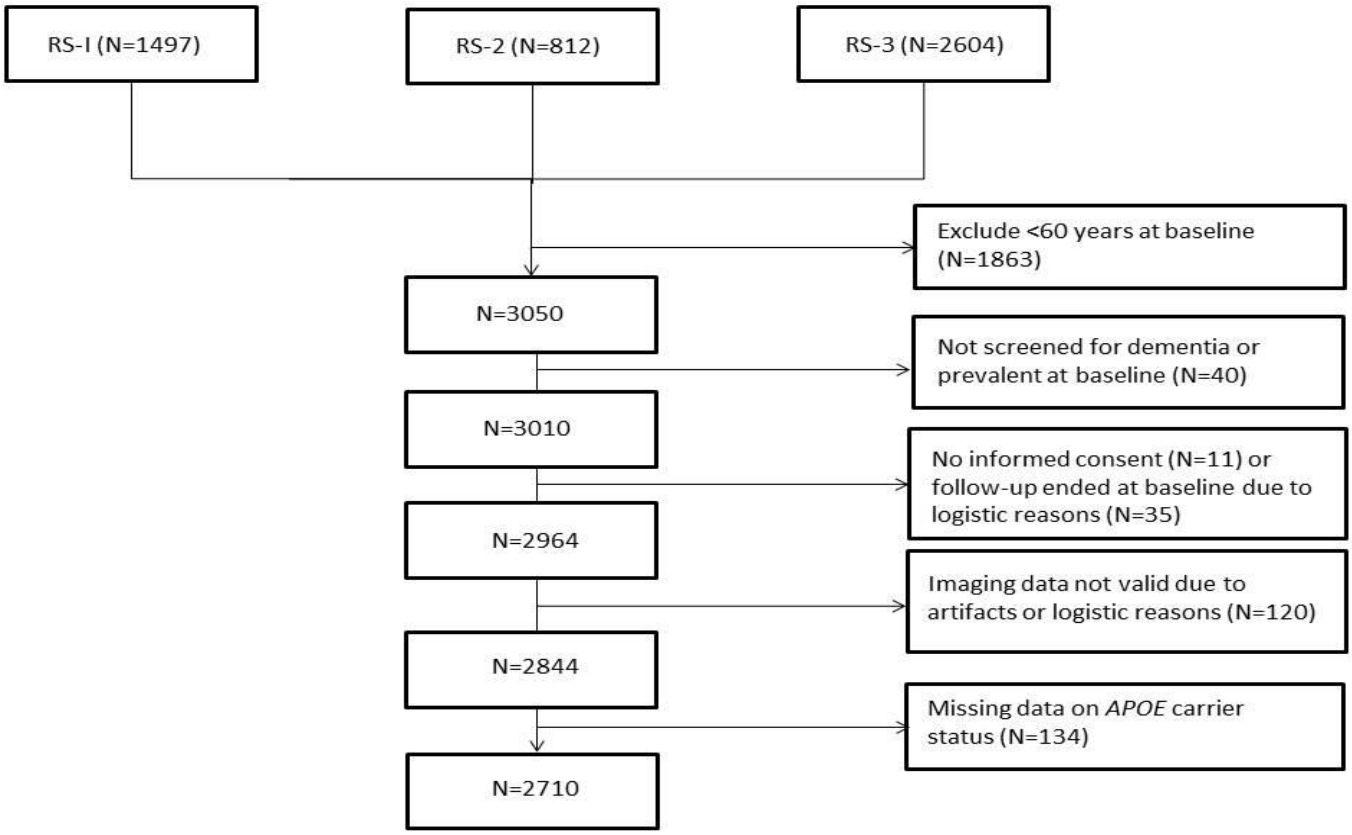
Data Supplement for Licher et al.,Development and Validation of a Dementia Risk Prediction Model in the General Population: An Analysis of Three Longitudinal Studies. Am J Psychiatry (doi: 10.1176/appi.ajp.2018.18050566)

Contents

Figure S1. Flowchart of study participants



Abbreviations: RSS= Rotterdam Scan Study (1995-1996), RS-1, RS-2, RS-3: denote the Rotterdam Study subcohorts.

