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Comparison of subjective cognitive decline and polygenic risk score in the prediction of all-cause dementia, Alzheimer's disease and vascular dementia

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Abstract

Background Polygenic risk scores (PRS) and subjective cognitive decline (SCD) are associated with the risk of developing dementia. It remains to examine whether they can improve the established cardiovascular risk factors aging and dementia (CAIDE) model and how their predictive abilities compare.

Methods The CAIDE model was applied to a sub-sample of a large, population-based cohort study ($n = 5,360$; aged 50–75) and evaluated for the outcomes of all-cause dementia, Alzheimer's disease (AD) and vascular dementia (VD) by calculating Akaike's information criterion (AIC) and the area under the curve (AUC). The improvement of the CAIDE model by PRS and SCD was further examined using the net reclassification improvement (NRI) method and integrated discrimination improvement (IDI).

Results During 17 years of follow-up, 410 participants were diagnosed with dementia, including 139 AD and 152 VD diagnoses. Overall, the CAIDE model showed high discriminative ability for all outcomes, reaching AUCs of 0.785, 0.793, and 0.789 for all-cause dementia, AD, and VD, respectively. Adding information on SCD significantly increased NRI for all-cause dementia (4.4%, $p = 0.04$) and VD (7.7%, $p = 0.01$). In contrast, prediction models for AD further improved when PRS was added to the model (NRI, 8.4%, $p = 0.03$). When *APOE* ε4 carrier status was included (CAIDE Model 2), AUCs increased, but PRS and SCD did not further improve the prediction.

Conclusions Unlike PRS, information on SCD can be assessed more efficiently, and thus, the model including SCD can be more easily transferred to the clinical setting. Nevertheless, the two variables seem negligible if *APOE* ε4 carrier status is available.

Keywords Subjective cognitive decline, Polygenic risk score, Risk prediction, Cohort study, Dementia, Alzheimer's disease, Vascular dementia, CAIDE

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Introduction

Fifty-five million people are living with dementia worldwide, and this number is projected to rise to nearly 80 million by 2030 [1]. However, according to the latest report of the Lancet standing Commission, up to 45% of all dementia cases can be prevented or delayed by altering 14 risk factors associated with daily living [2]. This indicates a high potential for early intervention and prevention.

To date, many different dementia risk prediction models have been developed based on varying requirements and settings. While some models are used as predictive models for long-term risk, others are used for diagnostic purposes or short-term risk prediction. Although such models can aid early detection of dementia, existing models require further improvement [3, 4]. For example, most existing models lack external validation [5–7]. Furthermore, since the field of dementia risk factors is highly dynamic and new factors keep being reported, dementia risk prediction models must be dynamic and easily modifiable [7, 8].

The Cardiovascular Risk Factor Aging and Dementia (CAIDE) model is an established and well-validated, multifactorial risk prediction model including modifiable as well as non-modifiable dementia risk factors [9]. In the same-titled development cohort, an AUC of 0.776 (95% confidence interval (CI): 0.717–0.836) was reached for predicting dementia diagnoses during 20 years of follow-up. Nevertheless, the CAIDE model only contains a general set of risk factors and might be further improved.

Previous studies have shown that patients reporting subjective cognitive decline (SCD), e.g., in the form of memory complaints, are at higher risk of mild cognitive impairment (MCI) and dementia [10–12]. It is assumed that SCD emerges 10–15 years before the onset of objective cognitive decline [12]. Thus, SCD is one of the earliest indicators of dementia [13]. In addition, the use of polygenic risk scores (PRSs) for risk prediction has been established during the last decades [14]. PRSs derived from genome-wide association studies (GWAS) calculate a person's total genetic risk of disease and provide an emerging tool to differentiate the risk of developing AD at an individual level. They are thus commonly used for research purposes as well as in clinical settings [14–16]. Numerous studies have proven the successful prediction of the risk of developing dementia, specifically AD, by PRSs [16–19].

Therefore, this study aims to extend the well-established CAIDE model for dementia by PRS and SCD to assess as well as compare their predictive abilities for all-cause dementia, AD, and VD within 17 years of follow-up of a large population-based cohort of older adults. In addition, the models' discrimination performances are evaluated in subgroups for mid-life (50–64) and late-life (65–75) to examine whether the performance of the extended models varies by age.

Methods

Study population

Analyses for this study were conducted using the ESTHER study. The ESTHER study (German name: Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung) is a prospective cohort study initiated between 2000 and 2002. Participants were recruited throughout Saarland, a German federal state, when visiting one of 420 cooperating physicians for a general health checkup at their general practitioners (GPs). The GPs asked their patients for consent to participate in the ESTHER study during this visit. Overall, the study comprises 9,940 participants aged 50 to 75, who were followed up 2, 5, 8, 11, 14, and 17 years after baseline. Details have been described elsewhere [20, 21]. Compared to a National Health Survey performed in a representative sample of the German population in 1998, sociodemographic baseline characteristics were similarly distributed in the respective age categories of the ESTHER study [22]. The ethics committees of the Heidelberg Medical Faculty of Heidelberg University and the state medical board of Saarland, Germany, approved the study.

Dementia assessment and study sample

Dementia diagnoses were assessed during the 14- and 17-year follow-ups of the ESTHER study. The mean follow-up time was 14.8 years (±SD 3.5 years) with a maxiumum of 19.8 years due to the duration of 2 years of baseline recruitment. Standardised questionnaires were sent to the study participants' GPs, including whether they were aware of a dementia diagnosis of their patient. If so, the GPs were asked to provide details such as the type of dementia, the date of diagnosis, and all available medical records from other specialised providers like neurologists or memory clinics. Questionnaires were also sent to the GPs of participants lost to follow-up due to ill health or death.

