ONLINE SUPPLEMENAL MATERIAL 1

Cognitive test descriptions

Mini-Mental State Examination (MMSE)

The MMSE is a brief mental status test measuring orientation, concentration, immediate and delayed memory, language and constructional praxis. (1) Scores range from 0 to 30, with higher scores indicating better cognitive performance. The MMSE has been administered in the BLSA since the mid-1980s.

Benton Visual Retention Test (BVRT)

The BVRT is a test of short-term visual memory and constructional abilities.(2) Administration A has been used in the BLSA since 1960, with a modified error scoring system, based on the BVRT Manual scoring, such that higher scores indicate poorer visual memory.

California Verbal Learning Test (CVLT)

The CVLT is a 16-item shopping list measuring verbal learning and memory. The variables of interest in this study were List A sum across five learning trials and long delay free recall. Scores ranged from 0 to 80 for List A sum and 0 to 16 for long delay free recall. Higher scores indicate better verbal memory. The CVLT has been administered in the BLSA since 1993, and is described in detail elsewhere. (3)

Verbal Fluency Tests (VFT-L and VFT-C)

The verbal fluency measures of both letter (F, A, S) (4-5) and category (fruits, animals, vegetables) fluency (6) were included. Letter fluency measures phonemic, and category fluency measures semantic fluency. Participants were required to generate as

many words as possible starting with either a specific letter or category, for 60 seconds. Higher scores indicate better verbal fluency, with the total number of words, minus intrusions and perseverations analyzed for each test. The verbal fluency tests have been administered in the BLSA since the mid 1980s.

Trails A and B

Trail Making Tests A and B (Trails A and B) are tests of attention (Trails A) and executive functioning (Trails B), specifically cognitive control and visuo-motor scanning. (7) When errors were committed the participant corrected the error by returning to his/her last correct response and continuing from there. The stop-watch recorded the time while corrections were made. Scores reflected time to completion (in seconds) separately for Trails A and B. Higher scores indicate poorer performance.

Digits Span Forward (DS-F) and Backward (DS-B)

The Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span Forward and Backward tests (8) assess attention and working memory, respectively. Digits forward involves orally presenting a series of single digit numbers at increasing digit span lengths, for participants to repeat in the same order. The span length of numbers ranges from three to nine digits. Two trials at each span are presented. The test is discontinued when the participant incorrectly repeats both trials at a specified span. Digits backward is similar to digits forward, except that participants repeat a series of increasingly longer spans of single digit numbers in reverse order. The length of the span of numbers ranges from two to eight digits. Total scores for digits forward and backward are 14.

References:

1. 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.
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3. Delis DC, Freeland J, Kramer JH, Kaplan E. Integrating clinical assessment with cognitive neuroscience: construct validation of the California Verbal Learning Test. J Consult Clin Psychol 1988;56:123-30.
4. Lezak MD. Neuropsychological assessment, 2nd edition. New York: Oxford University Press, 1983.
5. Lezak MD. Neuropsychological assessment, 3rd edition. New York: Oxford University Press, 1995.
6. Rosen W. Verbal fluency in aging and dementia. Journal of Clinical Neuropsychology 1980;2:135-146.
7. Reitan R. Trail Making Test: Manual for Administration and Scoring. Tucson, AZ: Reitan Neuropsychological Laboratory, 1992.
8. Wechsler D. WAIS-R manual. Cleveland: The Psychological Corporation, 1981.

ONLINE SUPPLEMENAL MATERIAL 2

Linear mixed models for prediction of cognitive performance, factor analysis of LARCC

A standard taxonomy of models (1) was used, starting from the unconditional means model (Model A), unconditional growth model (Model B), growth model with level-2 controlled effects of other factors namely sex, race/ethnicity, education and smoking status (Model C), growth model with level-2 controlled effects of other factors, adding a squared-age term that would allow the rate of change to vary with time (Model D). In all models, age was centered at 50 years, while education was centered at 16 years. The following equations apply to each of the models considered:

Model	Level-1 model	Level-2 model	Composite model
A	$Y_{ij} = \pi_{0i} + \varepsilon_{ij}$	$\pi_{0i} = \gamma_{00} + \zeta_{0i}$	$Y_{ij} = \gamma_{00} + (\zeta_{0i} + \varepsilon_{ij})$
B	$Y_{ij} = \pi_{0i} + \pi_{1i} Age_{50} + \varepsilon_{ij}$	$\pi_{0i} = \gamma_{00} + \zeta_{0i}$ $\pi_{1i} = \gamma_{10} + \zeta_{1i}$	$Y_{ij} = \gamma_{00} + \gamma_{10} Age_{50} + (\zeta_{0i} + \zeta_{1i} Age_{50} + \varepsilon_{ij})$
C	$Y_{ij} = \pi_{0i} + \pi_{1i} Age_{50} + \varepsilon_{ij}$	$\pi_{0i} = \gamma_{00} + \sum_{k=1}^{7} \gamma_{0k} Z_{ik} + \zeta_{0i}$ $\pi_{1i} = \gamma_{10} + \sum_{k=1}^{7} \gamma_{1k} Z_{ik} + \zeta_{1i}$	$Y_{ij} = \gamma_{00} + \sum_{k=1}^{7} \gamma_{0k} Z_{ik} + \gamma_{10} Age_{50} + \sum_{k=1}^{7} \gamma_{1k} Z_{ik} Age_{50} + (\zeta_{0i} + \zeta_{1i} Age_{50} + \varepsilon_{ij})$
D	$Y_{ij} = \pi_{0i} + \pi_{1i} Age_{50} + \varepsilon_{ij}$	$\pi_{0i} = \gamma_{00} + \sum_{k=1}^{7} \gamma_{0k} Z_{ik} + \zeta_{0i}$ $\pi_{1i} = \gamma_{10} + \sum_{k=1}^{8} \gamma_{1k} Z_{ik} + \zeta_{1i}$	$Y_{ij} = \gamma_{00} + \sum_{k=1}^{7} \gamma_{0k} Z_{ik} + \gamma_{10} Age\ 50 + \sum_{k=1}^{8} \gamma_{1k} Z_{ik} Age_{50} + (\zeta_{0i} + \zeta_{1i} Age_{50} + \varepsilon_{ij})$

Notations: Y_{ij} is the response variable for each individual "i" and age at visit "j". π_{0i} is the level-1 intercept for individual i; π_{1i} is the level-1 slope for individual i; γ_{00} is the level-2 intercept of the

random intercept π_{0i}; γ_{10} is the level-2 intercept of the slope π_{1i}; Z_{ik} is a vector of fixed covariates for each individual i that are used to predict level-1 intercepts and slopes; ζ_{0i} and ζ_{1i} are level-2 disturbances; ε_{ij} is the within-person level-1 disturbance. In model D, an additional Z_{ik} variable is added for Age_{50}, to account for quadratic age changes in the fixed effects portion of the model, which increased the number of k terms from 7 to 8 between models C and D.

Model D's improvement in fit compared to the simpler models was evaluated using Deviance, AIC and BIC statistics as well as pseudo-R^2. In addition, residuals were plotted against predicted values to assess their normality. It is worth noting that the models were fit using the entire BLSA cohort (n=3005) and not only those who were eligible for the main analysis to improve reliability of predicted estimates. Finally, empirical Bayes estimators of outcomes Y_{ij} were predicted from Model D at specific ages using the following method, after estimating the random effects (ζ_{0i} for the intercept and ζ_{1i} for the slope) for each individual *i*:

Intercept $$\pi_{0i} = \gamma_{00} + \sum_{k=1}^{7} \gamma_{0k} Z_{ik} + \zeta_{0i}$$

Slope $$\pi_{1i} = \gamma_{10} + \sum_{k=1}^{8} \gamma_{1k} Z_{ik} + \zeta_{1i}$$

Prediction $$Y_{ij} = \pi_{0i} + \pi_{1i}(Age_{50})_i$$

where $(Age_{50})_l$ is assigned individual mean age at follow-up values centered at age 50, thus positive values if Age>50 and negative values if Age<50.

Y_{ij} in this case is the cognitive score for a specific test j and individual i. Slopes π_{1i} were estimated for each test j and individual i, taking into account non-linear changes with age (i.e. the age-square term) at individual-level mean follow-up age and those were labeled as LARCC (Longitudinal annual rate of cognitive change) and interpreted as annual rate of change in each cognitive score between ages 50 y and mean follow-up age.