Table S1. Description of predictors

Variables	Description
Age at baseline	Age range 60-105 years. Age at baseline was calculated as the age at date of MRI scan date.
Gender	Self-report.
Education	The variable education was derived from self-reported history harmonized in years of education according to the UNESCO classification.(1) Scale was created using number of years.
Body mass index	Body mass index.
Systolic blood pressure	Systolic and diastolic blood pressures were assessed at the right arm and the mean of two measurements was used in the analyses.
Smoking	During a structured interview, smoking status was obtained. Smoking was coded for the analyses as current smoking or never/past smoking.
Parental history of dementia	Participants were questioned about family history of dementia by trained interviewers using structured questionnaires.(2)
History of diabetes	Diabetes was defined as fasting serum glucose levels ≥ 7.0mmol/L or the use of anti-diabetic therapy.
History of symptomatic stroke	At baseline, history of stroke was assessed by interview and verified using medical records. Study participants were continuously followed up for occurrence of incident stroke, by digital linkage of the general practitioners' medical records with the study database.(3) Information from GPs and hospital records was collected from participants with a potential stroke. Research physicians reviewed the information and an experienced vascular neurologist verified the diagnoses according to World Health Organization criteria.(3)
Depressive symptoms	A structured interview to screen for depressive symptoms was performed by trained interviewers. Participants were screened with the Center for Epidemiologic Studies Depression (CES-D) Scale during home interviews. Depressive symptoms were defined as present with a CES-D score of (20 item) > 16.(4)
Subjective memory complaints	The presence of subjective memory complaints was assessed by question during home interviews by trained interviewers: 'Did you experience more difficulty in remembering?'
Assistance needed with money or medication	Study participants were enquired about medication use and financial management by trained interviewers with a questionnaire about instrumental activities of daily living (IADL).
APOE-ε4 carrier status	*APOE* genotype was determined with an one-stage PCR and bi-allelic TaqMan assay(5, 6)
Word Fluency Test (WFT)	Mentioning as many animals as possible within one minute. Latent cognitive skills that are tested include the efficiency of searching in long-term memory.(7)
Letter Digit Substitution Test (LDST)	Writing down numbers underneath corresponding letters (range 0–125). Latent cognitive skills that are tested include processing speed, and executive function.
Stroop interference task	Stroop color-word interference task.(8) Naming colors of color names printed in incongruous ink color(time in seconds taken). Latent cognitive skills that are tested include Interference of automated processing and attention.
Word Learning Test (WLT), delayed	15-word verbal learning test based on Rey's recall of words.(9) Delayed recall of words 10 min after visual presentation (range 0–15). latent cognitive skills that are tested include retrieval from verbal memory.
Hippocampal volume	Left and right hippocampal volumes were segmented separately using an automated segmentation method as described in detail earlier.(10) The mean volume of the left and right hippocampus was used in the analyses.

Total brain volume	Total brain volume was defined as the sum of gray matter and total white matter.(11)
White matter hyperintensity (WMH) volume	White matter hyperintensity volume was calculated by summing the volumes of all white matter lesions detected using an automated post-processing step based on the fluid-attenuated inversion recovery image and the tissue segmentation.
Infarcts	Lacunar infarcts were rated visually as focal hyperintensities on T2-images, ≥3 mm in size, and in case of involvement of cortical gray matter, infarcts were classified as cortical infarcts.

Abbreviations: NA=not applicable, PCR-RFLP=Polymerase Chain Reaction-Restriction fragment length polymorphism, GP=general practitioner, and CES-D=Center for Epidemiologic Studies Depression Scale.

Details on brain imaging

Between 1995 and 1996, brain MRI was performed in the Rotterdam Scan Study on a 1.5-Tesla MRI System (VISION MR, Siemens AG) and included T1, proton-density and T2 scans. In addition, a high-resolution T1, inversion-recovery, 3-D HASTE sequence was acquired. Slice thickness was 5mm for T1, T2 and proto-density sequences, and 1.25 mm for the HASTE sequence. Pre-processing steps, the segmentation algorithm, and validation results have been described previously.(11) Due to the availability of newer MRI techniques and a new MR scanner in 2005, the MRIs from participants included in the Rotterdam Study subcohorts RS-2-2, RS-3-1 and RS-1-5 were performed with a 3D T1-weighted sequence. There was strong correlation between volume measurements across the different MRI sequences derived in a small subsample to estimate the effect of the different MRI sequences. The measurements from both MRI sequences within a short time period were indeed approximately identical. Based on common availability and on literature showing strong associations with cognitive decline and dementia,(12-15) we selected four MRI measures for analysis including white matter hyperintensity (WMH) volume, total brain and hippocampal volume, and infarcts (lacunar/cortical). White matter lesion volume was calculated by summing the volumes of all white matter lesions detected using an automated postprocessing step based on the fluid-attenuated inversion recovery image and the tissue segmentation.(16) Left and right hippocampal volumes were segmented separately using an automated segmentation method as described in detail earlier.(17) The mean volume of the left and right hippocampus was used in the analyses.(10) All segmentations were inspected and manually corrected if required. All scans were appraised by trained research physicians blinded to clinical data for the presence of lacunar and cortical infarcts. Lacunar infarcts were rated visually as focal hyperintensities on T2-images, ≥3 mm in size, and in case of involvement of cortical gray matter, infarcts were classified as cortical infarcts. WMH, brain and hippocampal volume were all expressed as a percentage of intracranial volume (ICV) to correct for differences in head size.(18)

