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Development and validation of a dementia risk prediction model in the general population: an analysis of three longitudinal studies

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Abstract

Objective: Identification of individuals at high-risk of dementia is essential for development of prevention strategies, but reliable tools for risk stratification in the population are lacking. The authors developed and validated a prediction model to calculate the 10-year absolute risk of developing dementia in an ageing population.

Method: Within a large, prospective population-based cohort, data on demographic, clinical, neuropsychological, genetic and neuroimaging parameters were collected from 2710 non-demented individuals ≧60 years, examined between 1995 and 2011. A basic and an extended model was derived to predict 10-year risk of dementia, while taking into account competing risks from death due to other causes. Model performance was assessed using optimism-corrected C-statistics and calibration plots, and the models were externally validated in the Dutch population-based EPOZ Study and in Alzheimer's Disease Neuroimaging Initiative-1 (ADNI-1).

Results: During a follow-up of 20,324 person-years, 181 participants developed dementia. A basic dementia risk model using age, history of stroke, subjective memory decline, and assistance needed with finance or medication yielded a C-statistic 0.78, 95%CI: 0.75;0.81. Subsequently, an extended model incorporating the basic model and additionally cognitive, genetic, and imaging predictors yielded a C-statistic of 0.86 (95%CI: 0.83;0.88). The models performed well in external validation cohorts from Europe and the United States.

Conclusions: In community-dwelling individuals, 10-year dementia risk can be accurately predicted by combining information on readily available predictors in a primary care setting. Dementia prediction can be further improved using data on cognitive performance, genotyping, and brain imaging. These models can be used to identify individuals at high-risk of dementia in the population and are able to inform trial design.

Keywords: dementia, Alzheimer's disease, prediction, development, validation, model, competing risks, epidemiology

Introduction

Reliable identification of individuals at increased risk of dementia is essential for individualized risk management in both primary and clinical care, but also optimal design of preventive trials (1). This necessity was aptly demonstrated by the recent findings from large randomized controlled trials that showed potential efficacy of multi-domain interventions to prevent cognitive decline in high-risk individuals (2-5). The FINGER trial (2) showed that an multi-domain lifestyle intervention resulted in a significant protective effect on cognition. The success of this trial has in part been attributed to the tailored approach of targeting these preventive interventions only to an at-risk segment of the general population (2). This strategy was further corroborated by secondary analyses from the preDIVA trial (3), demonstrating that intensive vascular risk management had the strongest effect among participants with untreated hypertension (3). It is now increasingly recognized that such preventive strategies might be most effective in an at-risk population (3, 4, 6-8).

Several models have been developed to predict dementia in the general population (9), but external validation recently showed that these have limited incremental predictive value above and beyond age (10). These models were mostly based on lifestyle factors, social factors, and comorbidities. So far, models are lacking that include information on markers that reflect the underlying disease process, especially in its early stages. Such markers include subjective memory decline, *APOE* genotype and neuroimaging (11-14). On the other hand, such markers are usually not available in a primary care setting. It is therefore conceivable that different models are required, depending on the setting: simple non-laboratory models for a primary care setting and extended biomarker-based models for a clinical setting. Note however, that for purposes of risk stratification in healthy individuals in a primary care setting, models should preferably be based on risk factors that can be obtained without invasive diagnostics such as CSF-sampling or imaging requiring substantial amounts of ionizing radiation such as PET.

Another important consideration is that dementia prediction models should take into account the competing risk of death from other causes, given the generally late-life onset of dementia among community-dwelling individuals. Failure to account for such competing risks inflates apparent dementia risk predictions, limiting the practical utility of currently available models (15).

In this study, we aimed to develop a dementia prediction model for use in a primary care setting and we examined whether an extended model including cognitive, genetic, and imaging markers could improve the performance. Both models were developed while accounting for competing risks.