Information about a dementia diagnosis was received from 6,357 ESTHER study participants (Fig. 1). For the outlined analyses, participants without information on SCD ($n=167$), without genetic information for PRS calculation ($n=528$), and with missing values in any of the CAIDE model variables ($n=266$) were excluded. Hence, the study sample comprised 5,360 study participants.

CAIDE model and covariates

The CAIDE model is an established and well-validated dementia risk prediction model developed using a sample of 1,409 participants of the CAIDE study [9]. The CAIDE

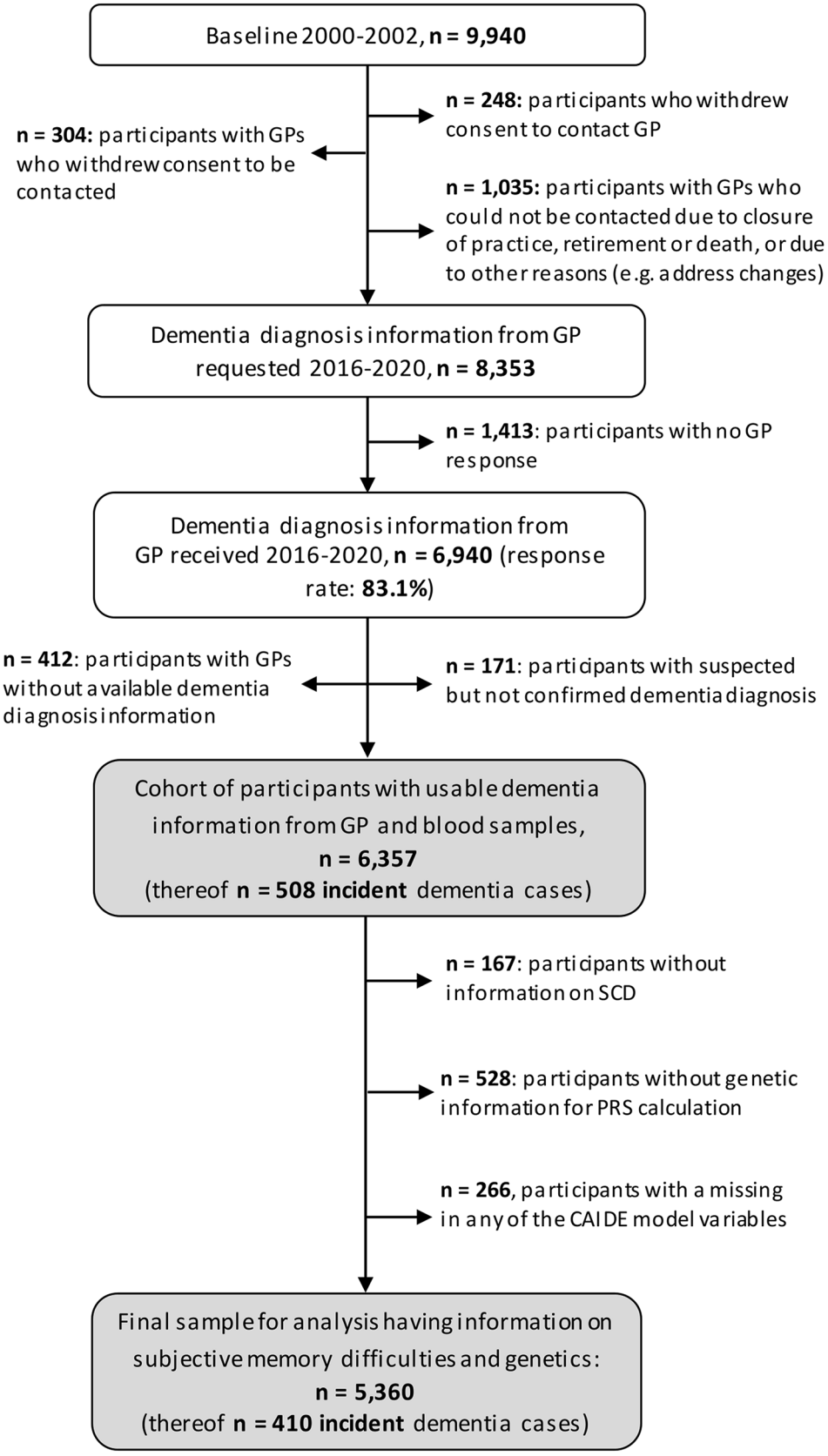

Fig. 1 Flowchart of selected study participants based on the ESTHER study. Abbreviations: GP, general practitioner; SCD, subjective cognitive decline; PRS, polygenic risk score, CAIDE, Cardiovascular Risk Factors Aging and Dementia

study is a Finnish population-based cohort study investigating cardiovascular risk factors, aging and dementia. Participants aged 39 to 64 at baseline were followed up for 20 years. During this follow-up period, 61 participants developed dementia. The CAIDE model includes age, education, sex, systolic blood pressure, body mass index (BMI), total cholesterol, and physical activity. A second version of the model (CAIDE Model 2) also comprises participants' *APOE* ε4 carrier status.

All variables included in the CAIDE model were available in the ESTHER study. Categorization of variables had to be recalibrated due to differences in the age range, the education system and the assessment of physical activity between the studies. In detail, age was used as a continuous variable, education categories have been changed from 0 to 6, 7–9, ≥10 years to ≤9, 10–11, ≥12 years, and physical activity has been changed from two categories (inactive and active) to three categories (inactive, low, and medium or high). Furthermore, the continuous variables age, systolic blood pressure, BMI, and total cholesterol were tested for their best-fitting function using fractional polynomials [23]. Since the linear function was the best-fitting function for all variables in predicting all-cause dementia, AD, and VD (data not shown), they were kept as continuous variables.

