Cognitive dispersion and ApoEe4 genotype predict dementia diagnosis in 8 years follow-up of the oldest-old

Abstract

Background

Cognitive dispersion, or inconsistencies in performance across cognitive domains, has been posited as a cost-effective tool to predict conversion to dementia in older adults. However, there is a dearth of studies exploring cognitive dispersion in the oldest-old (>80 years) and its relationship to dementia incidence.

Objective

The main aim of this study was to examine whether higher cognitive dispersion at baseline was associated with dementia incidence within an eight-year follow-up of very old adults, while controlling for established risk factors and suggested protective factors for dementia.

Methods

Participants (n=468) were from the Origins of Variance in the Old-Old: Octogenarian Twins study, based on the Swedish Twin Registry. Cox regression analyses were performed to assess the association between baseline cognitive dispersion scores and dementia incidence, while controlling for sociodemographic variables, ApoEe4 carrier status, co-morbidities, zygosity and lifestyle engagement scores. An additional model included a composite of average cognitive performance.

Results

Cognitive dispersion and ApoEe4 were significantly associated with dementia diagnosis. These variables remained statistically significant when global cognitive performance was entered into the model. Likelihood ratio tests revealed that cognitive dispersion and cognitive composite scores entered together in the same model, was superior to either predictor alone in the full model.

Conclusions

The study underscores the usefulness of cognitive dispersion metrics for dementia prediction in the oldest-old and highlights the influence of ApoEe4 on cognition in very late age. Our findings concur with others suggesting that health and lifestyle factors pose little impact upon cognition in very advanced age.

Keywords: cognitive dispersion; ApoE4; Alzheimer's disease; dementia risks; dementia prediction

Key points:

- Cognitive dispersion, a measure of inconsistency across cognitive performance, has gained research attention as a possible marker for cognitive impairment and disease pathology

- Cognitive dispersion in the oldest-old predicts functional disability and cognitive decline, but to date, no study has explored whether it can predict dementia incidence in the oldest-old

- In our cohort of oldest-old, cognitive dispersion and ApoEe4 predicted dementia incidence within an 8-year follow-up

- Cognitive dispersion is a useful adjunct metric for dementia prediction

Introduction

Alzheimer's disease (AD) is now accepted to have a protracted nonclinical period whereby elevations in AD-related pathologies are present years before the emergence of mild cognitive symptoms and a later dementia syndrome [1]. Similarly, cognitive changes are detectable years prior to a diagnosis of vascular dementia [2]. There remains little consensus on the best method to capture and quantify these more subtle changes in cognitive performance. Traditionally, in more progressed stages, cognitive impairment has been determined by comparing performance against cut-off scores from normative data or reference group means, but these methods show limited sensitivity to the cognitive changes emerging in preclinical AD [3]. Recently, there has been a shift towards monitoring individual variation in cognitive performance either between cognitive domains (cognitive dispersion) or within repeated trials of a neuropsychological test (intra-individual variability) at one or several time-points. Here, we will use the term cognitive dispersion to denote all approaches of variation assessment.

In older adults, dispersion estimates have been associated with reduced white matter volumes in frontal and parietal regions and the corpus collosum [see 4 for review], accelerated atrophy in entorhinal and hippocampal regions [5], as well as levels of amyloid beta [6,7] and neurofibrillary tangles [8], across healthy individuals and those with mild cognitive impairment (MCI) and AD dementia. Furthermore, dispersion estimates vary with severity of cognitive impairment [9] and baseline dispersion scores are associated with subjective memory complaints [10] as well as increased risk and shorter conversion times for dementia in longitudinal studies [11,12]. Holtzer *et al* [13] demonstrated a significant association between incident dementia and baseline dispersion scores even after adjusting for education, gender, comorbidities and baseline cognitive performance. More recently, other cohort studies have included biological risk factors into their models, finding that dispersion estimates performed comparably with ApoEe4 genotype and hippocampal volume [11] and independently improved

model fit compared to CSF analytes [14] in predicting AD. Only one cross-sectional study has explored the influence of protective factors, finding that an engaged lifestyle reduced the likelihood of being classified as MCI but not AD in models including a dispersion index that itself independently predicted AD but not MCI classification [15]. The influence of lifestyle factors, such as engagement in physical and cognitive stimulating activities, alongside cognitive dispersion metrics to predict dementia incidence longitudinally is yet to be examined.

Our understanding of cognitive dispersion in older adults is still vague, given that some studies demonstrate that cognitive dispersion increases with advancing age [16], while other studies show a decrease [17]. These heterogenous findings may be a function of study sample age, since participants aged 65 – 80 years show increased dispersion with age, while those older than 80 years at baseline show reduced dispersion towards terminal decline [18].

