Lifetime risk of common neurological diseases in the elderly population

Silvan Licher, PhD student*, Sirwan K.L. Darweesh, PhD student*, Frank J. Wolters, PhD student*, Lana Fani, PhD student, Alis Heshmatollah, PhD student, Unal Mutlu, PhD student, Peter J. Koudstaal, professor of neurology, Jan Heeringa, general practitioner, Maarten J.G. Leening, postdoctoral research associate, M. Kamran Ikram, associate professor of neuroepidemiology**, M. Arfan Ikram, professor of neuroepidemiology**

* These authors contributed equally.

** Joint last authors.

Appendix A. Ascertainment methods of dementia, stroke, and parkinsonism.

Dementia

Participants were screened for dementia at baseline and subsequent center visits with the Mini-Mental State Examination and the Geriatric Mental Schedule organic level.[1] Those with a Mini-Mental State Examination score <26 or Geriatric Mental Schedule score >0 underwent further investigation and informant interview, including the Cambridge Examination for Mental Disorders of the Elderly. All participants also underwent routine cognitive assessment. In addition, the entire cohort was continuously under surveillance for dementia through electronic linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental health care. Available information on cognitive testing and clinical neuroimaging was used when required for diagnosis of dementia subtype. A consensus panel led by a consultant neurologist established the final diagnosis according to standard criteria for dementia (DSM-III-R), Alzheimer's disease (NINCDS–ADRDA) and vascular dementia (NINDS-AIREN).

Stroke

Stroke was defined according to the World Health Organization criteria. Information on stroke was collected continuously from general practitioners and nursing home physicians. Research physicians reviewed potential strokes using hospital discharge letters and information from general practitioners, and a consensus panel led by a consultant neurologist verified the stroke diagnoses.[2] Strokes were classified in ischaemic or haemorrhagic stroke based on neuroimaging reports. If no neuroimaging was performed, strokes were classified as unspecified.

Parkinsonism

At baseline, we used a two-phase design to identify participants with parkinsonism or Parkinson's Disease (PD). In the first phase, all subjects were asked about previous diagnosis of PD, and any drug use was coded according to the Anatomical Therapeutic Chemical (ATC) classification index.[3] In addition, every participant was neurologically examined by one of the research physicians. All subjects who either used antiparkinsonian drugs (ATC code N04), reported that they had PD, or had at least one possible cardinal sign of parkinsonism (i.e., resting tremor, cogwheel rigidity, hypo- or bradykinesia, or impaired postural reflexes) at the neurologic screening examination were invited for further evaluation in a second phase. In this phase, those who screened positive during the first phase were examined by a research physician specialized in neurological disorders. A structured clinical work-up, including the motor examination of the Unified Parkinson's Disease Rating Scale (UPDRS), a neurologic examination, and standardized history taking, was used to establish the diagnosis and classification of parkinsonism. Additional information from medical records of specialists and general practitioners of these individuals was obtained.

We used four overlapping modalities to detect potential cases of parkinsonism during follow-up: in-person screening (on average every 4 years), self-reporting of PD during in-person interviews, antiparkinsonian medication use, and alerts from continuous monitoring of clinical records. For the in-person screening the aforementioned two-phase design was used. In addition, the cohort was continuously monitored through a surveillance system for detection of new parkinsonism cases by computer linkage with the general practitioners' automated medical record systems, which encompass diagnostic codes and narrative clinical notes from general practitioners as well as documentation from neurologists, geriatricians, and other medical specialists. Nearly all participants in the study were registered at one of the community pharmacies that serve the study

area, which made it possible to identify subjects who used antiparkinsonian medication at any time during follow-up. For all persons who screened positive in any of these methods, complete medical records (including letters from medical records of specialists and general practitioners) were studied and case reports were compiled to establish the subtype of parkinsonism and the degree of certainty in the diagnosis. The final diagnoses were adjudicated in a consensus panel led by an experienced neurologist. We used diagnostic criteria agreed upon in EUROPARKINSON (European Community Concerted Action on the Epidemiology of Parkinson's Disease).[4] Parkinsonism was diagnosed as 'definite' if at least two of the cardinal signs were present in a subject not taking antiparkinsonian drugs, or if in a subject treated with antiparkinsonian medication one or more signs had improved by treatment (documented by medical history). PD was defined in a person with parkinsonism by exclusion of all other possible causes of parkinsonism.