Information about age, sex, education, BMI, and physical activity was collected via standardised self-administered questionnaires during the baseline assessment of the ESTHER study, while the systolic blood pressure was measured by the participants' GPs. Serum samples drawn at baseline were used to measure the study participant's total cholesterol levels by an enzymatic colorimetric test with the Synchron LX multicalibrator system (Beckman Coulter, Galway, Ireland). To determine *APOE* genotypes, DNA was extracted from whole blood samples through a sorting-out procedure. Genotyping of blood cell-derived DNA was carried out using the Illumina Infinium OncoArray and Global Screening Array BeadChips (Illumina, San Diego, CA, USA). Quality control assessment was performed according to the Nature Protocols article by Anderson and colleagues [24]. The Michigan Imputation Server was utilized for the imputation of the quality-controlled data. For this, SHAPEIT2 was used to phase the data, and MiniMac 4 was used to impute to the HRC Version r1.1 2016 reference panel [25, 26]. *APOE* genotypes were finally determined using TaqMan single-nucleotide polymorphism (SNP) assays (Applied Biosystems, California, USA) were used. Missing APOE information (5% of *APOE* data) was imputed based on quality-controlled imputed genetic data. Further details have been described elsewhere [27].

Polygenic risk score calculation and subjective cognitive decline

PRS were calculated based on AD-associated SNPs identified by Kunkle et al., with a GWAS significance threshold of $p<5^{*}10^{-8}$ [28]. For this purpose, the number of risk alleles was summed and weighted according to the extent of the association as previously described in detail [17]. SNPs in the APOE locus (chromosome 19, 45,404,000–45,418,000) were not included in this PRS.

SCD was assessed via self-administered health questionnaires during the baseline assessment, including a yes or no question regarding short-term memory complaints (*Do you have difficulty remembering things that have happened in the recent past (hours to a few days)?*).

Statistical analyses

Baseline characteristics of included ESTHER study participants were calculated for participants with incident all-cause dementia, AD, and VD diagnosis as well as participants without dementia diagnosis during follow-up. Additional comparisons of, baseline characteristics of ESTHER study participants included and excluded from the analyses showed reasonably comparable results (Supplemental Table 1).

Cox proportional hazard regression models adjusted for age, sex, education, systolic blood pressure, BMI, total cholesterol, physical activity and *APOE* ε4 carrier status were calculated to assess the association between CAIDE model variables and the outcomes of all-cause dementia, AD, and VD. Furthermore, the associations between the predictors of interest (PRS and SCD) and the three dementia outcomes were examined. Statistical significance was assessed by the Wald test.

The discriminative ability of CAIDE Model 1 and CAIDE Model 2 for all-cause dementia, AD, and VD was determined by Akaike's information criterion (AIC) and the area under the receiver operating characteristic (ROC) curve (AUC) and 95% confidence intervals (CIs). For this purpose, the "survcstd" macro of SAS was used. Model calibration of all prediction models was examined by May-Hosmer's simplification of the Gronnesby-Borgan test [29]. To examine the improvement of the CAIDE Model by PRS and SCD, the net reclassification improvement (NRI) method was applied [30, 31]. For this, three cut-offs were chosen individually for each outcome with an equal distribution of incident dementia diagnoses and applied to the analyses. In addition, the extent of the model's improvement was assessed by the integrated discrimination improvement (IDI) [30, 31]. In both methods, CAIDE Model 1 and CAIDE Model 2 were used as reference models, and PRS and SCD were added to the models. The latter was modelled as a binary categorical variable, while the PRS was modelled continuously (per one standard deviation increase). Analyses were carried

out in the total sample, as well as in subgroups for mid-life (50–64 years) and late-life (65–75 years) for all outcomes and CAIDE Model 1 and 2, respectively.

All analyses were conducted using the Statistical Analysis System (SAS, version 9.4, Cary, North Carolina, USA). Statistical tests were two-sided using an alpha level of 0.05.

Results

Baseline characteristics for all variables included in the basic CAIDE model are described separately for participants with incident all-cause dementia, AD, and VD diagnosis as well as for those without a dementia diagnosis in Table 1. Among the included 5,360 study participants, 410 were diagnosed with dementia. Of those, 139 participants had an AD diagnosis, and 152 were diagnosed with VD. The mean age at baseline of participants who later developed incident all-cause dementia was five years higher (mean (±SD): 66.3 (5.2) years) compared to participants without dementia diagnosis (61.7 (6.5) years). Most participants (>70%) had an education of no more than 9 years. Systolic blood pressure, BMI and total cholesterol levels of study participants were comparable between participants with and without later dementia diagnoses. Those who were later diagnosed with dementia more frequently reported low or inactive levels of physical activity than those with no dementia diagnosis (71.2% compared to 62.9%). Finally, the proportion of *APOE* ε4 carriers was much higher among those who later developed dementia, in particular among those who were diagnosed with AD (50.4%), than among participants with no dementia diagnosis (25.0%).

In a Cox regression model adjusted for all CAIDE model variables, age and *APOE* ε4 carrier status in Model 2 were statistically significantly associated with all dementia outcomes (Supplemental Tables 2–4). In addition, higher education (inverse), male sex, and higher physical activity (inverse) showed significant associations with all-cause dementia (Supplemental Table 2). In analyses focusing on the AD outcome, only physical activity was significantly associated (Supplemental Table 3). In analyses focusing on VD, only male sex was significantly associated (Supplemental Table 4).

