1 n events=231, n total=3,409			Model 2 n events=214, n total=3,263		
Total:	HR	95% CI	p	HR	95% CI	p
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	2.12	1.37 – 3.30	<0.001	1.85	1.16 – 2.95	0.009
Isolated IADL-I	0.84	0.60 – 1.17	0.29	0.77	0.54 – 1.11	0.16
SMC + IADL-I	3.16	2.25 – 4.44	<0.001	2.21	1.48 – 3.30	<0.001
Men: *	n events=100, n total=1,553			n events=90, n total=1,479		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	2.13	1.20 – 3.79	<0.01	1.54	0.83 – 2.88	0.17
Isolated IADL-I	0.86	0.51 – 1.46	0.59	0.83	0.48 – 1.45	0.51
SMC + IADL-I	2.96	1.75 – 4.99	<0.001	1.48	0.77 – 2.83	0.24
Women: *	n events=131, n total=1,856			n events=124, n total=1,784		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	2.15	1.08 – 4.28	0.03	1.95	0.93 – 4.09	0.08
Isolated IADL-I	0.84	0.55 – 1.29	0.42	0.77	0.48 – 1.23	0.28
SMC + IADL-I	3.39	2.16 – 5.32	<0.001	3.03	1.78 – 5.13	<0.001

Risk of dementia in individuals with isolated SMC (SMC), isolated impairments in IADL (IADL-I), or both (SCM + IADL-I), compared to individuals with neither (No SMC/IADL-I), in the total population and stratified according to sex. Hazard ratio's (HR) and 95% confidence intervals (95%CI) from Cox regression analyses accounting for age and sex (model 1), additionally adjusted for education, living-status, history of stroke, heart disease, diabetes, antihypertensive use, and Mini-Mental Examination, Geriatric Depression Scale, and Visual Association Test scores (model 2).

* p-interactions, compared to reference categories (no SMC/no IADL-Impairments):

Model 1: Isolated SMC*sex, p=0.99; Isolated IADL-I*sex, p=0.87; SMC+IADL-I*sex=0.76

Model 2: Isolated SMC*sex, p=0.78; Isolated IADL-I*sex, p=0.71; SMC+IADL-I*sex=0.15

* p-values for the overall interaction (models including versus not including sex interaction terms):

Model 1: p=0.97, Model 2: p=0.35

Supplementary Table 2B. Sensitivity analyses defining IADL-Impairment using separate cut-off scores for men and women based on the sex specific median ALDS score, with mortality as outcome

	Model 1 n events=549, n total=3,405			Model 2 n events=526, n total=3,259		
Total:	HR	95% CI	p	HR	95% CI	p
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.47	1.05 – 2.07	0.03	1.32	0.93 – 1.87	0.12
Isolated IADL-I	1.87	1.53 – 2.28	<0.001	1.52	1.23 – 1.88	<0.001
SMC + IADL-I	2.17	1.66 – 2.83	<0.001	1.52	1.13 – 2.05	0.01
Men: *						
	n events=316, n total=1,551			n events=300, n total=1,477		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.33	0.88 – 2.02	0.17	1.30	0.85 – 2.00	0.22
Isolated IADL-I	1.96	1.51 – 2.54	<0.001	1.71	1.30 – 2.25	<0.001
SMC + IADL-I	2.12	1.49 – 3.00	<0.001	1.67	1.13 – 2.46	0.01
Women: *						
	n events=233, n total=1,854			n events=226, n total=1,782		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.93	1.06 – 3.52	0.03	1.48	0.80 – 2.73	0.21
Isolated IADL-I	1.77	1.29 – 2.42	<0.001	1.34	0.95 - 1.87	0.09
SMC + IADL-I	2.25	1.49 – 3.41	<0.001	1.37	0.86- 2.20	0.19

Risk of mortality in individuals with isolated SMC (SMC), isolated impairments in IADL (IADL-I), or both (SCM + IADL-I), compared to individuals with neither (No SMC/IADL-I), in the total population and stratified according to sex. Hazard ratio's (HR) and 95% confidence intervals (95%CI) from Cox regression analyses accounting for age and sex (model 1), additionally adjusted for education, living-status, history of stroke, heart disease, diabetes, antihypertensive use, and Mini-Mental Examination, Geriatric Depression Scale, and Visual Association Test scores (model 2).