There is a dearth of studies exploring cognitive dispersion in oldest-old individuals and consequently of its subsequent importance. Cross-sectional analyses found that cognitive dispersion predicted functional disability in an oldest-old sample (>80 years) of nursing home and community-dwelling residents [17] and baseline dispersion scores across domain subscales of a global cognitive measure predicted 18-month cognitive decline from baseline in a centenarian sample [19].

To our knowledge, no study has so far assessed whether cognitive dispersion might be useful in the prediction of incident dementia in the very old. Similarly, findings regarding the influences of biological, health and lifestyle factors upon cognition and dementia incidence in this age-group are inconsistent [20]. Therefore, the aims of the current work were to assess the relative predictive value of cognitive dispersion, alongside other dementia risk and protective factors, as well as existing comorbidities, for the development of dementia in an eight-year cohort of the oldest-old who were free of dementia at the time of enrolment.

Methods

Study design, participants and cohort information for The Origins of Variance in the Old-Old: Octogenarian Twins (OCTO-Twin study) is found in Appendix A. The study received approval from the Ethics Committee at the Karolinska Institute in Stockholm and from the Swedish Data Inspection Authority in Sweden.

Dementia diagnosis information is shown in Appendix A. Neuropsychological tests are reported in Appendix A and described elsewhere [21]. A dispersion score was created according to previous criteria [13]. Raw scores of each test were z-transformed on the basis of the distribution of scores from the sample and the variability between scores was calculated across the eight tests within the full assessment. A global cognitive composite (GCC) was also created by summing the z-scores of each task and dividing by the number of tasks. See Appendix A for formulae.

Statistical analyses

To assess the relationship between cognitive dispersion and subsequent dementia, we performed generalised Cox regression analyses using the Weibull distribution, with study time as the time scale for all analyses. Detailed information on the models building procedures as well as the assessment of model fit are provided in Appendix B. We excluded participants with missing values in the predictor variables, as well as those with an MMSE score <=24, leaving a total sample size of 421 participants.

Results

Baseline characteristics of the full cohort are shown in Table 1. The number of participants receiving a dementia diagnosis within the follow-up period was 87 (20.7%). During the study 382 participants died, of whom 86 developed dementia.

The model indicated significant positive associations between baseline cognitive dispersion scores and ApoEe4 carrier status with dementia diagnosis. No other factors contributed a significant association with this outcome (see Table 2). The estimated Log-hazards changed with increasing cognitive dispersion and for each time point (see Figure 1). For further ease of interpretation, Figure 2 shows the predicted risk for cognitive dispersion for each year in the study.

Additional analyses revealed that cognitive dispersion and ApoEe4 remained significantly associated with dementia diagnosis, even after entering the GCC into the model (see Table 3). Predicted risk over time by cognitive dispersion values are shown in Appendix C, Figure S1. The different models a). with only cognitive dispersion; b). with only GCC; and c). with both cognitive dispersion and GCC were compared. Information criteria for separate models are shown in Appendix B, Table S1. The AIC and BIC values were slightly lower for the GCC-only model compared with the cognitive dispersion-only model. However, likelihood ratio tests revealed that cognitive dispersion and GCC entered together in the same model, was superior to either predictor entered into the full model alone (all $p < 0.001$). The correlation between GCC scores and cognitive dispersion indices was small ($r=-0.25$).

A sensitivity analysis, with CES-D scores entered into the model (n=407 due to missing CES-D data), revealed that the significant positive associations between baseline cognitive dispersion scores and ApoEe4 carrier status with dementia diagnosis persisted; shown in Table S2.

Discussion

In the present study, we investigated the predictive value of cognitive dispersion scores, in relation to established AD risk factors, comorbidities and protective lifestyle indicators, for the incidence of dementia in a longitudinal cohort of older adults who were free of dementia symptoms at baseline.

Our main finding is that cognitive dispersion, along with ApoEe4, was the strongest predictor of receiving a dementia diagnosis within eight years of follow-up. To our knowledge, this is the first longitudinal study of the oldest-old that examined the role of cognitive dispersion as a predictor of dementia risk.