Cox regression models further showed significant associations of PRS and SCD with all-cause dementia in Model 1 (Table 2). When *APOE* ε4 carrier status was added in Model 2, the association between PRS and all-cause dementia lost statistical significance, but SCD

Table 1 CAIDE model variables of the study population ($n = 5,360$)

CAIDE model variables	No dementia ($n = 4,950$)	All-cause dementia ($n = 410$)		Alzheimer's disease ($n = 139$)		Vascular dementia ($n = 152$)	
	Data	Data	*p*-value[a]	Data	*p*-value[a]	Data	*p*-value[a]
Age (years), mean (SD)	61.2 (6.4)	66.9 (5.2)	**< 0.001**	66.7 (5.2)	**< 0.001**	66.9 (5.0)	**< 0.001**
Mid-life (50–64 years), n (%)	3330 (67.3)	128 (31.2)		46 (33.1)		47 (30.9)	
Late-life (65–75 years), n (%)	1620 (32.7)	282 (68.8)		93 (66.9)		105 (69.1)	
Education (years), n (%)			**0.001**		**0.036**		0.135
≤9	3592 (72.6)	331 (80.7)		115 (82.7)		122 (80.3)	
10–11	752 (15.2)	38 (9.3)		13 (9.4)		16 (10.5)	
≥ 12	606 (12.2)	41 (10.0)		11 (7.9)		14 (9.2)	
Sex, n (%)			0.072		0.968		0.076
Female	2680 (54.1)	203 (49.5)		75 (54.0)		71 (46.7)	
Male	2270 (45.9)	207 (50.5)		64 (46.0)		81 (53.3)	
SBP (mmHg), mean (SD)	138.9 (19.5)	142.4 (19.2)	**< 0.001**	142.2 (19.2)	**0.046**	142.8 (19.5)	**0.007**
BMI (kg/m^2), mean (SD)	27.7 (4.4)	27.6 (3.9)	0.924	27.1 (3.8)	0.304	27.7 (4.0)	0.957
Total cholesterol (mmol/L), mean (SD)	5.69 (1.3)	5.69 (1.3)	0.975	5.73 (1.3)	0.545	5.68 (1.3)	0.925
Physical activity[b], n (%)			**< 0.001**		**0.001**		0.178
Inactive	830 (16.8)	108 (26.3)		43 (30.9)		34 (22.4)	
Low	2284 (46.1)	184 (44.9)		57 (41.0)		71 (46.7)	
Medium or high	1836 (37.1)	118 (28.8)		39 (28.1)		47 (30.9)	
***APOE* genotypes, n (%)**			**< 0.001**		**< 0.001**		**0.014**
ε4 non-carrier	3710 (75.0)	243 (59.3)		69 (49.6)		99 (65.1)	
ε4 carrier	1240 (25.0)	167 (40.7)		70 (50.4)		53 (34.9)	

Abbreviations: *APOE*, apolipoprotein E; SBP, systolic blood pressure; BMI, body mass index

Note: Numbers printed in bold are statistically significant.

[a] Result of statistical test (Mann-Whitney-U, Wilcoxon Rank-sum, or χ^2 test as appropriate) for comparison with group "No dementia".

[b] "Inactive" was defined by < 1 h of vigorous or < 1 h light physical activity per week. "Medium or high" was defined by ≥ 2 h of vigorous and ≥ 2 h of light physical activity/week. All other amounts of physical activity were grouped into the category "Low".

Table 2 Associations between predictors of interest and common subtypes of dementia

Predictors	n_{total}	n_{cases}	Model 1[a]		Model 2[b]	
			HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
All-cause dementia						
SCD	5,360	410	**1.49 (1.21–1.82)**	**<0.001**	**1.48 (1.21–1.82)**	**<0.001**
Kunkle PRS per 1SD[c]			**1.22 (1.11–1.34)**	**<0.001**	1.03 (0.93–1.15)	0.350
Alzheimer's disease						
SCD	5,089	139	1.27 (0.89–1.83)	0.191	1.27 (0.88–1.83)	0.197
Kunkle PRS per 1SD[d]			**1.51 (1.29–1.76)**	**<0.001**	**1.20 (1.00-1.43)**	**0.049**
Vascular dementia						
SCD	5,102	152	**1.62 (1.16–2.25)**	**0.005**	**1.62 (1.16–2.25)**	**0.005**
Kunkle PRS per 1SD[e]			1.04 (0.88–1.23)	0.680	0.91 (0.76–1.09)	0.291

Note: Numbers printed in bold are statistically significant ($P<0.05$)

Abbreviations: HR, hazard ratio; CI, confidence interval; SD, standard deviation; SCD, subjective cognitive decline; PRS, polygenic risk score;

[a]Model 1 was adjusted for age, education, sex, systolic blood pressure, BMI, total cholesterol and physical activity

[b]Model 2 was adjusted for all variables listed in Model 1 and *APOE* ε4 carrier status

[c]1 SD of Kunkle's PRS = 0.0100

[d]1 SD of Kunkle's PRS = 0.0010

[e]1 SD of Kunkle's PRS = 0.0099

remained a significant predictor. For dementia subtypes, PRS was statistically significantly associated with AD, while SCD was statistically significantly associated with VD.

The performance of CAIDE Models 1 and 2 for all-cause dementia, AD, and VD are shown in Table 3. May-Hosmer's simplification of the Gronnesby-Borgan test verified good calibration for all models (data not shown). Overall, the CAIDE model showed a high discriminative ability in the total population with an AUC > 0.78 in Model 1. AUCs further improved to 0.800, 0.827, and 0.793 for the outcomes of all-cause dementia, AD, and VD, respectively, when *APOE* ε4 carrier status was added to the CAIDE model (Model 2).