Method

Study population

This study was embedded in the Rotterdam Study, a prospective population-based cohort study (16). Since 1990, inhabitants aged 55 and older residing in Ommoord, a district of Rotterdam, the Netherlands, were invited. Of the 20 744 invited inhabitants, 14 926 (72%) agreed to participate. Follow-up examinations take place every three to four years. In addition, a random sample of Rotterdam Study participants was invited for brain MRI in 1995-1996 (N=563). From 2005 onwards, brain MRI became part of the core study protocol of the Rotterdam Study (17). For the current study, we selected participants aged ≥60 years who had baseline data available on clinical, cognitive, genetic, and MRI parameters (Appendix A, Figure 1). We excluded participants who had dementia or incomplete screening for dementia at baseline (N=40), did not provide informed consent to access medical records (N=11), or were no follow-up was available due to logistic reasons (N=35). In addition, we excluded participants without valid imaging data due to artifacts or logistic reasons (e.g. contraindications, or signs of claustrophobia during acquisition) (N=124), or had missing data on *APOE* carriership (N=134). Therefore, in total 2710 participants were included in analysis for this study.

Candidate predictors

Detailed methods on predictor data collection and predictor definitions are described in Appendix B. We pre-specified candidate predictors based on previous literature, expert knowledge, and availability in clinical practice. For a primary care model, we considered the following candidate predictors: age, sex, level of education, systolic blood pressure, smoking, history of diabetes, history of stroke, presence of depressive symptoms, parental history of dementia, presence of subjective memory decline, and assistance needed with finance or medication. For the extended model, we considered the addition of cognitive tests (Word Fluency Test, Letter Digit Substitution Test, Stroop Interference, and Delayed Word Learning Test), *APOE*-ε4 genotype, and brain MRI parameters (white matter hyperintensity volume, total brain volume, hippocampal volume, and presence of infarcts [lacunar/cortical]). White matter hyperintensity, total brain and hippocampal volume were all entered into the models as a percentage of intracranial volume to correct for differences in head size.

Assessment of dementia

Participants were screened in-person for dementia at baseline and subsequent centre visits with the MMSE and the Geriatric Mental Schedule organic level (18). Those with a MMSE <26 or Geriatric Mental Schedule score >0 underwent further investigation and informant interview, including the Cambridge Examination for Mental Disorders of the Elderly. The information from in-person screening was supplemented by data from the electronic linkage of the study database with medical records from all general practitioners and the regional institute for outpatient mental health care. In the Dutch healthcare system, the entire population is entitled to primary care that is covered by their (obligatory) health insurance. The entire cohort is thus continuously monitored for detection of interval cases of dementia or cognitive disturbances between centre visits. Study physicians biannually evaluate all records, and combine information from medical records with in-person screening to draw up individual case reports. In these reports, the physicians covered all

gathered relevant information to establish the presence, probability and subtype of dementia. A consensus panel led by a consultant neurologist established the final diagnosis according to standard criteria for dementia (DSM-III-R) and Alzheimer's disease (NINCDS–ADRDA). All participants were followed for incident dementia until Jan 1, 2015. Follow-up was virtually complete (97.2% of potential person-years).

External validation

For external validation of the models, we used the EPOZ (Epidemiologic Preventive Investigation Zoetermeer) Study from the Netherlands and the Alzheimer's Disease Neuroimaging Initiative cohort-1 (ADNI-1) from the United States. The EPOZ study started in 1975 and aimed to assess the prevalence of several chronic diseases and their determinants in the city of Zoetermeer, the Netherlands (19). Response rates were similar to those of the Rotterdam Study (72%). Between 1995 and 1996, a random subsample of the participants aged 60-90 years old underwent cognitive testing and brain MRI (N=514) and is considered as baseline for the current study. Participants were screened at study entry and follow-up visits for dementia using a strict protocol (20). All participants were followed for incident dementia until the end of study, on Jan 1, 2007 (completeness of follow-up: 90.8% of potential person-years). For validation within ADNI, we selected 228 cognitively unimpaired individuals aged ≥60 years. Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer's disease. Further details on ADNI have been described elsewhere (21).

Statistical analysis

To reduce extreme effects of the predictors, we truncated the distribution of continuous variables at the 1st and 99th percentile. Distributions for white matter hyperintensity volume and Stroop Interference score were skewed. We obtained normal distributions of these parameters using a natural logarithmic transformation. We modelled potential non-linear effects of age by using restricted cubic spline transformations and by adding an age^2 term, to capture the effects of age as most important risk factor for dementia most accurately.