* p-interactions, compared to reference categories (no SMC/no IADL-Impairments):

Model 1: Isolated SMC*sex, p=0.32; Isolated IADL-I*sex, p=0.62; SMC+IADL-I*sex=0.83

Model 2: Isolated SMC*sex, p=0.59; Isolated IADL-I*sex, p=0.37; SMC+IADL-I*sex=0.81

* p-values for the overall interaction (models including versus not including sex interaction terms):

Model 1: p=0.60, Model 2: p=0.65

Supplementary Table 3A. Sensitivity analyses with IADL-Impairment based on cognitive IADL items only, with dementia as outcome

	Model 1 n events=204, n total=3,083			Model 2 n events=189, n total=2,958		
Total:	HR	95% CI	p	HR	95% CI	p
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	2.51	1.81 – 3.48	<0.001	2.08	1.45 – 2.97	<0.001
Isolated IADL-I	1.05	0.62 – 1.78	0.84	0.79	0.45 – 1.39	0.41
SMC + IADL-I	4.93	3.06-7.95	<0.001	3.30	1.92 – 5.66	<0.001
Men: *						
	n events=84, n total=1,389			n events=76, n total=1,329		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	2.37	1.49 – 3.80	<0.001	1.39	0.81 – 2.38	0.24
Isolated IADL-I	0.68	0.24 – 1.89	0.46	0.40	0.13 – 1.22	0.11
SMC + IADL-I	3.62	1.44 – 9.14	<0.01	1.57	0.52 – 4.74	0.43
Women: *						
	n events=120, n total=1,694			n events=113, n total=1,629		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	2.62	1.66 – 4.12	<0.001	2.75	1.69 – 4.47	<0.001
Isolated IADL-I	1.30	0.70 – 2.42	0.40	1.09	0.56 – 2.14	0.80
SMC + IADL-I	5.80	3.31 – 10.20	<0.001	4.65	2.45 – 8.80	<0.001

Risk of dementia in individuals with isolated SMC (SMC), isolated impairments in IADL (IADL-I), or both (SCM + IADL-I), compared to individuals with neither (No SMC/IADL-I), in the total population and stratified according to sex. Hazard ratio's (HR) and 95% confidence intervals (95%CI) from Cox regression analyses accounting for age and sex (model 1), additionally adjusted for education, living-status, history of stroke, heart disease, diabetes, antihypertensive use, and Mini-Mental Examination, Geriatric Depression Scale, and Visual Association Test scores (model 2).

The cognitive items were: shopping groceries for at least 3 days, travel by public transport, make arrangements at the bank or post office, prepare an egg or beans on toast, read and understand the newspaper, make coffee or tea. Interviewers were instructed to take cognitive performance into account in this assessment. People who were not able to perform at least one of these tasks, were considered to have IADL-I.

* p-interactions, compared to reference categories (no SMC/no IADL-Impairments):

Model 1: Isolated SMC*sex, p=0.76; Isolated IADL-I*sex, p=0.27; SMC+IADL-I*sex=0.39

Model 2: Isolated SMC*sex, p=0.06; Isolated IADL-I*sex, p=0.13; SMC+IADL-I*sex=0.10

* p-values for the overall interaction (models including versus not including sex interaction terms):

Model 1: p=0.66, Model 2: p=0.35.

Supplementary Table 3B. Sensitivity analyses with IADL-Impairment based on cognitive IADL items only, IADL-I with mortality as outcome

	Model 1 n events=496, n total=3,079			Model 2 n events=476, n total=2,954		
Total:	HR	95% CI	p	HR	95% CI	p
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.34	1.06 – 1.70	0.02	1.13	0.87 – 1.45	0.36
Isolated IADL-I	1.82	1.41 – 2.35	<0.001	1.43	1.09 – 1.88	0.01
SMC + IADL-I	2.11	1.41 – 3.18	<0.001	1.29	0.84 – 1.99	0.25
Men: *						
	n events=280, n total=1,387			n events=266, n total=1,327		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.22	0.90 – 1.64	0.20	1.08	0.79 – 1.50	0.62
Isolated IADL-I	1.32	0.90 – 1.94	0.15	1.11	0.73 – 1.70	0.62
SMC + IADL-I	1.47	0.75 – 2.87	0.26	0.88	0.44 – 1.77	0.72
Women: *						
	n events=216, n total=1,692			n events=210, n total=1,627		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.56	1.05 – 2.32	0.03	1.20	0.80 – 1.82	0.38
Isolated IADL-I	2.50	1.77 – 3.53	<0.001	1.89	1.30 – 2.75	<0.001
SMC + IADL-I	2.88	1.71 – 4.86	<0.001	1.89	1.07 – 3.35	0.03

Risk of mortality in individuals with isolated SMC (SMC), isolated impairments in IADL (IADL-I), or both (SCM + IADL-I), compared to individuals with neither (No SMC/IADL-I), in the total population and stratified according to sex. Hazard ratio's (HR) and 95% confidence intervals (95%CI) from Cox regression analyses accounting for age and sex (model 1), additionally adjusted for education, living-status, history of stroke, heart disease, diabetes, antihypertensive use, and Mini-Mental Examination, Geriatric Depression Scale, and Visual Association Test scores (model 2).