Generally, the extension of CAIDE Model 1 by PRS and SCD only led to marginal improvements in AUCs. However, IDI and NRI revealed statistically significant improvements for some models. Adding SCD to CAIDE Model 1 led to a statistically significant improvement of NRI (4.4%, $p=0.04$) and IDI in predicting all-cause dementia. In contrast, in the case of AD, extending CAIDE Model 1 by PRS but not SCD revealed statistically significantly better prediction with an NRI of 8.4% ($p=0.03$) and significant IDI. For VD, the extension by SCD again led to a significant improvement of the NRI (7.7%, $p=0.01$) but IDI was not statistically significant.

When *APOE* ε4 carrier status was included in CAIDE Model 2, AUCs did not further improve by adding PRS and SCD to the models. Also, NRI and IDI statistics showed no statistically significant changes except for CAIDE Model 2 plus SCD for the outcome of all-cause dementia. In this case, IDI was statistically significant, and NRI showed an improvement of 3.1% but did not reach statistical significance ($p=0.06$).

In addition to the total population, the discriminative abilities of the CAIDE model were evaluated in mid-life (50–64 years) and late-life (65–75 years) subgroups (Tables 4, 5 and 6). Overall, AUCs were consistently higher in the mid-life compared to the late-life subgroup for all outcomes. In contrast to the total population, PRS significantly improved the prediction of CAIDE Model 1 for all-cause dementia in mid-life with an NRI of 6.9% ($p=0.008$) (Table 4). In addition, as observed in the total population, the extension by SCD also led to a significant improvement in IDI for all-cause dementia in this subgroup. However, the increase in NRI was only modest in this case and not statistically significant (2.0%, $p=0.62$). The overall strongest improvement of the CAIDE model was achieved for AD when CAIDE model 1 was extended by PRS in the mid-life subgroup (NRI, 19.6%, $p=0.008$) (Table 5). Also, IDI was statistically significant. For the outcome of VD, SCD led to significant improvements in NRI but not IDI in the late-life subgroup for CAIDE Model 1, whereas PRS led to a statistically significant NRI but not IDI in CAIDE Model 2 in both agegroups (Table 6).

Discussion

In this prospective cohort study, we evaluated potential improvement in dementia prediction with the established and well-validated CAIDE model by adding information about a PRS and SCD. While the PRS significantly improved the prediction of AD only, information on SCD significantly improved the predictive ability of the CAIDE Model 1 for all-cause dementia and VD. However, no relevant improvement in prediction was achieved when *APOE* ε4 carrier status was included in CAIDE Model 2.

Table 3 Evaluation of prediction models for all-cause dementia, Alzheimer's disease and vascular dementia

Model performance measures	Model 1[a]			Model 2[b]		
	CAIDE	CAIDE + PRS	CAIDE + SCD	CAIDE	CAIDE + PRS	CAIDE + SCD
All-cause dementia (*n* = 410)						
AIC	6364.8	6351.6	6352.9	6318.2	6319.9	6306.5
AUC (95% CI)	0.785 (0.765–0.806)	0.790 (0.769–0.810)	0.788 (0.768–0.809)	0.800 (0.780–0.820)	0.800 (0.780–0.820)	0.803 (0.782–0.823)
Reclassification						
Events n_{up}/n_{down}	Ref.	37/29	44/30	Ref.	6/4	40/29
Nonevents n_{up}/n_{down}	Ref.	237/264	258/307	Ref.	37/45	244/266
NRI %[c] (*p*-value)	Ref.	2.5% (0.219)	**4.4% (0.040)**	Ref.	0.6% (0.335)	3.1% (0.064)
IDI % (*p*-value)	Ref.	0.07% (0.070)	**0.04% (0.011)**	Ref.	0.005% (0.968)	**0.05% (0.008)**
Alzheimer's disease (*n* = 139)						
AIC	2163.7	2141.0	2164.1	2124.0	2122.2	2124.4
AUC (95% CI)	0.793 (0.758–0.827)	0.808 (0.774–0.841)	0.793 (0.759–0.827)	0.827 (0.795–0.859)	0.827 (0.795–0.859)	0.827 (0.795–0.859)
Reclassification						
Events n_{up}/n_{down}	Ref.	28/20	7/7	Ref.	8/9	7/3
Nonevents n_{up}/n_{down}	Ref.	396/525	143/162	Ref.	181/193	138/153
NRI %[d] (*p*-value)	Ref.	**8.4% (0.026)**	0.4% (0.859)	Ref.	-0.5% (0.841)	3.2% (0.128)
IDI % (*p*-value)	Ref.	**0.05% (0.030)**	-0.004% (0.510)	Ref.	0.01% (0.132)	0.0003% (0.296)
Vascular dementia (*n* = 152)						
AIC	2331.9	2363.7	2356.3	2355.4	2356.3	2349.8
AUC (95% CI)	0.789 (0.757–0.822)	0.790 (0.757–0.822)	0.794 (0.761–0.828)	0.793 (0.760–0.826)	0.794 (0.761–0.827)	0.798 (0.764–0.831)
Reclassification						
Events n_{up}/n_{down}	Ref.	4/2	24/14	Ref.	7/7	17/18
Nonevents n_{up}/n_{down}	Ref.	45/32	287/344	Ref.	99/97	289/317
NRI %[e] (*p*-value)	Ref.	1.1% (0.316)	**7.7% (0.010)**	Ref.	-0.04% (0.981)	-0.09% (0.975)
IDI % (*p*-value)	Ref.	0.002% (0.837)	0.003% (0.093)	Ref.	-0.004% (0.359)	-0.007% (0.068)