For the basic model, we used competing risk regression proposed by Fine & Gray with all candidate predictors included and fitted into the model to calculate 10-year risk of dementia (22). Appendix C provides further details on the development steps of the model and testing of the assumptions. We subsequently used the least absolute shrinkage and selection operator (LASSO) technique adapted to a competing risk setting to simultaneously penalize the model's regression coefficients and select important predictors for the final model (23, 24). The LASSO method is particularly useful to prevent model overfitting and model misspecification (25). An overfitted model tends to underestimate the probability of an event in low risk groups and overestimate an event in high risk groups.

For the development of the extended model, we used the predictors selected by the LASSO technique in the basic model as a starting point and extended it with addition of objective cognitive tests, *APOE*-ε4 carrier status, and brain MRI parameters. As a reference, we used a model based on age alone for all analyses. In a step-wise, exploratory analysis, we investigated the additive predictive value for each domain separately (cognition, imaging, and genetic information) of the final extended model, compared to the basic model. All presented C-statistics from the development sample represent optimism-corrected C-statistics.

Internal validation

We evaluated the robustness of the model using bootstrap samples for each model and found consistent results in selection steps and coefficient shrinkage using the LASSO technique based on 200 bootstrap samples (Appendix D) (26). We quantified the discriminative ability of these models using the C-statistic for survival data with competing outcomes (27, 28). The C-statistic is an adapted AUC-metric for use in survival analyses. It indicates the overall proportion of all pairs of participants that can be ordered such that the participant who developed dementia during follow-up, indeed had a higher predicted risk. We used the cumulative incidence function to calculate the absolute 10-year risk of dementia (29). We used the DeLong test adapted for survival analyses to infer whether C-statistics of the basic and extended models were statistically different from those of a model based on age alone.(30)

Stratified analyses

We assessed the predictive accuracy for the most common subtype Alzheimer's disease specifically and assessed model performance for men and women separately. Next, we excluded the first four years of follow-up to assess whether the predictive value extended beyond the first years of follow-up since some of the predictors may reflect prodromal or undiagnosed dementia. To further investigate model robustness across varying time horizons, we evaluated the predictive ability of the model using a 3-,5-, and 15-year time horizon. Finally, we stratified on age (80 years) at baseline, given the median age of diagnosis (31) and steep increase in incidence of dementia beyond this age in order to investigate the performance of the model at different ages. Missing data on predictors were imputed using multiple imputation, based on all predictors, outcome status, and follow-up time. All analyses were done using R, CRAN version 3.3.2 (rms, cmprsk, mycrr (27), and crrp (24)).

Results

Study population of the development cohort

Baseline characteristics of the 2,710 participants of the development cohort are shown in Table 1. The mean age was 71.2 years, 52.8% of the participants were women and 33.3% had subjective memory decline. During a median follow-up of 7.0 years for those who were censored alive (interquartile range: 5.1-9.1), with a total follow-up of 20,324 person-years, 181 participants developed dementia of whom 146 developed Alzheimer's disease and 578 participants died due to other causes. This corresponds to a crude incidence rate for dementia of 9.2 per 1,000 person-years. During the 10-year predicted time horizon, 131 participants developed dementia and 444 participants died free of dementia.

Model development and internal validation

There was evidence for a non-linear relationship between age and the risk of dementia. We therefore added age^2 into the model to capture this non-linearity. The basic model considered age, age^2, sex, educational level, systolic blood pressure, current smoking, history of diabetes, history of symptomatic stroke, depressive symptoms, parental history of dementia, presence of subjective memory decline, and assistance needed with finance or medication. In Table 2, the subdistribution hazard ratios are presented.

Discriminative accuracy measured with the C-statistic of the full basic model was 0.79 (95%CI:0.76;0.83). After shrinkage and predictor selection using the LASSO, all statistically significant predictors remained in the model: age, history of symptomatic stroke, presence of subjective memory decline, and assistance needed with finance or medication. The C-statistic remained similar 0.79 (95%CI:0.76;0.82). Based on 200 bootstrap samples, model optimism was small (that is, the predictive performance of the models was not tied to a specific sample; optimism-corrected C-statistic basic model: 0.78 (95%CI:0.75;0.81), Appendix D, Tables 2 & 4).