Our results indicate that in very advanced aged, at least, cognitive dispersion and ApoEe4 genotype, are more valuable predictors of incident dementia, than other AD risk factors, medical illness and lifestyle habits, such as engagement with physical exercise and cognitively stimulating activities. In a slightly younger cohort [mean age (SD), 78.6 (5.3)], cognitive dispersion was significantly associated with incident dementia, after controlling for a range of variables similar to our own: gender, education and a medical illness index [13]. In another younger cohort [mean age (SD), 73.66 (7.01)], cognitive dispersion at baseline predicted incident MCI and AD and higher cognitive dispersion was associated with shorter conversion times to these clinical categories, even after controlling for ApoEe4 and hippocampal atrophy [11]. In the same cohort, cognitive dispersion independently improved the prediction model fit for incident AD when compared against other cerebrospinal fluid (CSF) analytes [14]. Our model did not include imaging or CSF biomarkers as these were not available as part of the study procedures. Compared to neural imaging and CSF ascertainment, genotyping from serum or saliva samples is comparatively less invasive procedure and does not require repeated evaluations making it possibly more feasible in oldest-old age groups. A previous analysis

using the same cohort here, found that ApoEe4 status predicted level of memory performance and steeper rates in memory decline, when controlling for age, sex, education and medical illness but that these associations disappeared when dementia diagnosis was entered as a covariate, indicating that the negative effect of ApoEe4 on cognition is strongly related to dementia incidence [22]. We found that our cognitive dispersion metric remained significantly associated with dementia diagnosis in our model even when including ApoeEe4 status, suggesting that a cognitive dispersion metric alone might be sufficient in identifying individuals at greater risk for the development of dementia in this age group. Nonetheless, much like Praetorius *et al's* study, our finding that ApoEe4 carrier status is predictive of dementia in our oldest-old cohort contradicts several studies proposing that ApoEe4 carrier risk for dementia decreases with very advanced age [23] and suggests that its relative importance in dementia prediction models for this age group should be re-assessed.

Age at baseline, gender, education, SES and several comorbidities, such as vascular (e.g. stroke, hypertension) or metabolic abnormalities (diabetes), did not influence the outcome. The age range for the cohort is naturally limited relative to younger cohorts and this might have restricted the predictive value of these variables in our study. While the underlying processes are not fully characterised, associations of health-related risk factors with dementia do appear to differ according to life-stage and these may pose their principal influences on the development of later-life dementia during mid-life [24].

We also did not find an association between lifestyle indicators, such as engagement with physical exercise and cognitively stimulating activities, with dementia risk. This agrees with previous research conducted in the oldest-old [25], although some other studies have reported that participation in cognitively stimulating activities and physical exercise in very old-age is found to be associated with lower dementia risk at this life stage [20,26]. Our lifestyle indicators were based on simple yes/no responses to a simple question in each category and

possess only face validity. A more detailed lifestyle interview may have found some protective associations with our outcome. Alternatively, our results might reflect the possibility that underlying neural pathologies may have accumulated to such an extent in the participants or that other unknown resilience factors associated with extreme longevity may have mitigated the predictive value of lifestyle factors at this late-age.

We computed a global cognitive composite to estimate average cognitive performance at baseline. When these latter scores were entered into the model, both cognitive dispersion and ApoEe4 remained significantly associated with dementia diagnosis, suggesting that cognitive dispersion metrics may possess incremental validity over mean test performance in predicting future cognitive impairment in the very old. Sensitivity analyses revealed that when both cognitive dispersion scores and global cognitive composite scores were entered into the full model, this combination performed better than models in which either predictor was entered alone. We also found that cognitive dispersion scores correlated poorly with global cognitive composite scores, suggesting that these indices might capture distinct phenomena of aging or, cognitive decline. Recently, there has been a strong interest in the use of global composite measures to detect and track cognitive decline in clinical trials [e.g. 27]. Our findings imply that cognitive dispersion, which itself is a composite of average variations in cognitive performance, might represent an alternative or adjunct measure more suitable for these clinical research efforts.

This study in not without shortcomings. While the dementia diagnosis did make use of clinical criteria, we did not differentiate between dementia types (e.g. AD, vascular dementia, or mixed) and thus we cannot comment on whether our dispersion index is less or more sensitive to dementia with distinct pathological and cognitive profiles, given the set of neuropsychological tests available here. Holtzer et al [13] found that dispersion was sensitive to both AD and vascular dementia subtypes in their sample, suggesting that dispersion may