Appendix B. Ascertainment methods of study population characteristics

Ascertainment methods of study population characteristics

During home interviews, educational levels were assessed and categorized as primary education, lower/intermediate general education or lower vocational education, intermediate vocational education or higher general education, and higher vocational education or university. Smoking habits were assessed during the same interviews and participants were subsequently categorized as current, former and never smokers. At the research center, blood pressure was measured twice in sitting position on the right arm using a random-zero sphygmomanometer, and the average of two measurements was used for analysis. Hypertension was defined as a resting blood pressure exceeding 140/90 mmHg or the use of blood pressure lowering medication. Depressive symptoms were assessed by using the Center for Epidemiology Depression Scale (CES-D), a score of 16 or higher is considered suggestive of depressive symptoms. Prevalent atrial fibrillation was diagnosed based on medical records through continuous linkage with the study database, and on available ECGs. In addition, nonfasting blood samples were collected and glucose levels were determined. In the first subcohort, diabetes mellitus wasdefined as a random or post-load serum glucose concentration≥11.1 mmol/L, or the use of drugs to lower blood glucose. In the second and third, diabetes mellitus was defined as a fasting serum glucoseconcentration ≥7.0 mmol/L, a non-fasting serum glucose concentration ≥11.1 mmol/L (only if fasting serum was unavailable), or the use of drugs to lower blood glucose. Serum total cholesterol and high-density lipoprotein cholesterol were acquired by an automated enzymatic procedure (Boehringer Mannheim System). Hypercholesterolemia was defined as a serum total cholesterol exceeding 6.2 mmol/L. *APOE* genotype was obtained using polymerase chain reaction in the original cohort and was determined with a bi-allelic TaqMan assay in the extended cohort on coded DNA samples without knowledge of the dementia diagnosis.[5,6] *APOE*-ε4 carrier status was defined as carrier of one or two ε4 alleles.**Appendix C.** Supplementary tables and figure

Table 1. Overview of clinical diagnoses during follow-up

Diagnosis	Men (N=5120) No. of individuals with diagnosis	Women (N=6982) No. of individuals with diagnosis
Alzheimer's disease	339	847
Parkinson's disease	74	65
Parkinson's disease dementia	16	16
Vascular dementia	48	64
Ischemic stroke	373	459
Hemorrhagic stroke	58	68
Unspecified stroke	106	221
Frontotemporal lobar degeneration	3	3
Herpes encephalitis	0	2
Semantic dementia	0	1
Spinocerebellar ataxia	0	1
Creutzfeldt Jacob disease	0	1
Post anoxic encephalopathy	1	2
Huntington dementia	1	1
Korsakov dementia	2	1
Progressive Supranuclear Palsy (PSP)	0	4
Drug-induced parkinsonism	10	16
Vascular parkinsonism	4	7
Lewy Body Disease (LBD)	3	5
Parkinsonism caused by dementia syndrome other than LBD	6	3
Corticobasal degeneration	0	2
Multiple System Atrophy	3	5
Parkinsonism caused by tumor	0	2
Unspecified dementia	46	72
Unspecified parkinsonism	23	42

Table 2. Baseline differences in risk factors of individuals who were not and who were diagnosed with stroke, dementia, or parkinsonism during follow-up

	No event during follow-up (N=9531)	Event during follow-up (N=2571)	P-value for difference
Age in years, mean (SD)	62.8 (9.0)	70.6 (8.3)	<0.001
Women, n (%)	5360 (56.2)	1622 (63.1)	<0.001
Educational level, n (%)			<0.001
Primary	1314 (13.8)	629 (24.5)	
Lower	3778 (39.6)	1042 (40.5)	
Further	2668 (28.0)	638 (24.8)	
Higher	1644 (17.2)	204 (7.9)	
Smoking, n (%)			<0.001
Never	2949 (30.9)	945 (36.8)	
Past	4178 (43.8)	1078 (41.9)	
Current	2348 (24.6)	523 (20.3)	
Systolic blood pressure in mmHg, mean (SD)	137 (21)	143 (23)	<0.001
Diastolic blood pressure in mmHg, mean (SD)	78 (12)	75 (12)	<0.001
Hypertension, n (%)	4899 (51.4)	1582 (61.5)	<0.001
Depression, n (%)	626 (6.6)	175 (6.8)	<0.001
Atrial fibrillation, n (%)	402 (4.2)	197 (7.7)	<0.001
Type 2 Diabetes, n (%)	836 (8.8)	288 (11.2)	<0.001
Total cholesterol, mmol/L	6.10 (1.23)	6.49 (1.22)	<0.001
High-density lipoprotein cholesterol, mmol/L	1.38 (0.40)	1.35 (0.37)	<0.001
Hypercholesterolemia, n (%)	4049 (42.5)	1440 (56.0)	<0.001
APOE genotype, n (%)			<0.001
ε2/ε2 or ε2/ε3	1215 (12.8)	295 (11.5)	
ε3/ε3	5346 (56.1)	1329 (51.7)	
ε2/ε4, ε3/ε4, or ε4/ε4	2418 (25.4)	821 (31.9)	

Abbreviations: SD: standard deviation, *APOE* Apolipoprotein E.