Following this estimation, LARCC for each cognitive test score were entered into a factor analysis model as measured variables (2) in which a number of common factors were extracted

based on common variance, factor loadings estimated and the residual variance labeled as uniqueness for each LARCC. The common factor model can be summarized as follows:

$$\text{LARCC}_i = \sum_{j=1}^{k} \lambda_{ij} * Domain_j + \varphi_i$$

Where LARCCi is the standardized z-score for each cognitive test LARCC, λ_{ij} is the factor loading for each LARCC and each factor, Domain_j is the standardized z-score for each factor j, and φ_i is the residual error, the squared value of which is the uniqueness. The sum of squared factor loadings for each LARCC_i is the communality or the common variance that is accounted for by the extracted factors.

An eigenvalue>1 rule was used and the scree plot was observed to determine the adequate number of extracted factors that would produce the best model fit. The factor loadings were then rotated using varimax orthogonal rotation and the factors were interpreted and cognitive domains labeled accordingly, with cutoff point of 0.40 or more for significant loading. The factor scores (*z*-scores) were predicted and used as markers of LARCC for specific cognitive domains.

Appendix Table 1. Varimax rotated two-factor solution of LARCC, using nine cognitive test scores LARCC as measured variables.

	Factor loadings, λ_{ij}		**Uniqueness, φ_i**
LARCC_i	Domain 1	Domain 2	
BVRT	-0.62*	-0.27	0.54
CVLT-List A	+0.84*	0.12	0.29
CVLT-DR	+0.82*	-0.06	0.33
VFT-L	+0.26	+0.59*	0.58
VFT-C	+0.16	+0.43*	0.79
Trails A	-0.44*	-0.33	0.70
Trails B	-0.56*	-0.51*	0.42
DS-F	-0.26	+0.48*	0.70
DS-B	+0.07	+0.65*	0.57
Eigenvalue	2.92	1.15	
% var explained	0.57	0.39	

Note: See list of abbreviations.

*factor loading>0.40. Domains were labeled as follows: "Domain 1: "Memory and executive function: earlier decline", Domain 2: "Verbal fluency and attention: later decline", based on the combination of significantly high factor loadings and the corresponding measured variables or LARCC_i. With the exception of Trails B, all LARCC_i factor loadings were significant only for one of the two domains, creating a relatively simple structure that is easy to label and interpret. The labels were determined based on the nature of the cognitive test and the timing that decline in those domains is usually observed during the life course (earlier vs. later).

Sources:

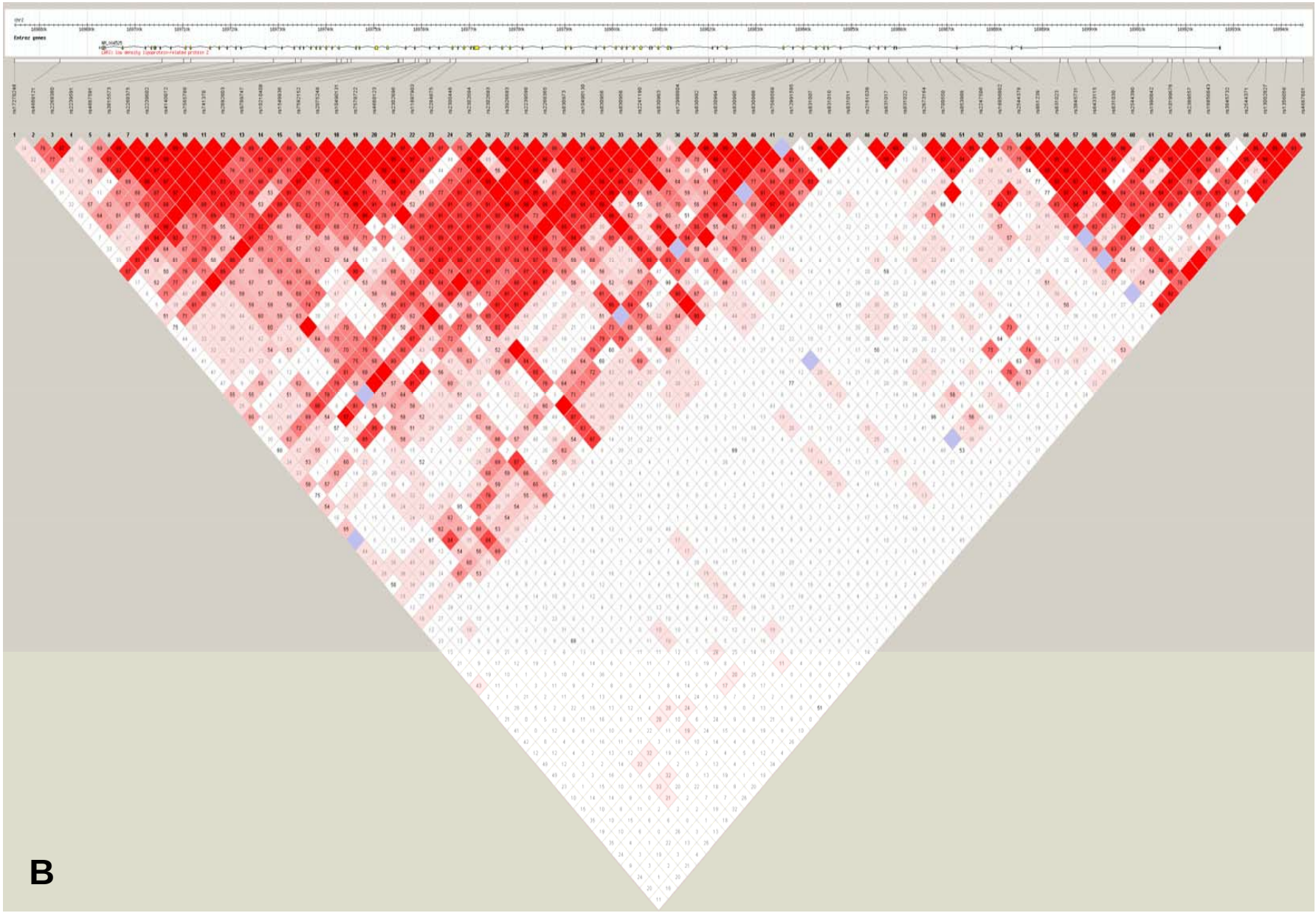
1. Singer JD, Willet JB, eds. Applied Longitudinal Data Analysis: Modeling change and event occurrence. New York: Oxford University Press, 2003.
2. Sharma S. Applied multivariate techniques. USA: Wiley, 1996.

Online Supplemental Material 3

Linkage disequilibrium (LD) structure in 20kb region of VDR and LRP2 gene.

Pairwise linkage disequilibrium (D') of SNP in the Illumina 550K panel within 20kb of VDR (A) and LRP2 (B) is presented. The strength of LD is displayed using the standard color scheme from Haploview (bright red - LOD score >2, D'=1; shade of pink – LOD score <2, D'=1; blue - LOD score > 2, D' <1; white - LOD score <2, D' = 1).


chr12
46510k
46520k
46530k
46540k
46550k
46560k
46570k
46580k
46590k
46600k
Entrez genes
NM_000376
VDR: vitamin D (125-dihydroxyvitamin D3) receptor
NM_001017535
VDR: vitamin D (125-dihydroxyvitamin D3) receptor
rs1859281
rs12721364
rs7968585
rs11574143
rs757343
rs1544410
rs7967152
rs11574077
rs2239182
rs2107301
rs2283342
rs2239181
rs1540339
rs2239179
rs886441
rs2189480
rs3819545
rs2239186
rs2254210
rs2238136
rs2853564
rs4760648
rs4328262
rs4334089
rs4237855
rs11574027
rs11574026
rs3890733
rs7299460
rs4516035
rs7132324
rs11168302
rs7970472
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33
A



B

Online Supplemental Material 4. VDR gene single nucleotide polymorphisms' (SNP) associations with predicted annual rate of cognitive change between age 50y and mean age of follow-up: Multiple OLS regression analysis with VDR SNPs entered alternatively; Baltimore Longitudinal Study of Aging