Table S2. Additional details on the development steps of the statistical model and testing of the assumptions

Assumptions/Modeling Steps	Test/comparison/predictor	Result	Decision
Observation of extreme data points (outliers)	Boxplots used to compare original data with truncated data at 1st and 99th percentile	Some evidence for outliers in the following variables: systolic blood pressure, Stroop interference task, LDST, Word Delayed Task, Word Fluency test, hippocampal volume and white matter lesions.	Data winsorized at 1st and 99th percentile
Linearity assumptions of continuous predictors	Restricted cubic spline transformation, 2 to 4 knots; LRT test against non-transformed (linear) term and assessed visually by plotting the Martingale residuals.(19)	Based on BIC values the most parsimonious model chosen.	Reject linearity assumption; age + age^2 appropriate
Proportional subdistribution hazard assumption	-Age -Age+ Age^2 -Remaining predictors	There was no evidence that these assumptions were evidently violated.	Valid use of Fine & Gray model
Interactions	-Age * stroke -Age * Memory complaints -Age * ADL -Age * *APOE-ε4*	BIC worsened, likelihood only modestly decreased.	No interactions included in the model
LASSO penalty	Varying LASSO penalty (lambda), while repeating this approach for 200 bootstrap samples. Subsequently, the most optimal penalty was chosen based on the BIC values of the model.	A consistent selection pattern of predictors was observed.	LASSO penalty was appropriate.

Table S3. Baseline characteristics across the development (Rotterdam Study) and validation (EPOZ, ADNI-1) studies

	Rotterdam Study N=2710	Missing data (%)	EPOZ Study, N=514	Missing data (%)	ADNI-1, N=228	Missing data (%)
Age, years	71.2 (8.2)	0	70.8 (6.5)	0	75.9 (4.9)	0
Women	1430 (52.8%)	0	274 (53.3%)	0	110 (48.0%)	0
Education, years*	10 (7-13)	1.0	10 (7-13)	0	16 (14-18)	0
Systolic blood pressure, mmHg	145 (21)	0.3	149 (23)	1.0	134.5 (17)	0
Ever smoking	1884 (69.5%)	1.4	326 (63.4%)	0	85 (37.3%)	0
Current	446 (16.5%)		86 (16.7%)		-	
History of diabetes	345 (12.7%)	1.7	38 (7.4%)	0	18 (7.9%)	0
History of symptomatic stroke	106 (3.9%)	0	18 (3.5%)	0	3 (1.3%)	0
Depressive symptoms	457 (16.9%)	4.6	39 (7.6%)	1.8	34 (14.9%)	0
Parental history of dementia	185 (6.8%)	19.2	-	-	100 (43.9%)	0
Subjective memory decline	903 (33.3%)	4.1	177 (34.4%)	1.2	17 (7.5%)	0
Assistance needed with finance or medication	262 (9.7%)	23.8	24 (4.7%)	1.4	13 (5.7%)	0
APOE-ε4 carrier	759 (28.0%)	0	143 (27.8%)	4.7	61 (26.8%)	0
Cognitive tests						
Word Fluency Test, words	21 (5)	2.7	21 (5)	0.8	20 (5)	0
Letter Digit Substitution Test, letters	28 (7)	2.8	27 (7)	3.7	46 (10)	44.6
Stroop Interference Task, seconds	57 (27)	6.6	56 (22)	2.6	-	-
Delayed Word Learning Test, words	7 (3)	7.4	6 (3)	0.4	6 (2)	0.8
Imaging markers						
Total brain volume, mL	880.1 (126.1)	1.2	839.8 (100.6)	40.1†	1008 (100.5)*	0.9
Mean hippocampal volume, mL	3.7 (0.5)	3.3	2.7 (0.4)	40.1†	3.6 (0.4)	3.1
White matter hyperintensity volume, mL**	4.7 (0-143.6)	1.2	1.5 (0-25.6)	40.1†	0.24 (0-25.5)	1.3
Presence of infarcts	410 (15.1%)	0	92 (17.9%)	2.9	18 (7.9%)	0.4