index the sum of disease processes to various brain regions or networks rather than a specific isolated region. Clinically, this may mean that dispersion, at a baseline assessment at least, is useful as a screening tool to differentiate healthy individuals from those with pending dementia diagnoses but limited in terms of its specificity or ability to differentiate between dementia subgroups. Future work including other dementia subtypes and pathologies is needed to realise the metric's differential diagnostic potential. Better characterisation of oldest-old cohorts, at the biological and cognitive level, could become possible with the advent of existing middle-older-adult cohorts (60 years plus). This will also offer the opportunity to explore lifelong cognitive, medical and lifestyle factors on dementia development in very advanced age. Finally, the study did not consider death as a competing risk within our models. Cognitive change in later adulthood may be driven by an individual's proximity to their death and is observed through a steeper decline in cognitive abilities a few years before this event [28]. Greater baseline dispersion scores were associated with increased risk of death five to eight years later in one study of cognitively normal community-dwelling elders (60-94 years old). However, this relationship was partially explained by cardiovascular factors, indicating that dispersion may be a proxy for health status [10]. Although our study was focussed on dementia outcome, and not mortality, and we did control for medical illnesses such as diabetes, stroke and high blood pressure, it is possible that our study failed to capture terminal decline and/or other comorbidities that may have influenced the observed associations. Finally, the dispersion metric adopted in the current study is the most widely used in dementia research [e.g. 8,13,29]. Nonetheless, other metrics, such as coefficient of variation (CoV, a ratio of the intra-individual standard deviation and intra-individual mean performance), are available. The CoV is usually applied upon reaction time data within tasks assessing this over several trials; it is distinct from our metric, in that it accounts for overall performance, thereby mitigating confounds associated

with the mean. However, the CoV has been criticised for obscuring underlying contributions towards any observed effects that might be explained by mean performance [30].

In conclusion, our findings underscore the usefulness of cognitive dispersion for predicting dementia diagnoses in the very old. They also highlight the influence of ApoEe4 in dementia development and concur with previous studies' [25] findings that health and lifestyle factors pose little impact upon this outcome in very advanced age. Future work examining cognitive dispersion in adults from middle, older and oldest-old age-groups and its relation to biological and modifiable factors will further delineate its role over the lifespan as well as its value as a marker of insidious disease onset.

Conflicts of Interest

None.

Declaration of Sources of Funding

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Table 1. Cohort baseline characteristics

	Full cohort (N=421)
Age (SD)	82.25 (2.57)
Years of education (SD)	7.28 (2.24)
MMSE (SD)	27.97 (1.66)
BMI (SD)	24.57 (3.68)
Gender (%)	
Male	145 (34.44)
Female	276 (65.56)
SES (%)	
High	232 (55.11)
Low	189 (44.89)
ApoEe4 (%)	102 (24.23)
Cognitively inactive (%)	259 (61.52)
Physically Inactive (%)	143 (33.97)
Stroke ever (%)	69 (16.39)
Diabetes ever (%)	51 (12.11)
High BP ever (%)	188 (44.66)
CES-D (SD)	7.82 (7.3) (n=407)

MMSE – Mini-mental Status Exam; SES – Socioeconomic status; CES-D – Center for Epidemiologic Studies Depression Scale.

Table 2. Regression coefficients derived from generalised Cox regression for final model

Variable	Coefficient (SE)	p-Value
Baseline Hazard 1	-11.20 (3.95)	0.01
Baseline Hazard 2	-7.88 (3.82)	0.04
Baseline Hazard 3	-7.595 (3.83)	0.05
NPH (cogd, time):1	-1.597 (1.93)	0.41
NPH (cogd, time):2	**2.53 (0.70)**	**< 0.001**
NPH (cogd, time):3	**-3.28 (1.03)**	**0.002**
NPH (cogd, time):4	**2.04 (0.97)**	**0.04**
Cognitively inactive (yes vs. no)	0.29 (0.23)	0.21
Physically inactive (yes vs. no)	-0.10 (0.24)	0.68
BMI	0.02 (0.03)	0.55
SES (Low vs. High)	0.15 (0.24)	0.52
Gender (Female vs. Male)	-0.33 (0.23)	0.15
Years of education	-0.03 (0.06)	0.64
Age at baseline	0.06 (0.05)	0.19
Stroke ever (yes vs. no)	0.02 (0.32)	0.96
High BP ever (yes vs. no)	-0.04 (0.23)	0.86
Diabetes ever (yes vs. no)	0.34 (0.31)	0.27
Zygosity (yes vs. no)	-0.12 (0.22)	0.59
ApoEe4 (yes vs. no)	**0.62 (0.24)**	**0.01**

Note: NPH- nonproportional hazards; cogd – cognitive dispersion; BMI – body mass index; SES – social economic status; cogd was modelled with an NPH spline with one knot positioned at 4 (study time)

Table 3 - Regression coefficients derived from generalised Cox regression in OCTO (including the global composite score)