	Predicted annual rate of cognitive change between age 50y and mean age of follow-up[1]							
	All time points: Prediction I				Time points prior to dementia onset: Prediction II			
	N	β[2]	SEE	p-value for trend	N	β[2]	SEE	p-value for trend
MMSE: Models 1-4								
VDR: rs11568820 (CdX-2: T/C)	492			0.511[5]	485			0.095
TC vs. TT		-0.024	0.021			-0.010	0.011	
CC vs. TT		-0.010	0.020			+0.002	0.011	
VDR: rs1544410 (BsmI: G/A)	494			0.139	487			0.371
GA vs. GG		-0.001	0.009			-0.004	0.005	
AA vs. GG		+0.021	0.012			+0.008	0.006	
VDR: rs7975232 (ApaI: A/C)	492			0.080[3]	485			0.113
AC vs. AA		-0.008	0.010			-0.009	0.005	
CC vs. AA		-0.021	0.012			-0.008	0.006	
VDR: rs731236 (TaqI: G/A)	492			0.261	485			0.613
GA vs. GG		-0.022	0.011			-0.011	0.006	
AA vs. GG		-0.017	0.012			-0.006	0.006	
BVRT: Models 1-4								
VDR: rs11568820 (CdX-2: T/C)	616			0.541	609			0.523
TC vs. TT		+0.005	0.014			+0.000	0.012	
CC vs. TT		-0.000	0.014			-0.003	0.012	
VDR: rs1544410 (BsmI: G/A)	621			0.956	614			1.000
GA vs. GG		+0.002	0.006			+0.002	0.005	
AA vs. GG		-0.002	0.007			+0.001	0.007	
VDR: rs7975232 (ApaI: A/C)	616			0.951	609			0.803
AC vs. AA		+0.003	0.006			+0.002	0.005	
CC vs. AA		-0.001	0.007			-0.002	0.006	
VDR: rs731236 (TaqI: G/A)	616			0.755	609			0.625
GA vs. GG		+0.002	0.007			+0.000	0.006	
AA vs. GG		-0.002	0.008			-0.003	0.007	
CVLT-List A: Models 1-4								
VDR: rs11568820 (CdX-2: T/C)	606			0.253	588			0.239
TC vs. TT		-0.049	0.049			-0.039	0.042	
CC vs. TT		-0.013	0.047			-0.008	0.040	

VDR: rs1544410 (BsmI: G/A)	611			0.875	593			0.829
GA vs. GG		-0.008	0.020			-0.007	0.017	
AA vs. GG		+0.008	0.026			+0.009	0.022	
VDR: rs7975232 (ApaI: A/C)	606			0.082	588			0.101
AC vs. AA		-0.017	0.021			-0.023	0.018	
CC vs. AA		-0.045	0.025			-0.034	0.022	
VDR: rs731236 (TaqI: G/A)	606			0.973	588			0.955
GA vs. GG		-0.016	0.025			-0.016	0.021	
AA vs. GG		-0.005	0.026			-0.006	0.022	
CVLT-DR: MODEL 1-4								
VDR: rs11568820 (CdX-2: T/C)	606			0.190	588			0.237
TC vs. TT		+0.000	0.012			+0.000	0.010	
CC vs. TT		+0.007	0.011			+0.005	0.010	
VDR: rs1544410 (BsmI: G/A)	611			0.675	593			0.711
GA vs. GG		-0.007	0.005			-0.006	0.004	
AA vs. GG		-0.000	0.006			+0.000	0.005	
VDR: rs7975232 (ApaI: A/C)	606			0.449	588			0.576
AC vs. AA		-0.005	0.005			-0.005	0.004	
CC vs. AA		-0.004	0.006			-0.002	0.005	
VDR: rs731236 (TaqI: G/A)	606			0.487	588			0.496
GA vs. GG		-0.006	0.006			-0.006	0.005	
AA vs. GG		+0.002	0.006			+0.001	0.005	
VFT-C: MODEL 1-4								
VDR: rs11568820 (CdX-2: T/C)	512			0.800	505			0.568
TC vs. TT		-0.031	0.027			-0.016	0.017	
CC vs. TT		-0.025	0.026			-0.016	0.017	
VDR: rs1544410 (BsmI: G/A)	513			0.725[5]	506			0.674[5]
GA vs. GG		-0.006	0.011			-0.003	0.008	
AA vs. GG		+0.008	0.015			0.006	0.010	
VDR: rs7975232 (ApaI: A/C)	512			0.269[5]	505			0.188[5]
AC vs. AA		-0.006	0.012			-0.010	0.008	
CC vs. AA		-0.017	0.015			-0.012	0.010	
VDR: rs731236 (TaqI: G/A)	512			0.595[5]	505			0.520[5]
GA vs. GG		-0.014	0.014			-0.009	0.010	
AA vs. GG		-0.010	0.015			-0.007	0.010	
VFT-L: MODEL 1-4								
VDR: rs11568820 (CdX-2: T/C)	512			0.712	502			0.591
TC vs. TT		-0.034	0.024			-0.021	0.017	