Note: Numbers printed in bold are statistically significant ($P < 0.05$)

Abbreviations: SCD, subjective cognitive decline; PRS, polygenic risk score; AIC, Akaike's information criterion; AUC, area under the curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement

[a]CAIDE Model 1 includes age, education, sex, systolic blood pressure, BMI, total cholesterol and physical activity

[b]CAIDE Model 2 includes all variables listed in Model 1 and *APOE* ε4 carrier status

[c]The cutoffs for all-cause dementia were set to 7%, 15%, and 30%

[d]The cutoffs for AD were set to 3%, 6%, and 11%

[e]The cutoffs for VD were set to 3.5%, 7%, and 14%

Previous studies

Very few dementia risk prediction models include information on SCD. The self-administered Gerocognitive Examination (SAGE) score is a cognitive assessment tool for mild cognitive impairment (MCI) and early dementia, including information on subjective cognitive decline ("Have you had any problems with memory or thinking?" Yes / only occasionally / no) as well as measures of cognitive function of different domains [32]. In its development cohort of 254 participants (>59 years) from the cohort as well as the clinical setting, the model predicted the risk of developing dementia well with an AUC of 0.906. In a recent study, the authors tested the SAGE score compared to the Mini-Mental State Examination (MMSE) in 424 individuals and showed that SAGE predicts cognitive decline at least 6 months earlier than MMSE [33].

In the study of Licher and colleagues, a dementia risk prediction model was developed in a cohort based on the Rotterdam Study, including 20,324 individuals aged 60 and older [34]. The model includes subjective memory decline, age, history of stroke, and need for assistance with finances or medication. It predicted the risk of developing dementia with an AUC of 0.78 (95% CI: 0.75–0.81) and was externally validated in the Epidemiological Prevention Study of Zoetermeer (EPOZ), achieving a comparable predictive ability with an AUC of 0.75 (95% CI: 0.67–0.82).

PRSs are a widely used tool to assess an individual's risk of developing dementia, especially AD [14, 15]. Nevertheless, multifactorial dementia risk prediction models, including such a score, are still rare. In a study by Escott-Price and colleagues, several models, including information on polygenic scores, were tested in a subset

Table 4 Evaluation of the discriminative ability for all-cause dementia in mid-life and late-life

Model performance measures	Model 1[a]			Model 2[b]		
	CAIDE	CAIDE + PRS	CAIDE + SCD	CAIDE	CAIDE + PRS	CAIDE + SCD
[a]Mid-life (50–64 years) *[n_{total}=3458, n_{cases}=128]*						
AIC	1930.1	1919.4	1925.5	1908.0	1908.7	1903.3
AUC (95% CI)	0.731 (0.692–0.771)	0.744 (0.704–0.784)	0.735 (0.696–0.774)	0.758 (0.718–0.797)	0.759 (0.719–0.799)	0.760 (0.720–0.800)
Reclassification						
Events n_{up}/n_{down}	Ref.	25/21	23/24	Ref.	8/6	20/20
Nonevents n_{up}/n_{down}	Ref.	266/392	283/377	Ref.	106/112	260/321
NRI %[c] (*p*-value)	Ref.	**6.9% (0.008)**	2.0% (0.616)	Ref.	1.7% (0.455)	1.8% (0.631)
IDI % (*p*-value)	Ref.	**0.03% (0.018)**	**0.02% (0.018)**	Ref.	-0.0007% (0.798)	**0.02% (0.021)**
[b]Late-life (65–75 years) *[n_{total}=1902, n_{cases}=282]*						
AIC	3958.0	3955.4	3952.7	3935.5	3937.4	3930.4
AUC (95% CI)	0.673 (0.641–0.705)	0.678 (0.646–0.710)	0.678 (0.647–0.710)	0.697 (0.666–0.728)	0.697 (0.666–0.728)	0.699 (0.669–0.730)
Reclassification						
Events n_{up}/n_{down}	Ref.	23/23	39/41	Ref.	1/2	24/35
Nonevents n_{up}/n_{down}	Ref.	98/127	180/182	Ref.	3/4	156/164
NRI %[d] (*p*-value)	Ref.	1.8% (0.462)	-0.59% (0.851)	Ref.	-0.29% (0.531)	-3.4% (0.237)
IDI % (*p*-value)	Ref.	0.12% (0.119)	**0.05% (0.031)**	Ref.	-0.003% (0.874)	**0.07% (0.023)**

Note: Numbers printed in bold are statistically significant ($P<0.05$)

Abbreviations: SCD, subjective cognitive decline; PRS, polygenic risk score; AIC, Akaike's information criterion; AUC, area under the curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement

[a]CAIDE Model 1 includes age, education, sex, systolic blood pressure, BMI, total cholesterol and physical activity

[b]CAIDE Model 2 includes all variables listed in Model 1 and *APOE* ε4 carrier status

[c]The cutoffs for mid-life were set to 4.25%, 6.5%, and 10%

[d]The cutoffs for late-life were set to 15%, 22.5%, and 35%

of 4.603 participants from the International Genomics of Alzheimer's Project (IGAP) [18]. The model including the variables *APOE*, PRS, sex, and age, predicted the risk of developing AD the best, reaching an AUC of 0.78 (95% CI: 0.77–0.80).

Furthermore, Verhaaren et al. added a set of 10 risk genes to a model composed of age, sex, and *APOE* ε4 [35]. Like in our study, the AUC increased only marginally from 0.815 to 0.816. However, the authors did not apply further reclassification methods like NRI or IDI to determine the extent of improvement by the added risk genes.