Table 3. Risk of different subtypes of common neurological diseases from the age of 45, 55, 65, 75, and 85

Risk after age*	Subtype	Men (%)	Women (%)
45	Alzheimer's disease	15.2 (13.8;16.6)	27.9 (26.3;29.4)
	Vascular dementia	2.3 (1.7;2.9)	2.3 (1.8;2.8)
	Ischaemic stroke	14.4 (13.1;15.8)	13.6 (12.2;15.0)
	Haemorrhagic stroke	2.2 (1.6;2.8)	2.0 (1.5;2.5)
	Unspecified stroke	5.0 (4.2;5.9)	7.9 (7.0;8.7)
	Parkinson's disease	2.9 (2.2;3.5)	1.9 (1.5;2.4)
55	Alzheimer's disease	14.3 (13.0;15.7)	27.4 (25.9;28.9)
	Vascular dementia	2.3 (1.8;2.9)	2.3 (1.8;2.8)
	Ischaemic stroke	14.2 (12.9;15.5)	13.1 (12.1;14.2)
	Haemorrhagic stroke	2.2 (1.6;2.8)	1.9 (1.5;2.3)
	Unspecified stroke	5.1 (4.2;5.9)	8.1 (7.2;9.0)
	Parkinson's disease	3.1 (2.2;3.9)	1.9 (1.5;2.4)
65	Alzheimer's disease	12.3 (11.0;13.6)	24.4 (22.9;26.0)
	Vascular dementia	2.0 (1.4;2.5)	2.1 (1.6;2.5)
	Ischaemic stroke	11.1 (10.0;12.4)	11.0 (9.9;12.1)
	Haemorrhagic stroke	2.1 (1.5;2.7)	1.9 (1.4;2.4)
	Unspecified stroke	4.3 (3.6;5.1)	6.9 (6.1;7.8)
	Parkinson's disease	2.7 (2.0;3.5)	2.1 (1.4;2.7)
75	Alzheimer's disease	14.5 (12.9;16.1)	27.1 (25.4;28.9)
	Vascular dementia	2.5 (1.8;3.2)	2.5 (1.9;3.1)
	Ischaemic stroke	11.2 (9.8;12.6)	10.9 (9.8;12.0)
	Haemorrhagic stroke	2.1 (1.4;2.8)	1.9 (1.4;2.5)
	Unspecified stroke	5.3 (4.4;6.2)	7.8 (6.9;8.7)
	Parkinson's disease	2.4 (1.7;3.1)	1.7 (1.1;2.2)
85	Alzheimer's disease	15.1 (12.5;17.6)	26.6 (24.4;28.8)
	Vascular dementia	2.7 (1.7;3.8)	2.4 (1.7;3.1)
	Ischaemic stroke	11.1 (9.1;13.2)	10.1 (8.8;11.4)
	Haemorrhagic stroke	1.3 (0.5;2.1)	1.7 (1.1;2.3)
	Unspecified stroke	7.7 (6.0;9.4)	10.6 (9.3;11.9)
	Parkinson's disease	1.2 (0.1;2.0)	1.2 (0.1;1.7)

In these analyses, individuals remained at risk of the specific disease under study, irrespective of the occurrence of other diseases, e.g. individuals with an incident ischemic stroke or Parkinson's disease were still at risk of Alzheimer's disease.