From here, all presented C-statistics derived from the development study are corrected for optimism to represent optimism-corrected C-statistics.

Adding cognitive, *APOE*-ε4 carrier status, and imaging information to the basic model resulted in higher discriminative ability (C-statistic 0.86, 95%CI:0.83;0.88). In appendix Table 3, C-statistics are presented when cognitive, *APOE*-ε4 carrier status, or imaging information are added to the basic model separately. After shrinkage and selection, the Letter Digit Substitution Test, the Delayed Word Learning Test, *APOE*-ε4 carrier status, and all imaging markers except for brain infarcts were selected (C-statistic 0.86, 95%CI:0.83;0.88). Ten-year risks based on the basic model are easily calculated using a simple risk chart (Figure 1). An excel appendix is available to calculate risks for the extended model (Appendix).

Stratified analyses

The basic and extended models showed roughly similar results for Alzheimer's disease, and for men and women separately (Table 3). Discriminative ability only slightly attenuated while excluding the first four years of follow-up (C-statistic 0.79, 95%CI: 0.74;0.84). Using a 3-, and 5-year predicted time horizon, the basic and extended models had higher discriminative properties (C-statistic: 0.82, 95%CI: 0.78;0.86 and 0.91, 95%CI: 0.87;0.95 for a 3-year horizon, and 0.79, 95%CI: 0.74;0.83, and 0.88, 95%CI: 0.85,0.91, for a 5-year horizon), compared to the 10-year predicted time horizon. In contrast, when using a 15-year predicted time horizon, the basic and extended models had lower discriminative properties (C-statistic 0.67, 95%CI:0.62;0.74 and 0.71, 95%CI: 0.65;0.75, respectively). In individuals older than 80 years (N=456), the basic model showed considerable lower discriminative ability (C-statistic 0.57, 95%CI: 0.49;0.63). In contrast, the extended model retained substantial discriminative ability in this stratum (C-statistic 0.71, 95%CI: 0.64;0.76) and was considerably higher compared to age alone (C-statistic 0.53, 95%CI: 0.45;0.63).

External validation

Baseline characteristics for Rotterdam Study and EPOZ study participants were largely similar, whereas ADNI-1 participants were older, attainted a higher education, reported less memory decline and more often had a history of parental dementia (Table 1). During a median of 9.5 years (interquartile range: 7.6-11.4) of follow-up in EPOZ, 36 participants developed dementia and 120 participants died free of dementia. During a median follow-up time of 6.3 years (interquartile range: 2.0-8.0) in ADNI-1, 26 participants developed dementia. Within the EPOZ study, both the basic and the extended model showed discriminative performance in line with the performance in the development cohort (C-statistic basic 0.75 [95%CI: 0.67;0.82] and extended model 0.81 [95%CI: 0.74;0.88]). The models were well calibrated (Appendix E, Figure 2). As reference, a model based on age alone yielded a C-statistic of 0.73 (95%CI: 0.65;0.82) and resulted in significantly worse performance compared to the basic and extended model (for both $p<0.001$). Given that ADNI is not a population-based study and recruits participants via clinical study sites, we only tested the performance of the full model. This yielded a lower C-statistic of 0.72 (95%CI: 0.63;0.83), reflecting a more homogenous and older population, yet also performed significantly better than a model based on age alone (0.54, 95%CI: 0.42;0.64, $p=0.01$).

Discussion

In this study, we present a simple prediction model for dementia in an ageing population in primary care. In addition, we demonstrate that this performance can be further extended into a model including cognitive testing, *APOE* genotyping and brain MRI. These models can be used to calculate the 10-year risk of dementia to inform individuals and optimize risk stratification for clinical trials.

The discriminative ability of our basic model was similar compared to previously published models incorporating data for use in the primary care settings (9). Most previous studies only reported on discriminative ability, ranging from 0.65 to 0.80 as measured with the C-statistic. For instance, the Brief Dementia Screening Indicator using data available in primary care, yielded C-statistics between 0.68 and 0.78 across four cohorts. Notably, four other prediction models included in a recent external validation study did not provide additional predictive value in dementia risk prediction compared to a model with age as the only predictor (10). In our present study, the basic model we developed did show greater discriminative ability and improved calibration above and beyond age alone. Compared to the Brief Dementia Screening Indicator model, our basic model additionally included the presence of subjective memory decline. The strength of this predictor in relation to the occurrence of dementia (adjusted hazard ratio: 1.65) and the prevalence in the general population (33%), resulted in better predictive performance.