Interpretation of findings

The reclassification analyses showed that SCD significantly improved the prediction of the CAIDE model for all-cause dementia and VD. This result was further supported by Cox regression analyses showing a statistically significant association between SCD and all-cause dementia as well as VD. In the literature, participants reporting SCD have been shown to be at a higher risk of developing MCI and following dementia in a multitude of studies [10, 36, 37]. Meta-analyses revealed an annual conversion rate to MCI of 7% and to dementia of 5% [36]. Although SCD can be assessed in different ways, this does not appear to affect its effectiveness in predcting dementia risk [11, 37]. In our study, SCD was assessed by asking only one simple question to the participant. This is a major advantage in clinical translation of the created prediction model. In a clinical setting, obtaining all the necessary information to estimate an individual's risk of developing dementia with the created prediction model would only require a concise physical examination and a patient interview, along with the submission of a blood sample. In addition, a further advantage of adding SCD to the CAIDE model is that SCD is one of the earliest indicators that appears even before cognitive decline can be objectively measured [11, 38]. This makes early intervention and prevention possible.

In contrast to SCD, PRS calculation needs more resources. We found that adding PRS to the CAIDE model significantly improved prediction for AD only. This was even more distinct when the model was applied to the mid-life cohort. In this case, the prediction of AD was enhanced by nearly 20% (NRI: 19.6% $p=0.008$, IDI: 0.02% $p=0.02$). Moreover, Cox regression analyses showed a significant association between PRS and AD. This stands to reason, given that Kunkles' PRS was developed based on a cohort that included only AD cases [28]. Our findings indicate that Kunkles' PRS is unsuitable for a general

Table 5 Evaluation of the discriminative ability for Alzheimer's disease in mid-life and late-life

Model performance measures	Model 1[a]			Model 2[b]		
	CAIDE	CAIDE + PRS	CAIDE + SCD	CAIDE	CAIDE + PRS	CAIDE + SCD
[a]Mid-life (50–64 years) *[n_{total}=3330, n_{cases}=46]*						
AIC	698.6	680.4	699.2	677.5	674.5	677.9
AUC (95% CI)	0.767 (0.705–0.829)	0.794 (0.734–0.854)	0.765 (0.703–0.827)	0.809 (0.743–0.875)	0.811 (0.747–0.875)	0.808 (0.743–0.873)
Reclassification						
Events n_{up}/n_{down}	Ref.	12/6	5/2	Ref.	7/5	3/6
Nonevents n_{up}/n_{down}	Ref.	299/516	160/156	Ref.	175/230	113/119
NRI %[c] (*p*-value)	Ref.	**19.6% (0.008)**	6.4% (0.163)	Ref.	6.0% (0.250)	-6.3% (0.110)
IDI % (*p*-value)	Ref.	**0.02% (0.025)**	-0.0006 (0.243)	Ref.	0.002% (0.239)	-0.001 (0.504)
[b]Late-life (65–75 years) *[n_{total}=1713, n_{cases}=93]*						
AIC	1306.4	1301.5	1307.7	1290.1	1291.7	1291.5
AUC (95% CI)	0.689 (0.633–0.745)	0.708 (0.652–0.764)	0.688 (0.633–0.744)	0.740 (0.688–0.791)	0.738 (0.686–0.791)	0.739 (0.687–0.790)
Reclassification						
Events n_{up}/n_{down}	Ref.	16/15	4/9	Ref.	3/4	1/7
Nonevents n_{up}/n_{down}	Ref.	189/218	84/72	Ref.	40/51	65/88
NRI %[d] (*p*-value)	Ref.	2.9% (0.595)	-6.1% (0.068)	Ref.	-4.0% (0.877)	-5.0% (0.101)
IDI % (*p*-value)	Ref.	0.06% (0.109)	-0.01% (0.683)	Ref.	0.01% (0.199)	-0.004% (0.390)

Note: Numbers printed in bold are statistically significant ($P<0.05$)

Abbreviations: SCD, subjective cognitive decline; PRS, polygenic risk score; AIC, Akaike's information criterion; AUC, area under the curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement

[a]CAIDE Model 1 includes age, education, sex, systolic blood pressure, BMI, total cholesterol and physical activity

[b]CAIDE Model 2 includes all variables listed in Model 1 and *APOE* ε4 carrier status

[c]The cutoffs for mid-life were set to 1.5%, 3.5%, and 7%

[d]The cutoffs for late-life were set to 5%, 8%, and 15%

dementia risk assessment. Adding a PRS to the CAIDE model might only be helpful for specific risk prediction of AD in mid-life. This is also supported and might be explained by a recent report of young AD patients having fewer co-pathologies in addition to AD, which leads to a more accurate risk prediction [39]. Another reason might be a genetic difference which was assumed by Gunn and colleagues showing that a PRS for AD is not predictive of dementia in long-living individuals compared to controls [40].

Moreover, our results also indicate that Kunkles' PRS does not relevantly improve the prediction over CAIDE Model 2, including *APOE* ε4. Thus, the predictive value of other SNPs, in addition to the *APOE* ε4 polymorphism in PRSs, is questionable. *APOE* is a well-known risk factor for dementia, especially AD, and a fundamental component in most dementia risk prediction models [5, 41, 42]. In our study, *APOE* ε4 carrier status was one of the strongest predictors. Interestingly, not only the additional predictive value of PRS but also of SCD seemed negligible when APOE was part of CAIDE Model 2. This again emphasises the strength of *APOE* in dementia risk prediction.

When applied to the mid-life and late-life subgroups, the CAIDE model showed a clearly higher discriminative ability for all three outcomes in the mid-life subgroup. This has also been reported in previous studies replicating or applying the CAIDE model [3, 43] and is in line with the CAIDE model initially developed in a mid-life cohort. More research is needed about risk factors that can improve dementia risk prediction in older individuals.

