

Supplementary Online Content

Samieri C, Perier M-C, Gaye B, et al. Association of Cardiovascular Health Level in Older Age With Cognitive Decline and Incident Dementia. *JAMA*. doi:10.1001/jama.2018.11499

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Methods and Results

A global cognitive score was computed as the mean of Z-scores of four cognitive tests assessing (i) global cognition, (ii) verbal semantic fluency, (iii) working memory and attention, and (iv) executive functioning.

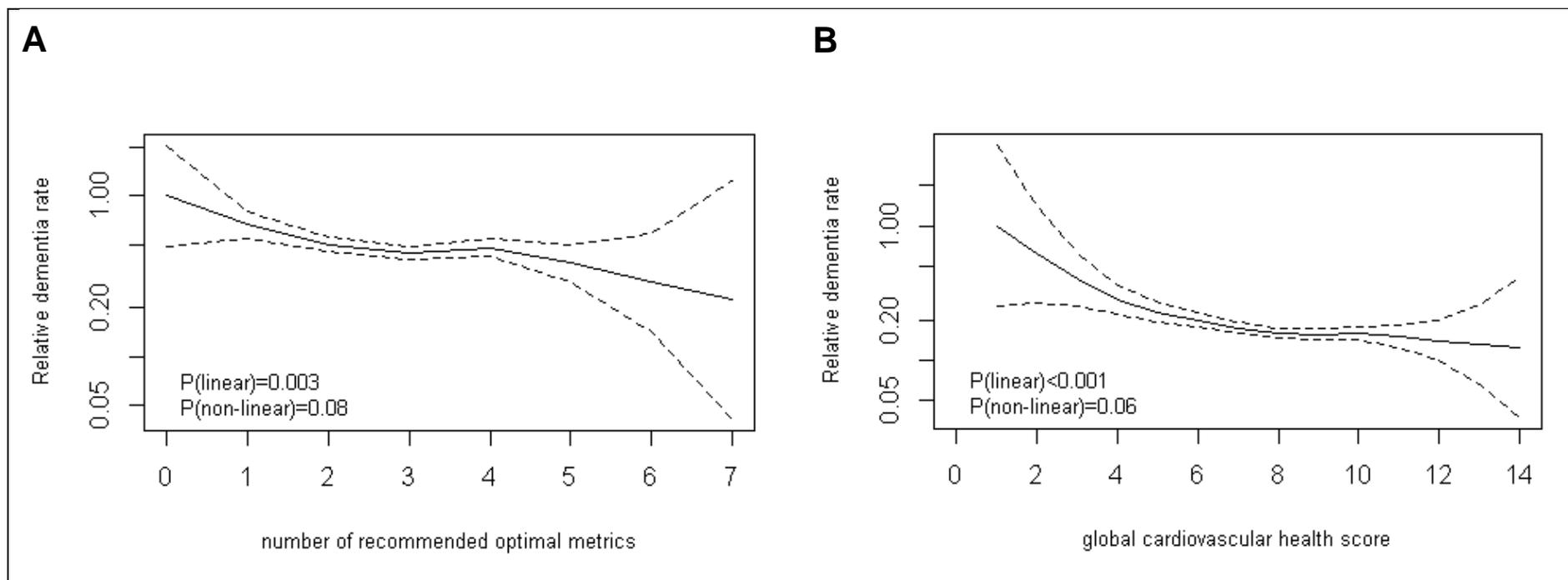
For global cognition, we used the Mini-Mental State Examination (MMSE)¹; total score ranged from 0 to 30 (with higher score indicating better performance). For verbal semantic fluency, we used the Isaacs' Set Test (IST)²; in the IST, participants are asked to cite as many words as possible (with a maximum of 10) belonging to a specific semantic category in 15 seconds. Four semantic categories are used successively (cities, fruits, animals, and colors) and scores range from 0 to 40. For working memory and attention, we used the Benton Visual Retention Test (BVRT),³ which consists of presentation for 10 seconds of a stimulus card displaying a geometric figure, after which individuals are asked to identify the initial figure among 4 possibilities. Fifteen figures are successively presented, and scores range from 0 to 15. For executive functioning, we used the trail making tests (TMT) parts A,⁴ which consists of connecting numbers from 1 to 25 in an ascending manner. We analyzed the number of correct displacements divided by the time required to perform each part of the test (higher scores indicating better performance).