The models in this study include a history of stroke instead of various individual cardiovascular risk factors included in several previous models (9). We did consider traditional cardiovascular risk factors, but these did not pass the mark for inclusion in the final models. Several explanations may underlie these observations. First, almost a quarter of all dementia cases can be attributed to vascular risk factors, illustrating their etiological importance in the development of dementia (18, 32, 33). However, similar to coronary heart disease prediction in the elderly (34, 35), the role of

cardiovascular risk factors in dementia prediction may strongly diminish with age. Second, cardiovascular risk factors are also strongly associated with various other diseases at old age, reducing their specific discriminative ability in predicting the occurrence of dementia. For instance, smoking could lead to potentially fatal competing events, such as cardiovascular events or cancer at younger ages and thereby preclude the occurrence of dementia. As a consequence, smoking has limited specificity to predict cardiovascular disease, cancer, or dementia at older ages. Dementia risk prediction models should take into account competing risks to avoid uninterpretable C-statistics and inflated absolute risks (15). We dealt with this issue in the current study by deriving our dementia prediction models within a competing risk framework.

In line with results from a previous model based on predictors derived in a primary care setting (36), our basic model had poor discriminative ability in participants aged 80 years or older. This finding is generally of a limited concern when using a prediction model to identify high risk individuals for clinical trials, since trials generally aim to recruit younger individuals. Yet, these findings provide insight into the complexity of dementia prediction using only clinical parameters in the oldest-old. In contrast, our extended model showed substantial higher discriminative ability for individuals aged 80 years and older, highlighting the significance of objective markers of cognition and brain structure in the oldest-old, including cognitive testing, genetics, and brain imaging.

In this study, we developed and validated two complementary risk models. One basic model that could be used by family doctors and general practitioners, and one extended model that could be used in a clinical setting and that incorporates cognitive testing, brain MRI and genetics. The strength of the extended model is that it uses information that reflects the underlying disease process. At the same time, it can be argued that presence of these markers indicates that the disease is already ongoing and whether it is thus prediction or in fact early diagnosis. Nevertheless, our sensitivity analyses excluding the first 4 years of follow up showed similar

predictive accuracies, suggesting that the effect of early diagnosis as opposed to prediction was marginal. Moreover, the ability to identify persons 10 years before clinical diagnosis can inform trials aimed at intervening in the earliest phase.

Indeed, it is now increasingly recognized that preventive or treatment strategies might be more effective when targeted to individuals at increased risk of dementia (1, 6-9, 37). In order to target such interventions at those who most likely benefit from it, a reliable way to identify individuals at high risk for dementia is needed. The prediction models presented here address this gap, and can be used to stratify individuals in future clinical trials. Absolute 10-year dementia risk thresholds for determining low- and high-risk groups need to be established and may depend on the research question at hand, as well as the availability, costs, and risks of the intervention. These models can be combined in a two-step design, providing opportunities to identify at-risk individuals from the general population with a simple yet predictive model. Subsequently, these individuals can be referred to a clinical setting where a more refined risk assessment can be done using the extended model. It would be interesting to investigate whether the performance of the basic model could be further improved with the addition of a simple blood test (38), or a brief cognitive test, such as the visual association test (39). The extended model could be further improved by adding (1) novel imaging modalities such as cerebral microbleeds or data on diffusor tensor imaging of the brain, by (2) including rare genetic variants, and functional genomics, or by (3) extending models with more in-depth neuropsychological tests (40-42). The predictive value of other predictors that were available either in the Rotterdam Study or in the validation studies could have been interesting to explore. However, in this study, we specifically aimed to develop a dementia prediction model and subsequently validate exactly that model in these validation studies. Exploring the predictive yield of additional predictors would technically lead to the development or extension of another prediction model, which subsequently would have to be externally validated again.