Variable	Coefficient (SE)	p Value
Baseline Hazard 1	-9.45 (4.04)	0.02
Baseline Hazard 2	-6.09 (3.91)	0.12
Baseline Hazard 3	-5.69 (3.93)	0.15
NPH (cogd, time):1	-1.78 (1.96)	0.36
NPH (cogd, time):2	**2.37 (0.72)**	**0.001**
NPH (cogd, time):3	**-3.54 (1.05)**	**< 0.001**
NPH (cogd, time):4	1.63 (0.98)	0.096
Cognitively inactive (yes vs. no)	0.14 (0.24)	0.56
Physically inactive (yes vs. no)	-0.14 (0.24)	0.57
BMI	0.01 (0.03)	0.78
SES (Low vs. High)	0.07 (0.24)	0.77
Gender (Female vs. Male)	-0.30 (0.23)	0.195
Years of education	0.03 (0.06)	0.65
Age at baseline	0.04 (0.05)	0.41
Stroke ever (yes vs. no)	-0.02 (0.31)	0.96
High BP ever (yes vs. no)	-0.04 (0.23)	0.87
Diabetes ever (yes vs. no)	0.36 (0.31)	0.25
Zygosity (yes vs. no)	-0.01 (0.23)	0.97
ApoEe4 (yes vs. no)	**0.47 (0.24)**	**0.05**
Global Composite Score	**-0.64 (0.197)**	**0.001**

Note: NPH- nonproportional hazards; cogd – cognitive dispersion; BMI – body mass index; SES – social economic status; cogd was modelled with a NPH spline with one knot positioned at 4 (study time)

Figure 1. Estimated log hazards over time from full model

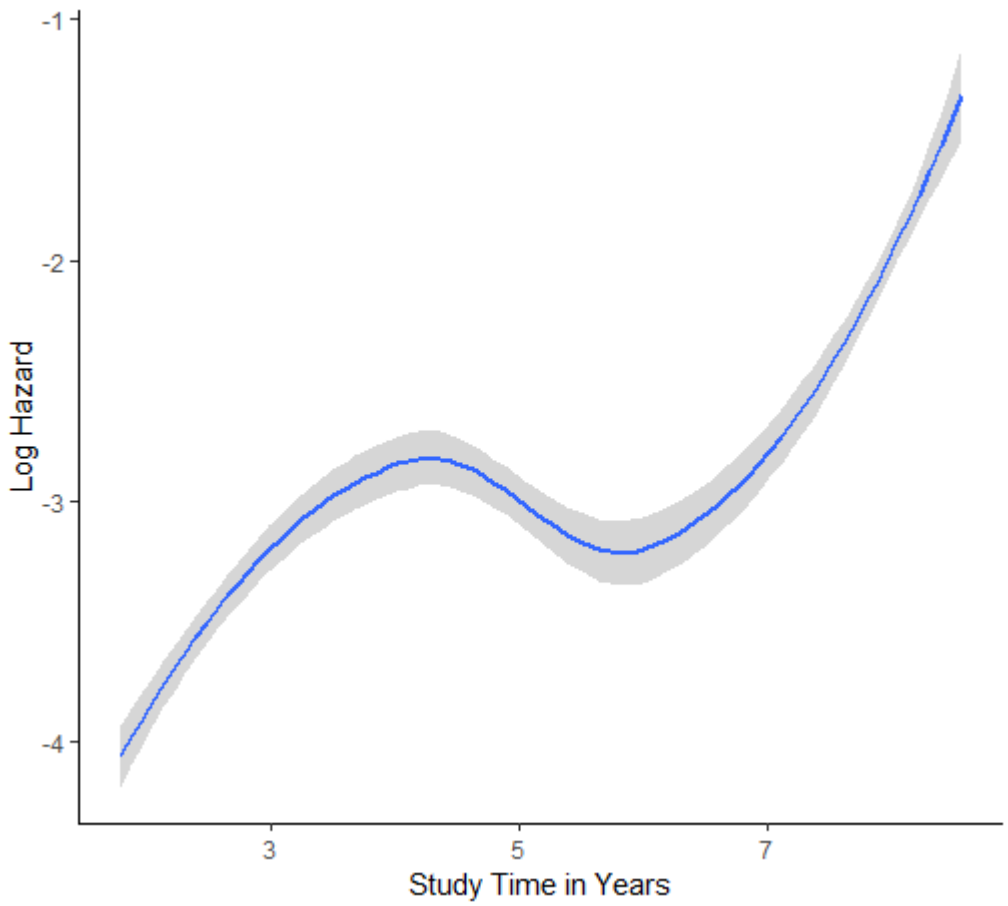
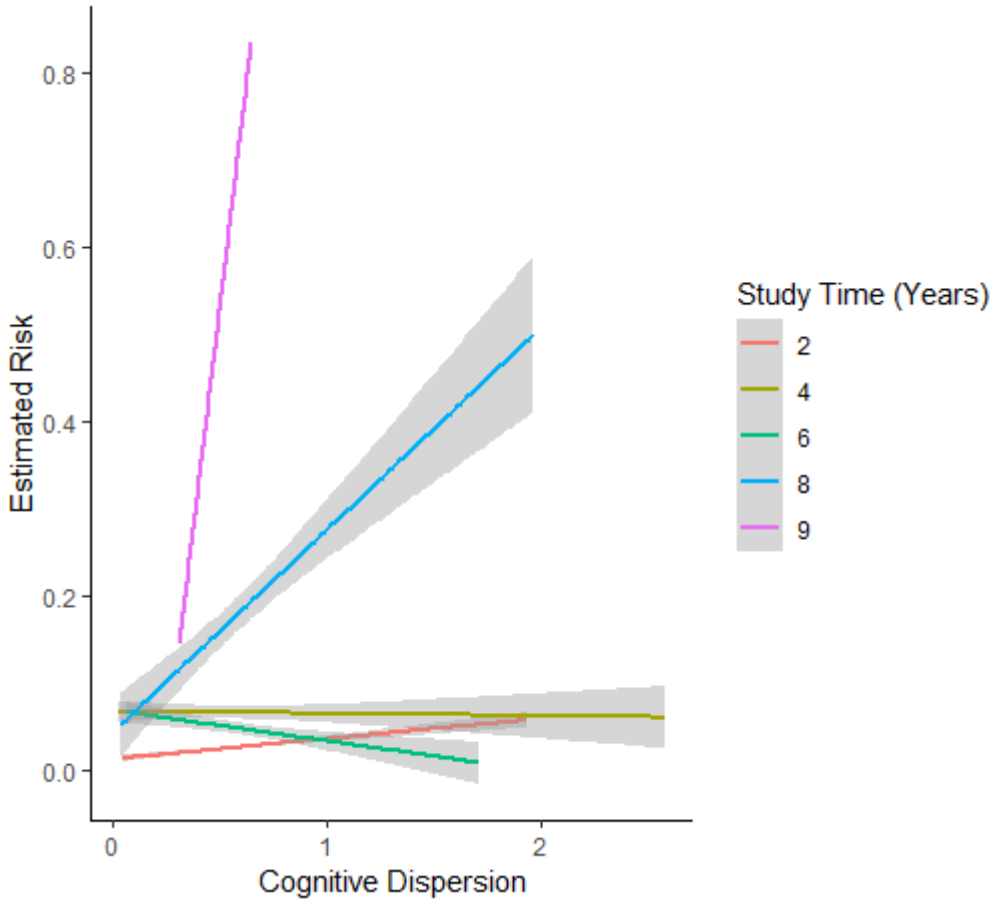