* p-interactions, compared to reference categories (no SMC/no IADL-Impairments):

Model 1: Isolated SMC*sex, p=0.02; Isolated IADL-I*sex, p=0.32; SMC+IADL-I*sex=0.13

Model 2: Isolated SMC*sex, p=0.70; Isolated IADL-I*sex, p=0.07; SMC+IADL-I*sex=0.10

* p-values for the overall interaction (models including versus not including sex interaction terms):

Model 1: p=0.06 Model 2: p=0.15

Supplementary Table 4A. Sensitivity analysis of participants with an MMSE-score ≥ 28 with dementia as outcome.

	Model 1 n events=117, n total=2,450			Model 2 n events=106, n total=2,342		
Total:	HR	95% CI	p	HR	95% CI	p
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.62	0.84-3.15	0.15	1.46	0.72-2.96	0.30
Isolated IADL-I	0.93	0.60-1.45	0.75	0.82	0.51-1.31	0.40
SMC + IADL-I	2.48	1.45-4.21	<0.001	1.92	1.03-3.59	0.04
Men: *						
	n events=49, n total=1,073			n events=43, n total=1,021		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.48	0.64-3.41	0.36	1.27	0.50-3.23	0.62
Isolated IADL-I	0.82	0.40-1.67	0.58	0.86	0.40-1.83	0.70
SMC + IADL-I	2.18	0.89-5.33	0.09	1.37	0.43-4.37	0.59
Women: *						
	n events=68, n total=1,377			n events=63, n total=1,321		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.87	0.63-5.52	0.26	1.60	0.52-4.96	0.41
Isolated IADL-I	1.03	0.57-1.85	0.92	0.86	0.46-1.61	0.63
SMC + IADL-I	2.74	1.37-5.46	0.004	2.39	1.09-5.27	0.03

Risk of dementia in individuals with isolated SMC (SMC), isolated impairments in IADL (IADL-I), or both (SCM + IADL-I), compared to individuals with neither (No SMC/IADL-I), in the total population and stratified according to sex. Hazard ratio's (HR) and 95% confidence intervals (95%CI) from Cox regression analyses accounting for age and sex (model 1), additionally adjusted for education, living-status, history of stroke, heart disease, diabetes, antihypertensive use, and Mini-Mental Examination, Geriatric Depression Scale, and Visual Association Test scores (model 2).

*p-interactions, compared to reference categories (no SMC/no IADL-Impairments):

Model 1: Isolated SMC*sex, p=0.74; Isolated IADL-I*sex, p=0.62; SMC+IADL-I*sex=0.69.

Model 2: Isolated SMC*sex, p=0.69; Isolated IADL-I*sex, p=0.93; SMC+IADL-I*sex=0.32

p-values for the overall interaction (models including versus not including sex interaction terms): model 1: p=0.95, model 2: p=0.75.

Supplementary Table 4B. Sensitivity analysis of participants with an MMSE-score <28 with dementia as outcome.

	Model 1 n events=113, n total=953			Model 2 n events=108, n total=921		
Total:	HR	95% CI	p	HR	95% CI	p
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	2.05	1.17-3.59	0.01	2.15	1.19-3.87	0.01
Isolated IADL-I	0.50	0.29-0.87	0.01	0.69	0.39-1.22	0.20
SMC + IADL-I	2.62	1.63-4.20	<0.001	2.59	1.50-4.47	<0.001
Men: *						
	n events=50, n total=476			n events=47, n total=458		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	2.14	1.09-4.19	0.03	1.78	0.86-3.67	0.12
Isolated IADL-I	0.41	0.14-1.21	0.11	0.52	0.17-1.55	0.24
SMC + IADL-I	2.34	1.11-4.97	0.03	1.64	0.67-4.02	0.28
Women: *						
	n events=63, n total=477			n events=61, n total=463		
No SMC/IADL-I	1.00	(reference)		1.00	(reference)	
Isolated SMC	1.93	0.65-5.74	0.24	2.28	0.73-7.16	0.16
Isolated IADL-I	0.57	0.30-1.11	0.10	0.88	0.43-1.82	0.73
SMC + IADL-I	2.78	1.49-5.20	0.001	3.59	1.71-7.55	<0.001

Risk of dementia in individuals with isolated SMC (SMC), isolated impairments in IADL (IADL-I), or both (SCM + IADL-I), compared to individuals with neither (No SMC/IADL-I), in the total population and stratified according to sex. Hazard ratio's (HR) and 95% confidence intervals (95%CI) from Cox regression analyses accounting for age and sex (model 1), additionally adjusted for education, living-status, history of stroke, heart disease, diabetes, antihypertensive use, and Mini-Mental Examination, Geriatric Depression Scale, and Visual Association Test scores (model 2).

*p-interactions, compared to reference categories (no SMC/no IADL-Impairments):

Model 1: Isolated SMC*sex, p=0.80; Isolated IADL-I*sex, p=0.73; SMC+IADL-I*sex=0.87.

Model 2: Isolated SMC*sex, p=0.99; Isolated IADL-I*sex, p=0.59; SMC+IADL-I*sex=0.32.

p-values for the overall interaction (models including versus not including sex interaction terms):
model 1: p=0.96, model 2: p=0.74.