* Including cerebellar volumes. **Median (range) presented because of skewed distribution. †Due to a data storage issues, some brain volumes were not correctly archived and could therefore not be processed for analysis. These data were most likely missing completely at random, and the distribution of variables was similar across non-imputed and imputed datasets. Abbreviations: EPOZ= Epidemiologic Preventive Investigation Zoetermeer, ADNI= Alzheimer's Disease, Neuroimaging Initiative, N=number of people at risk, *APOE*=apolipoprotein E, mL=milliliters.

Table S4. Frequencies of selected predictors by lasso using 200 bootstrap samples for the basic and extended model separately, by including all candidate predictors

Predictor	**No. times selected by Lasso (%)**	
Predictor	Basic model	Extended model
Age	**200 (100)**	**196 (98)**
Age^2	9 (5)	0 (0)
Sex	16 (6)	43 (22)
Education	18 (9)	11 (6)
History of diabetes	54 (27)	39 (20)
Depressive symptoms	37 (19)	62 (31)
Subjective memory complaints	**154 (77)**	**134 (67)**
Systolic blood pressure	30 (15)	22 (11)
Smoking	23 (12)	43 (22)
Parental history of dementia	15 (8)	23 (12)
Assistance needed with finance or medication	**141 (71)**	**141 (71)**
History of symptomatic stroke	**154 (77)**	**110 (55)**
***APOE*-ε4 carrier**	**-**	**199 (99)**
Letter Digit Substitution Test	**-**	**119 (60)**
Word Fluency Test	**-**	**193 (97)**
Delayed Word Learning Test	**-**	**200 (100)**
Stroop interference task	**-**	74 (37)
Total brain volume	**-**	**199 (99)**
Mean hippocampal volume	**-**	**200 (100)**
White matter hyperintensity volume	**-**	**145 (73)**
Infarct (cortical / lacunair)	**-**	26 (31)

The selected predictors in the final model are shown in bold.

Table S5. Predictive yield of the basic model when adding each domain (cognitive, genetic, and imaging markers) separately

	C-statistic (95% CI)
Basic model + cognitive markers	0.84 (0.81;0.86)
Basic model + *APOE*	0.81 (0.77;0.84)
Basic model + imaging markers	0.83 (0.80;0.86)

Table S6. Model optimism estimated using 200 bootstrap samples

	Original (95% CI)	**Selected and shrunken by lasso (95% CI)**
Basic model		
Optimism (bootstrap estimate – test performance)	0.016 (0.015;0.016)	0.008 (0.007;0.009)
Optimism corrected estimate	0.778 (0.744;0.818)	0.779 (0.745;0.818)
Extended model		
Optimism (bootstrap estimate – test performance)	0.015 (0.013;0.017)	0.010 (0.009;0.014)
Optimism corrected estimate	0.854 (0.819;0.887)	0.859 (0.826;0.890)