Figure 2. Predicted Risk for Cognitive Dispersion for each Year in the Study from full model



Cognitive dispersion and ApoEe4 genotype predict dementia diagnosis in 8 years follow-up of the oldest-old: Supplementary Materials

Appendix A

Study design, participants and cohort

The Origins of Variance in the Old-Old: Octogenarian Twins (OCTO-Twin study) is based in the Swedish Twin Registry and includes 702 participants born in 1913 and earlier, who were, or became, 80 years of age during the first data collection period (1991–1993). Participants were examined at two-year intervals, for a total of up to eight years of follow-up. The average attrition rate from one testing wave to the next was 20% (10% per year), in the majority of cases this was because of death.

Dementia diagnosis

Dementia was diagnosed according to the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders Third Edition[1] and by consensus from a multidisciplined team comprising a physician, a research nurse and two neuropsychologists, who reviewed the cognitive test results and medical records at each new wave. The Mini-Mental Status Evaluation (MMSE)[2] was also performed to assess global cognitive functioning. Further to meeting DSM-III criteria by clinical consensus, we also excluded participants whose MMSE performance at baseline fell within accepted criteria for either suspected mild cognitive impairment or dementia, i.e. MMSE score <=24.

Cognitive dispersion score

Neuropsychological testing at each wave visit included: Digit span forward, Digit span backward, Prose recall, Block design, Synonyms, Information Test, Digit Symbol, Figure Reasoning. Cognitive dispersion scores were created using the method described by Holtzer *et al* (2008). The method applies a z-transformation to the raw scores of each test using parameters from the distribution of the entire sample, and then, the application of the formula:

$$Dispersion = \sqrt{\frac{\sum_{k=1}^{k=N}(T_{ik}-S_i)^2}{K-1}}$$

where T_{ik} is the *k*-th test for participant *i, K* is the number of tests, and S_i is participant *i*'s mean of the transformed scores.

Global cognitive composite score

A global cognitive composite was also created by summing the individual z-scores of all test scores and dividing by the number of tests.