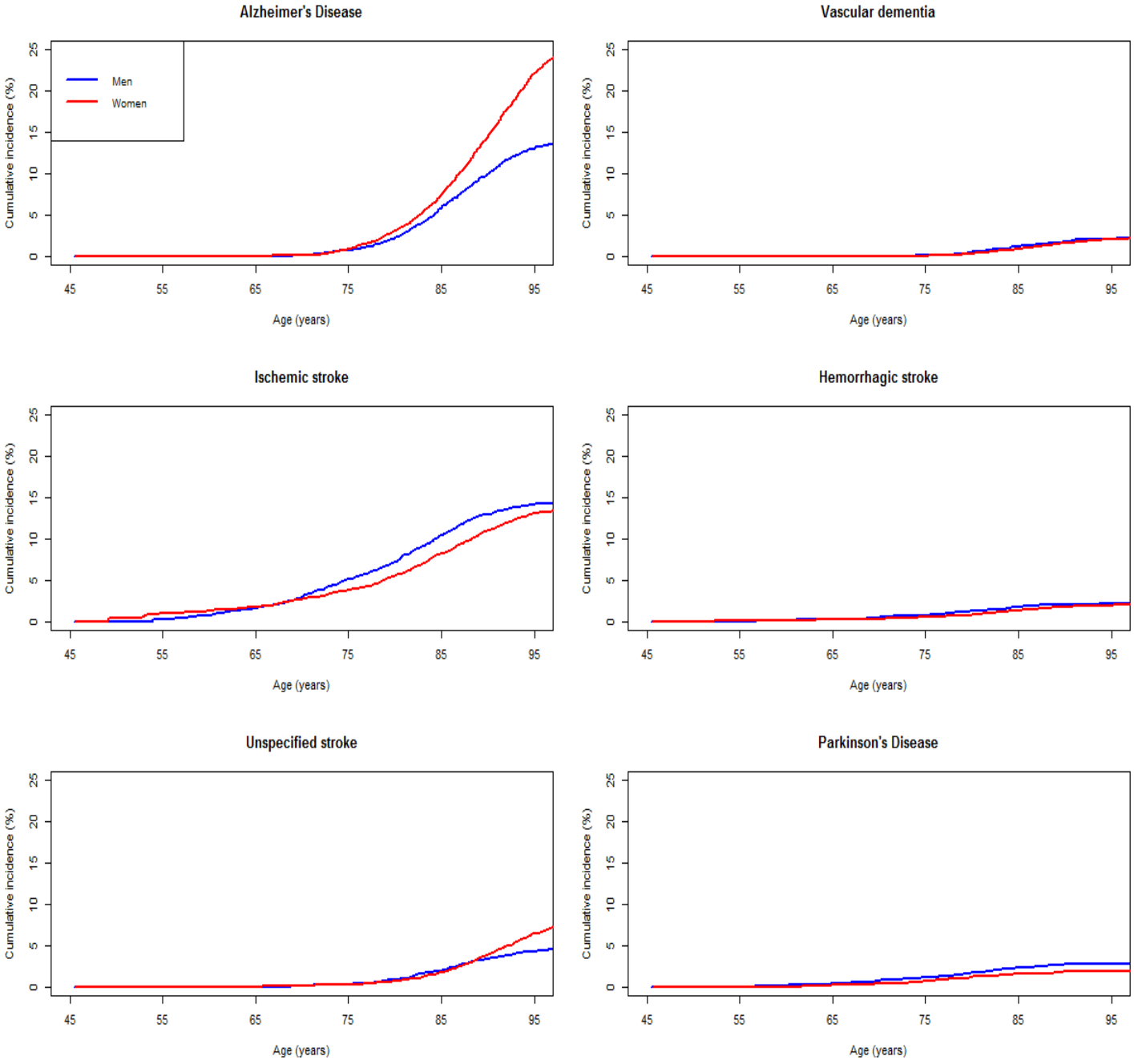

Figure 1. Risk of different subtypes of common neurological diseases for 45-years-old men and women.

References

1. de Bruijn RF, Bos MJ, Portegies ML, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. *BMC Med.* 2015;13:132.
2. Wieberdink RG, Ikram MA, Hofman A, Koudstaal PJ, Breteler MM. Trends in stroke incidence rates and stroke risk factors in Rotterdam, the Netherlands from 1990 to 2008. *Eur J Epidemiol.* 2012;27(4):287-295.
3. Anatomical Therapeutic Chemical (ATC) classification index. Oslo, Norway: WHO Collaborating Centre for Drug Statistics Methodology. 1992.
4. Breteler MMB AA, Lopez-Pousa S, et al. EUROPARKINSON: an European concerted action on incidence and risk factors for Parkinson's disease [abstract]. Neuroepidemiology 1993;12:17.
5. Wenham PR, Price WH, Blandell G. Apolipoprotein E genotyping by one-stage PCR. *Lancet.* 1991;337(8750):1158-1159.
6. Woodward J. Bi-allelic SNP genotyping using the TaqMan(R) assay. *Methods Mol Biol.* 2014;1145:67-74.