We should consider limitations of the present study. First, we used a regularization method (LASSO), which automatically selects and subsequently shrinks effect sizes of important predictors. This penalization strategy may have led to some underestimation of predictor effects in the development sample, yet it increases the likelihood of replication in validation studies. Second, this study focused on older adults of predominantly Caucasian descent (>97%). Therefore, these models may not generalize to younger individuals or other ethnicities and further validation work in these groups is needed. Third, we developed the models in a population-based setting, which matches the primary care setting, but this will likely affect model performance when validated or used in selected populations seen in clinical care. This was in part reflected by a slightly lower discriminative accuracy in ADNI, yet in addition to differences in case-mix including the homogenous character of this highly selected sample, and a relatively high-attrition rate, discrimination remained substantially better than a model based on age alone. Fourth, we used data on brain imaging with quantitative parameters, which might influence model performance compared with qualitative analyses, such as atrophy and white matter hyperintensity scales. Finally, dementia prediction without an effective therapy at hand raises ethical concerns. While such models are unlikely to be rolled out into clinical practice before further validation and assessment is undertaken, they have shown to be useful for selecting individuals into clinical trials (2). Strengths of this study include the large sample size and availability of detailed information on a wide selection of potential dementia predictors. Moreover, the basic model is based on questionnaire information and therefore simple to use, and requires no further testing or laboratory measurements. Finally, the models were well validated, both internally and externally.

Conclusions

In this study, we developed and validated a dementia prediction model providing accurate dementia risk stratification and estimation in a general ageing population. Addition of cognitive, imaging, and genetic features improved the predictive ability. These models can be used to identify individuals at high risk for dementia in the general population and might inform future clinical trial design.

Author contribution

All authors have made a substantial intellectual contribution to design of the study (MWV, MKI, MAI), acquisition of data (MKI, FJW, SL), analysis and interpretation of data (SL, MJGL, EWS, MKI, MAI), drafting the manuscript (SL), or revising it critically for important intellectual content (MJGL, PY, FJW, JH, PJEB, MWV, BCMS, EWS, MKI, MAI). All authors have read and approved the submitted manuscript and made substantial intellectual contributions to warrant co-authorship.

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Declaration of interests

None of the authors declare a competing interest in relation to this manuscript. The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

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http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Table 1. Baseline characteristics of the development (Rotterdam Study) and validation (EPOZ and ADNI-1) cohorts

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

Data are shown for non-imputed data. Data was virtually complete for the Rotterdam Study (<7.4% missing), except for family history of dementia (19.2%) and assistance needed with finance or medication (23.8%). Values are counts (percentages) or means (standard deviation). * Including cerebellar volumes. **Median (range) presented because of skewed distribution. Abbreviations: EPOZ= Epidemiologic Preventive Investigation Zoetermeer, ADNI= Alzheimer's Disease, Neuroimaging Initiative, N=number of people at risk, *APOE*=apolipoprotein E, mL=milliliters.

Table 2. Multivariate-adjusted risk factors for incident dementia, before and after penalized LASSO selection