Sociodemographic, Health and Lifestyle factors

Sociodemographic information was recorded as age, years of formal education and gender. Socioeconomic status (SES) was determined by asking "What has been your main occupation for most of your working life (during the longest period)?" and the responses were coded into low (manual occupations), medium (non-manual occupations) and high (intermediate and professional occupations) according to the Swedish Criteria Group for Occupational Standards (SCG) of the Swedish National Institute for Working Life (NIWL). Body mass index (BMI) was determined by dividing the participants weight in kilograms by their height in meters. Medical histories were taken to determine if participants had a history or diagnosis of stroke, high blood pressure or diabetes according to clinical criteria.[3] [see 22][see 21]ApoEe4 genotyping was performed on blood samples obtained at the baseline visit; this procedure has been described previously.[4] Carrier status was operationalised as carrying at least one allele. Lifestyle indicators were also recorded. Participants were asked "Do you train your body?" and "Do you train your mind?" to gauge engagement in physical and cognitive stimulating activities, respectively. Participants answered "yes" or "no". We also adjusted for zygosity, some participants were monozygotic (n=182) and others were dizygotic (n=239). Depression scores were recorded using the Centre for Epidemiologic Studies Depression Scale (CES-D).[5]

[1] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-III-R, third ed.*

American Psychiatric Association, Washington, DC. 1987.

[2] Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189–98. doi:10.1016/0022-3956(75)90026-6

[3]Reynolds, C.A., Hong, M.-G., Eriksson, et al, 2010. Analysis of lipid pathway genes indicates association of sequence variation near SREBF1/TOM1L2/ATPAF2 with dementia risk. Hum. Mol. Genet. 19, 2068–2078. https://doi.org/10.1093/hmg/ddq079

[4] Praetorius M, Thorvaldsson V, Hassing LB, *et al.* Substantial effects of apolipoprotein E epsilon4 on memory decline in very old age: longitudinal findings from a population-based sample. *Neurobiol Aging* 2013;**34**:2734–9. doi:10.1016/j.neurobiolaging.2013.06.002

[5] Radloff LS. The CES-D Scale: A Self-Report Depression Scale for Research in the General Population. *Appl Psychol Meas* 1977;**1**:385–401. doi:10.1177/014662167700100306

Appendix B

Cox regression model building

We included sociodemographic, genetic, health, lifestyle variables as well as zygosity and a global cognitive measure in our models. Study time was used as time scale for all analyses. To compute the full generalised Cox regression model, first, we tested if each predictor variable complied with the proportional hazards (PH) and/ or the log-linearity (LL) assumption. To test these assumptions each predictor variable was entered into a Cox model, a model relaxing the PH assumption, a model relaxing the LL assumption, and in a model relaxing both assumptions simultaneously. These flexible models use B-splines, which are piecewise polynomials, where the pieces are joint by knots. Here, the splines can have one or two knots. The knot selection has to follow one criterion: there must be roughly the same number of events in the subintervals defined by the selected knots. The decision if one or two knots are used is based on a goodness of fit test (i.e. Akaike information criterion, AIC). See Table S1, below. The computed models were compared by likelihood ratio test, and the best fitting model for each predictor variable was selected. All predictor variables were entered into the full model, while modelling each predictor with the best-identified knot and spline combination. Lastly, after fitting the model with all identified splines and knots, spline coefficients were eliminated systematically. We reduced spline coefficients if more than one coefficient was non-significant for a predictor, while comparing the smaller model with the previous one by likelihood ratio test – until the best fitting model was found. The full model included sociodemographic variables (age, gender, socio-economic status); established AD risk factors (ApoEe4 genotype; BMI) and comorbidities (history of stroke, high blood pressure, diabetes), zygosity and lifestyle indicators (engagement in cognitively stimulating activities; engagement in physical exercise). An additional model also included the global cognitive composite score.

All analyses were performed in R Studio Version 3.5.1 (R Core Team, 2018[1]) and the packages "flexrsurv"[2] "survival"[3] and "ggplot2"[4] were used.

Table S1. Comparison of models for likelihood criteria

AIC		BIC	
Dispersion index	Cognitive composite	Dispersion index	Cognitive composite
707.38	711.02	784.19	787.83

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

[1]R Core Team, 2018. R: A language and environment for statistical computing. R Foundation for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