Strengths and limitations

Strengths of this study include its prospective cohort design, a high number of participants, an extensive follow-up period of 17 years and its comparability to the German healthcare setting.

Nevertheless, limitations encompass a possibility of under- or misdiagnosis of dementia and dementia subtypes due to the community-based setting of the ESTHER study. In the ESTHER study, dementia diagnoses are made heterogeneously, and subtypes were often not diagnosed. Although this also reflects the reality of a community-based setting, which enhances the generalizability of the study and might explain the relatively low number of AD diagnoses, a possible under- or misdiagnosis of dementia might lead to an underestimation of results and may impact the strength and precision of prediction models created.

Given the recalibration of the CAIDE model to the ESTHER study, the direct comparability to the CAIDE

Table 6 Evaluation of the discriminative ability for vascular dementia in mid-life and late-life

Model performance measures	Model 1[a]			Model 2[b]		
	CAIDE	CAIDE + PRS	CAIDE + SCD	CAIDE	CAIDE + PRS	CAIDE + SCD
Mid-life (50–64 years) *[n_{total}=3377, n_{cases}=47]*						
AIC	707.6	709.3	709.4	708.9	710.9	710.8
AUC (95% CI)	0.757 (0.703–0.812)	0.759 (0.702–0.815)	0.758 (0.703–0.812)	0.762 (0.706–0.817)	0.761 (0.705–0.818)	0.762 (0.706–0.818)
Reclassification						
Events n_{up}/n_{down}	Ref.	4/1	3/4	Ref.	4/1	5/3
Nonevents n_{up}/n_{down}	Ref.	99/99	115/110	Ref.	26/39	93/122
NRI %[c] (*p*-value)	Ref.	6.38% (0.076)	-2.3% (0.554)	Ref.	**6.8% (0.001)**	5.1% (0.174)
IDI % (*p*-value)	Ref.	0.00007 (0.357)	-0.0005 (0.562)	Ref.	-0.0003 (0.451)	-0.0006 (0.588)
Late-life (65–75 years) *[n_{total}=1725, n_{cases}=105]*						
AIC	1475.2	1477.2	1468.5	1469.4	1469.7	1462.9
AUC (95% CI)	0.669 (0.616–0.721)	0.669 (0.616–0.721)	0.694 (0.643–0.745)	0.683 (0.628–0.737)	0.683 (0.628–0.738)	0.702 (0.649–0.755)
Reclassification						
Events n_{up}/n_{down}	Ref.	1/1	29/19	Ref.	12/3	25/17
Nonevents n_{up}/n_{down}	Ref.	9/3	283/334	Ref.	98/107	288/317
NRI %[d] (*p*-value)	Ref.	-0.4% (0.683)	**12.7% (0.043)**	Ref.	**9.1% (0.011)**	9.4% (0.127)
IDI % (*p*-value)	Ref.	0.002% (0.911)	0.01% (0.134)	Ref.	-0.01% (0.444)	0.3% (0.088)

Note: Numbers printed in bold are statistically significant ($P<0.05$)

Abbreviations: SCD, subjective cognitive decline; PRS, polygenic risk score; AIC, Akaike's information criterion; AUC, area under the curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement

[a]CAIDE Model 1 includes age, education, sex, systolic blood pressure, BMI, total cholesterol and physical activity

[b]CAIDE Model 2 includes all variables listed in Model 1 and *APOE* ε4 carrier status

[c]The cutoffs for mid-life were set to 1.75%, 2.5%, and 3.5

[d]The cutoffs for late-life were set to 6.25%, 10%, and 15.5%

model is affected. In addition, since our study population is mainly of European descent aged 50 to 75 at baseline, results cannot be applied to other ethnicities and age groups.

Conclusion

This study showed that although AUCs only marginally increased when SCD and PRS were added to the CAIDE model, reclassification analyses reveal a statistically significant improvement in the model's prediction accuracy. Adding SCD to the CAIDE model significantly improved the prediction of all-cause dementia and VD. In contrast, the addition of PRS statistically significantly improved the discriminative ability for AD, especially in mid-life. This represents an essential difference in terms of clinical translation. Since information on SCD can be more easily assessed than the calculation of PRS, this constitutes a major advantage. However, both a PRS and SCD seem to be of limited, if any, predictive value if information on *APOE* ε4 carrier status is available.

Abbreviations

AD	Alzheimer's disease
AIC	Akaike's information criterion
APOE	Apolipo-protein
AUC	Area under the curve
CAIDE	Cardiovascular risk factors aging and dementia
CI	Confidence interval
ESTHER	Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung
GPs	General practitioners
GWAS	Genome-wide association studies
IDI	Integrated discrimination improvement
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
NRI	Net reclassification improvement
PRS	Polygenic risk score
ROC	Receiver operating characteristic
SAGE	Self-administered Gerocognitive Examination
SAS	Statistical Analysis System
SCD	Subjective cognitive decline
SD	Standard deviation
SNP	Single-nucleotide polymorphism
VD	Vascular dementia

Supplementary Information

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Supplementary Material 1

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Author contributions

K.T., B.S., and H.B. contributed to the conception and design of the study as well as to the acquisition and analysis of data. K.T., H.S., J.S., L.P., B.H., K.B., B.S., and H.B. contributed to drafting the text, figures, or tables.

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Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the German Cancer Research Center.

Declarations

Ethics approval and consent to participate
The study was approved by the ethics committees of Heidelberg University and the state medical board of Saarland, Germany. Written informed consent was obtained from all participants in the study. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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