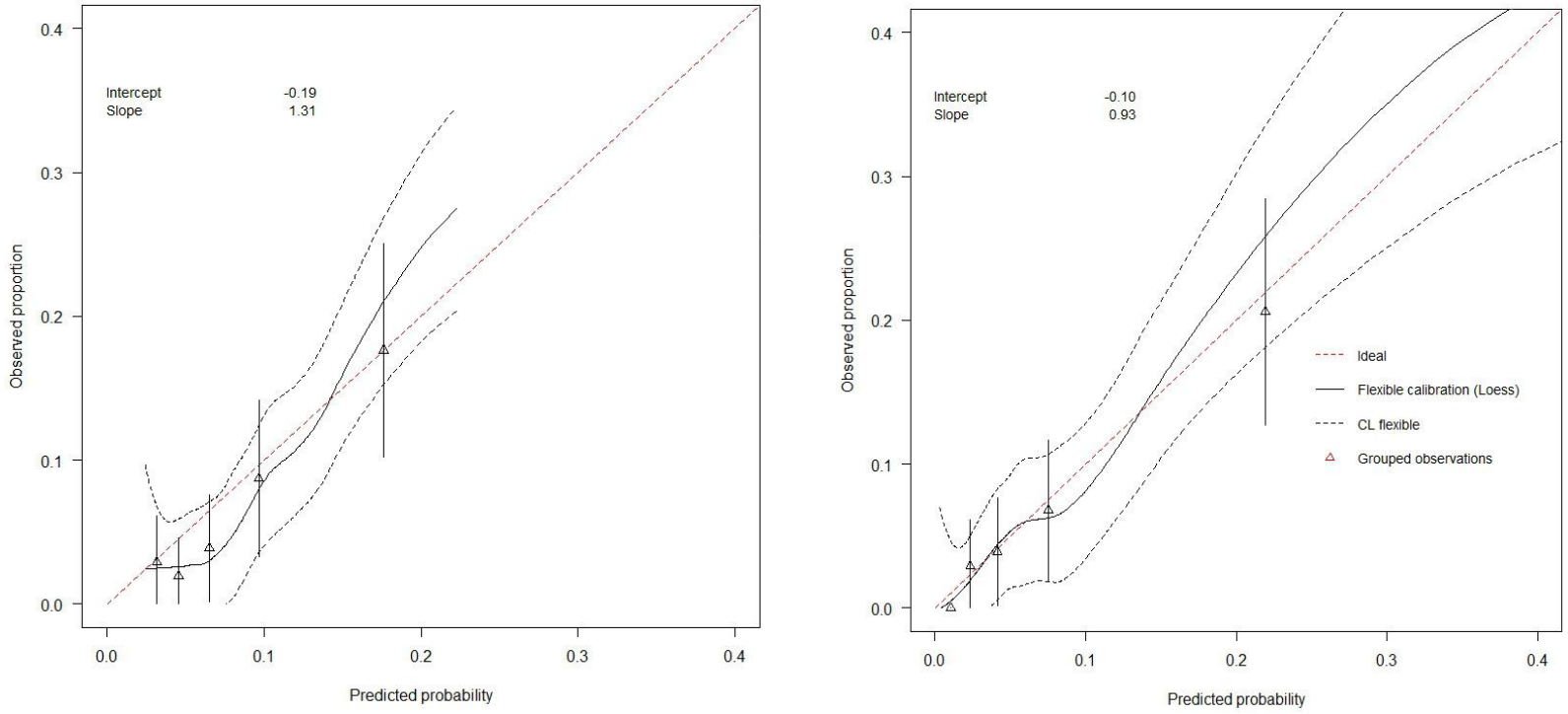
Table S7. Summary event table with 10-year cumulative incidence of dementia or competing death in the Rotterdam Study

Variable	**Rotterdam Study**	**EPOZ**	**ADNI**
Overall dementia events, n	131	36	26
Competing non-dementia death, n	444	120	69
Median follow-up, years (IQR)	6.6 (4.8-8.9)	9.5 (7.6-11.4)	6.3 (2.0-8.0)

Table S8. Cumulative baseline subdistribution hazard for different predicted time horizons

Population	**3 years**	**5 years**	**10 years**
Rotterdam Study	0.0174	0.0305	0.0614
EPOZ	0.0098	0.0355	0.0716
ADNI	0.0336	0.0401	0.1834

Figure S2. Calibration plots of the basic (left) and extended (right) models in the EPOZ validation cohort to predict 10-year risk of dementia. In case of perfect calibration all groups of predicted probabilities fit close to the red diagonal line, corresponding to an intercept of 0 and a slope of 1 for the calibration plot. Vertical bars in grouped observations represent 95% confidence intervals.



Risk score calculation

Probability of dementia within 10 years:

The baseline cumulative subdistribution hazard refers to a man or woman aged 71 years who does not have subjective memory complaints, did not have a clinical stroke, does not need assistance with money or medication and whose test results are 6.8 words on the Delayed Word Learning Test, 21.1 words on the Word Fluency Test, 28.2 letters on the Digit Letter Substitution Test, is not an *APOE*-ε4 carrier, and has a brain volume of 880.1 mL, with a mean hippocampal volume of 3.7 mL and white hypertensity volume of 4.7 mL.

A supplementary excel appendix is available to calculate risks for the extended model.

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