Predictor	**Basic model**		**Extended model**	
	Hazard ratio (95%CI), Original	Hazard ratio (95%CI), LASSO	Hazard ratio (95%CI), Original	Hazard ratio (95%CI), LASSO
Age, years	3.24 (2.04;5.14)	1.09 (1.07;1.11)	1.03 (1.01;1.06)	1.03 (1.01;1.04)
Age^2	0.99 (0.99;1.00)	Not selected	-	-
Sex, women	1.00 (0.70;1.43)	Not selected	-	-
Education, years	1.01 (0.95;1.06)	Not selected	-	-
Systolic blood pressure, per 10 mmHg	0.95 (0.87;1.03)	Not selected	-	-
Current smoking, (y/n)	0.85 (0.50;1.45)	Not selected	-	-
History of diabetes, (y/n)	1.26 (0.80;1.99)	Not selected	-	-
History of symptomatic stroke, (y/n)	2.29 (1.32;3.97)	1.82 (1.43;2.22)	1.26 (0.68;2.32)	1.09 (0.95;1.22)
Depressive symptoms, (y/n)	1.19 (0.79;1.78)	Not selected	-	-
Parental history of dementia, (y/n)	1.30 (0.72;2.35)	Not selected	-	-
Subjective memory decline, (y/n)	1.65 (1.16;2.35)	1.31 (1.13;1.48)	1.42 (0.99;2.04)	1.18 (1.03;1.33)
Assistance needed with IADL, (y/n)	1.80 (1.17;2.75)	1.46 (1.21;1.72)	1.38 (0.88;2.17)	1.25 (1.04;1.45)
Word Fluency Test, words	-	-	0.95 (0.91;0.99)	0.96 (0.94;0.98)
Letter Digit Substitution Test, letters	-	-	0.99 (0.95;1.02)	0.99 (0.98;1.00)
Stroop Interference Task, seconds *****	-	-	1.00 (0.99;1.01)	Not selected
Delayed Word Learning Test, words	-	-	0.82 (0.74;0.90)	0.84 (0.78;0.89)
APOE-ε4 carrier	-	-	1.91 (1.31;2.98)	1.89 (1.65;3.41)
Total brain volume, per 10% ICV	-	-	0.37 (0.19;0.71)	0.39 (0.05;0.74)
Hippocampal volume, per 10% ICV	-	-	0.46 (0.31;0.70)	0.52 (0.25;0.80)
Total white matter hyperintensity volume, % ICV *****	-	-	1.15 (0.94;1.41)	1.10 (1.02;1.18)
Infarcts (cortical / lacunar), (y/n)	-	-	0.92 (0.59;1.45)	Not selected

* Natural log transformed. Abbreviations: IADL= instrumental activities on daily living (assistance needed with finance or medication), *APOE*=apolipoprotein E, ICV=intracranial volume.

Table 3. Discriminative ability for the basic and extended dementia prediction model in both the development and validation studies

Study	**N/n**	**C-statistic**		
		Age alone (95% CI)	**Basic model (95%CI)**	**Extended model (95%CI)**
Rotterdam Study	2710/105	0.76 (0.73;0.78)*	0.78 (0.75;0.81)*	0.86 (0.83;0.88)*
EPOZ	514/36	0.73 (0.65;0.82)	0.75 (0.67;0.82)	0.81 (0.74;0.88)
ADNI-1	228/26	0.54 (0.42;0.64)	-	0.72 (0.63;0.83)**

* Optimism-corrected C-statistics. **ADNI recruits participants via clinical study sites, we therefore only tested the performance of the extended model. Abbreviations: CI=confidence interval, N=Number at risk, n=number of events.

Table 4. Sensitivity analyses of the discriminative ability for a model based on age alone, and the basic and extended dementia prediction models in the development sample

	N/n	**Optimism-corrected C-statistic**		
		Age alone (95% CI)	**Basic model (95%CI)**	**Extended model (95%CI)**
Alzheimer's disease only	2710/105	0.76 (0.72;0.80)	0.77 (0.75;0.81)	0.86 (0.83;0.88)
Men	1280/61	0.76 (0.72;0.82)	0.79 (0.75;0.83)	0.87 (0.84;0.92)
Women	1430/70	0.75 (0.71;0.79)	0.78 (0.73;0.80)	0.85 (0.81;0.88)
Excluding first 4 years of follow-up	2417/65	0.78 (0.74;0.81)	0.79 (0.76;0.82)	0.85 (0.82;0.89)
≤80 years old	2254/79	0.77 (0.74;0.81)	0.80 (0.75;0.84)	0.87 (0.84;0.91)
>80 years old	456/52	0.53 (0.45;0.63)	0.57 (0.49;0.63)	0.71 (0.64;0.76)
3-year time horizon	2710/47	0.80 (0.75;0.84)	0.82 (0.78;0.86)	0.91 (0.87;0.95)
5-year time horizon	2710/81	0.77 (0.74;0.80)	0.79 (0.74;0.83)	0.88 (0.85;0.91)
15-year time horizon*	523/81	0.62 (0.57;0.68)	0.67 (0.62;0.74)	0.71 (0.65;0.75)

*15-year predicted time horizon for all-cause dementia in a subsample of the study population with sufficient follow-up. Abbreviations: CI=confidence interval, N=Number at risk, n=number of events.