CC vs. TT		-0.028	0.023			-0.019	0.016	
VDR: rs1544410 (Bsml: G/A)	513			0.710	503			0.638
GA vs. GG		+0.005	0.010			+0.004	0.007	
AA vs. GG		-0.008	0.014			-0.007	0.010	
VDR: rs7975232 (ApAI: A/C)	512			0.743	502			0.846
AC vs. AA		+0.021	0.011			+0.010	0.008	
CC vs. AA		+0.001	0.013			+0.000	0.009	
VDR: rs731236 (TaqI: G/A)	512			0.787	502			0.677
GA vs. GG		+0.011	0.013			+0.009	0.009	
AA vs. GG		+0.006	0.014			+0.006	0.010	
Trails A: MODEL 1-4								
VDR: rs11568820 (CdX-2: T/C)	475			0.744	465			0.632
TC vs. TT		+0.195	0.221			+0.129	0.130	
CC vs. TT		+0.170	0.210			+0.118	0.124	
VDR: rs1544410 (Bsml: G/A)	476			0.826	466			0.638
GA vs. GG		+0.127	0.095			+0.041	0.057	
AA vs. GG		-0.080	0.124			-0.058	0.074	
VDR: rs7975232 (ApAI: A/C)	475			0.898	464			0.169
AC vs. AA		-0.064	0.100			+0.032	0.059	
CC vs. AA		+0.030	0.122			+0.103	0.073	
VDR: rs731236 (TaqI: G/A)	475			0.818	465			0.652
GA vs. GG		+0.197	0.117			+0.093	0.070	
AA vs. GG		+0.076	0.124			+0.054	0.074	
Trails B: MODEL 1-4								
VDR: rs11568820 (CdX-2: T/C)	475			0.683	464			0.820
TC vs. TT		+0.073	0.369			+0.085	0.317	
CC vs. TT		+0.118	0.351			+0.092	0.301	
VDR: rs1544410 (Bsml: G/A)	476			0.459	465			0.443
GA vs. GG		+0.152	0.158			+0.164	0.136	
AA vs. GG		-0.236	0.207			-0.232	0.181	
VDR: rs7975232 (ApAI: A/C)	475			0.169	464			0.093
AC vs. AA		+0.055	0.165			+0.080	0.143	
CC vs. AA		+0.296	0.204			+0.308	0.177	
VDR: rs731236 (TaqI: G/A)	475			0.422	464			0.405
GA vs. GG		+0.368	0.196			+0.375	0.171	
AA vs. GG		+0.238	0.206			+0.233	0.180	

DS-F: MODEL 1-4	608			0.889	593			0.778
VDR: rs11568820 (CdX-2: T/C)		-0.000	0.004			+0.000	0.001	
TC vs. TT		+0.000	0.004			+0.000	0.001	
CC vs. TT								
VDR: rs1544410 (BsmI: G/A)	614			0.869	599			0.917
GA vs. GG		-0.000	0.001			-0.000	0.001	
AA vs. GG		+0.000	0.001			+0.000	0.001	
VDR: rs7975232 (ApaI: A/C)	608			0.750[5]	593			0.829
AC vs. AA		-0.001	0.001			-0.001	0.001	
CC vs. AA		-0.000	0.001			-0.000	0.001	
VDR: rs731236 (TaqI: G/A)	608			0.862[5]	593			0.921[5]
GA vs. GG		-0.000	0.001			+0.000	0.001	
AA vs. GG		-0.000	0.001			+0.000	0.001	
DS-B: MODEL 1-4								
VDR: rs11568820 (CdX-2: T/C)	608			0.719	593			0.605
TC vs. TT		+0.000	0.003			-0.000	0.003	
CC vs. TT		+0.000	0.003			+0.004	0.003	
VDR: rs1544410 (BsmI: G/A)	614			0.373	599			0.407
GA vs. GG		+0.001	0.001			+0.001	0.001	
AA vs. GG		+0.001	0.001			+0.001	0.002	
VDR: rs7975232 (ApaI: A/C)	608			0.502	593			0.491
AC vs. AA		-0.001	0.001			-0.001	0.001	
CC vs. AA		-0.001	0.001			-0.001	0.002	
VDR: rs731236 (TaqI: G/A)	608			0.407	593			0.444
GA vs. GG		-0.000	0.001			+0.000	0.001	
AA vs. GG		-0.001	0.001			-0.001	0.002	
Cognitive Domain 1: MODEL 1-4								
VDR: rs11568820 (CdX-2: T/C)	466			0.596	445			0.552
TC vs. TT		-0.10	0.21			+0.02	0.21	
CC vs. TT		-0.02	0.20			+0.07	0.20	
VDR: rs1544410 (BsmI: G/A)	467			0.957	446			0.937
GA vs. GG		-0.07	0.09			-0.09	0.09	
AA vs. GG		+0.02	0.12			+0.03	0.12	
VDR: rs7975232 (ApaI: A/C)	466			0.194	445			0.219
AC vs. AA		-0.02	0.09			-0.07	0.09	
CC vs. AA		-0.16	0.11			-0.14	0.12	
VDR: rs731236 (TaqI: G/A)	466			0.857	445			0.964