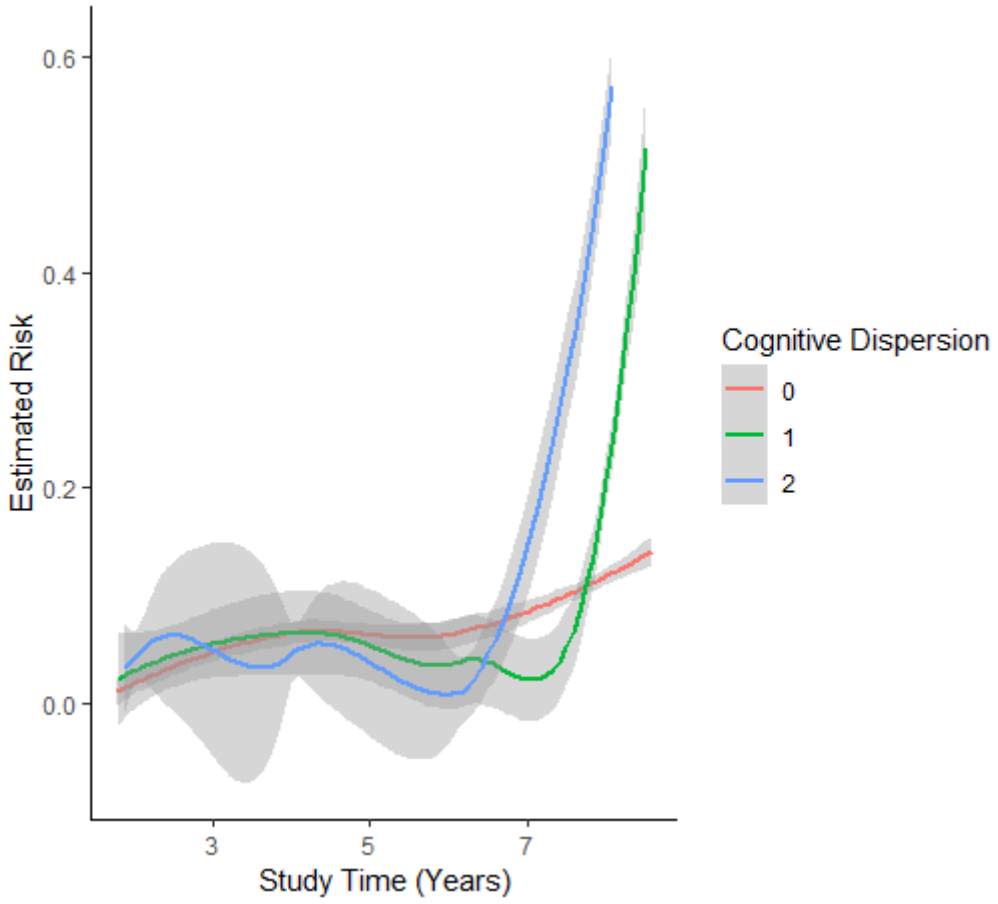
[2]Clerc-Urmès I, Grzebyk M, Hédelin G, C. working survival group., 2020. flexrsurv: An R package for relative survival analysis_. R package version 1.4.1, < [WWW Document]. URL https://cran.r-project.org/package=flexrsurv%3E

[3]Therneau T, 2015. A Package for Survival Analysis in S_. version 2.38, [WWW Document]. URL https://cran.r-project.org/package=survival%3E.

[4]Wickham, H., 2016. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag, New York, USA.

Appendix C

Figure S1. Predicted Risk over Time by Cognitive Dispersion Values from full model



Appendix D

Sensitivity analysis with depression scores entered into the model on smaller sample (n=407)

Table S2 - Regression coefficients derived from generalised Cox regression in OCTO (including Center for Epidemiologic Studies Depression Scale (CES-D))

Variable	Coefficient (SE)	p Value
Baseline Hazard 1	-11.01 (4.14)	0.01
Baseline Hazard 2	-7.62 (4.03)	0.06
Baseline Hazard 3	-7.47 (4.04)	0.06
NPH (wpv, time):1	-1.597 (1.95)	0.41
NPH (wpv, time):2	**2.398 (0.71)**	**< 0.001**
NPH (wpv, time):3	**-3.09 (1.04)**	**0.003**
NPH (wpv, time):4	**2.08 (0.999)**	**0.04**
Cognitively inactive (yes vs. no)	0.36 (0.24)	0.14
Physically inactive (yes vs. no)	-0.07 (0.25)	0.78
BMI	0.02 (0.03)	0.62
SES (Low vs. High)	0.21 (0.25)	0.39
Gender (Female vs. Male)	-0.23 (0.24)	0.35
Years of education	-0.03 (0.06)	0.64
Age at baseline	0.05 (0.05)	0.26
Stroke ever (yes vs. no)	-0.003 (0.32)	0.99
High BP ever (yes vs. no)	-0.03 (0.23)	0.91
Diabetes ever (yes vs. no)	0.38 (0.32)	0.24
Zygosity (yes vs. no)	-0.19 (0.23)	0.40
ApoEe4 (yes vs. no)	**0.66 (0.24)**	**0.01**
CES-D	0.02 (0.02)	0.22

Note: NPH- nonproportional hazards; cogd – cognitive dispersion; BMI – body mass index; SES – social economic status; cogd was modelled with a NPH spline with one knot positioned at 4.15 (study time); due to missing values for CES-D this model was derived from a sample N= 407