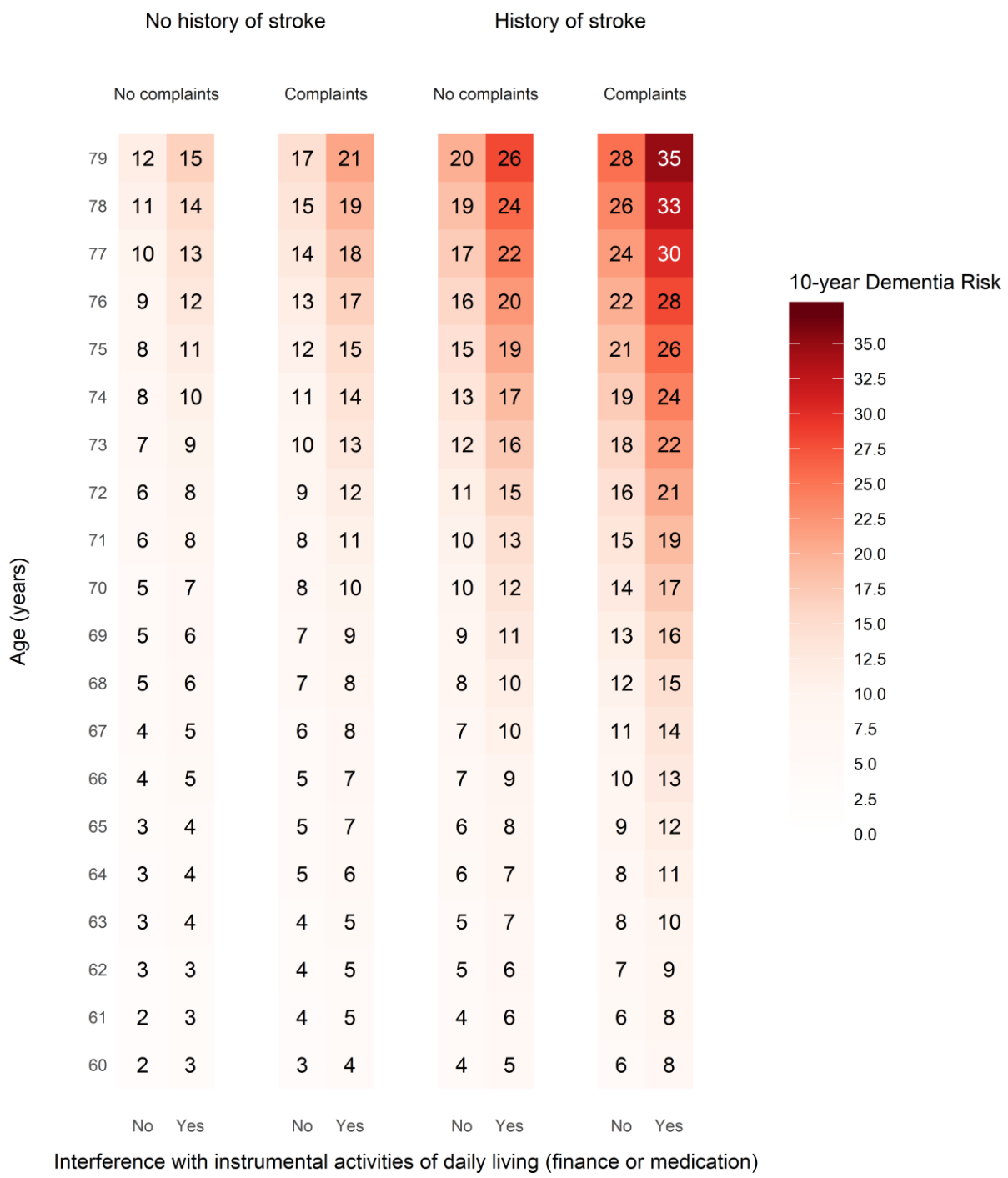

Figure 1. Risk chart for calculating 10-year risk of dementia using the basic model. For instance, a 67-year old man or woman without a history of stroke, with subjective memory complaints, and without difficulties managing his or her finance or medication, has a 6 % risk of developing dementia within 10 years.