GA vs. GG		-0.08	0.11			-0.11	0.11	
AA vs. GG		-0.01	0.12			-0.02	0.12	
Cognitive Domain 2: MODEL 1-4								
VDR: rs11568820 (CdX-2: T/C)	466			0.190	445			0.228
TC vs. TT		-0.21	0.15			-0.20	0.15	
CC vs. TT		-0.24	0.15			-0.22	0.14	
VDR: rs1544410 (BsmI: G/A)	467			0.549	446			0.577
GA vs. GG		-0.04	0.06			-0.04	0.06	
AA vs. GG		+0.08	0.08			+0.07	0.08	
VDR: rs7975232 (ApaI: A/C)	466			0.675	445			0.397
AC vs. AA		-0.01	0.07			-0.06	0.07	
CC vs. AA		-0.04	0.08			-0.06	0.08	
VDR: rs731236 (TaqI: G/A)	466			0.468	445			0.614
GA vs. GG		-0.10	0.08			-0.10	0.08	
AA vs. GG		-0.08	0.08			-0.06	0.08	

Abbreviations: BMI, body mass index (calculated as weight in kg/square of height in meters); BVRT=Benton Visual Retention Test; CVLT-List A=California Verbal Learning Test, List A; CVLT-DR=California Verbal Learning Test, Delayed Recall; DS-B=Digits Span Backwards; DS-F=Digits Span Forward; MMSE=Mini-Mental State Examination; OLS=Ordinary Least Square; SNP=Single Nucleotide polymorphism; Trails A and B= Trailmaking test, parts A and B; VDR=Vitamin D receptor gene; VFT-C=Verbal fluency test-categorical; VFT-L=Verbal fluency test-letter . **Note that each SNP is denoted by an rs number followed by the polymorphism in which one nucleotide is replaced by another (e.g. T/C or G/A).**

[1] Cognitive scores were predicted at mean age at follow-up prior to onset of dementia or for all time points using a linear mixed model controlling for sex, race/ethnicity, education (years), and smoking status, with age added among the fixed effect variables to allow for quadratic non-linear change. The slope or annual rate of change was predicted from these models at the mean age at follow-up (i.e. between age 50 and individual mean age of follow-up for each cognitive test)(See Online Supplemental Material 2 for more details).

[2] Based on multiple OLS regression models with outcome being cognitive annual rate of change and main exposures being the four VDR SNPs, entered alternatively in each model. The model controlled for first-visit age, mean age at follow-up, education, first-visit smoking status, first-visit self-reported type 2 diabetes, hypertension, cardiovascular disease, and body mass index.

[3] Marginally significant main effects after familywise bonferroni correction: $p<0.05$ for MMSE or BVRT or cognitive domains and $p<0.025$ for other cognitive tests;
[4]Significant main effects after familywise bonferroni correction: $p<0.025$ for MMSE and cognitive domains and $p<0.0125$ for other cognitive tests;
[5] $P<0.05$ for null hypothesis that sex*SNP interaction term=0 in a model where main effect of sex was added.