In addition, we combined memory tests in a composite memory score. Our memory score was calculated as the mean of Z-scores of the BVRT and a subset of the MMSE, defined as the sum of items related to orientation to time and the 3-word recall task. In a validation study,⁵ this sub-score correlated reasonably well ($p > 0.40$) with scores obtained on the Free and Cued Selective Reminding Test (FCSRT, a validated test of episodic memory⁶), and was equivalent to the FCSRT in predicting incident AD in 3C,⁵ demonstrating its validity for use as a proxy of episodic memory in our cohort.

References

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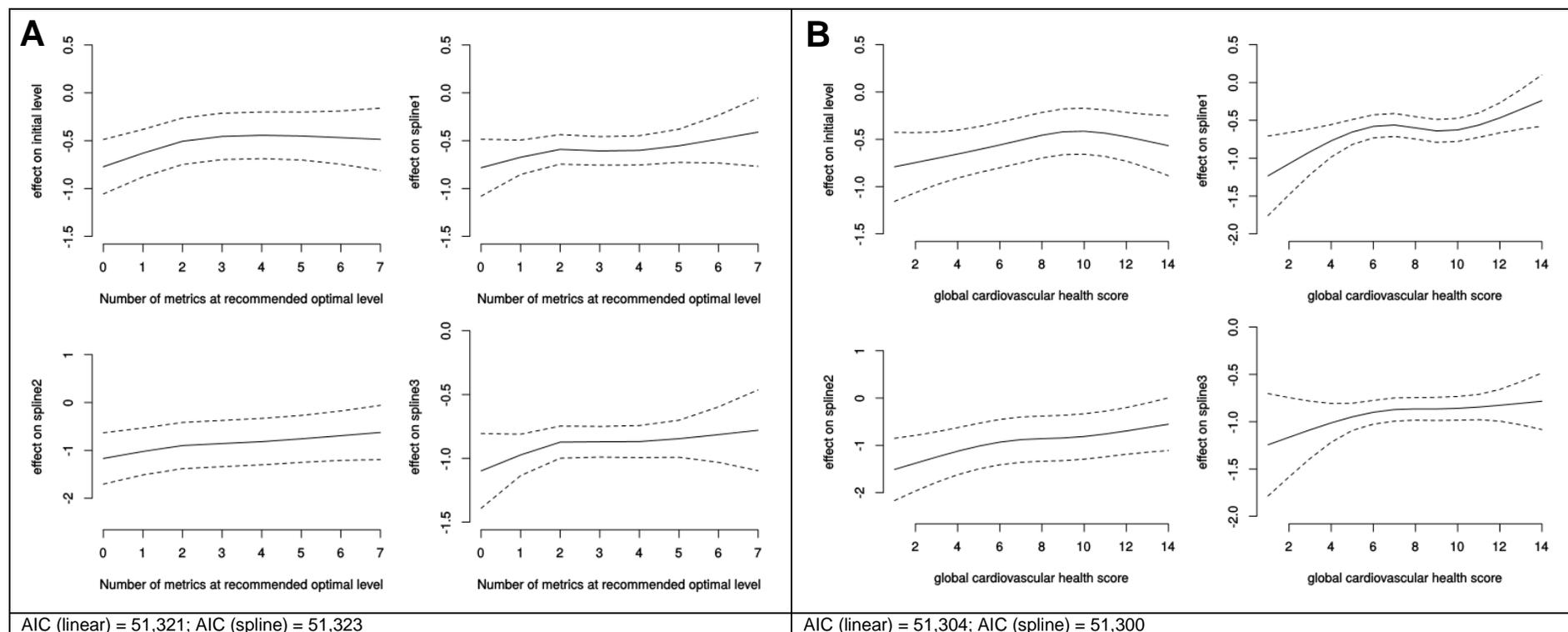
eFigure 1. Dose-Response Relationships Between Number of Recommended Optimal Metrics (Panel A), Global Cardiovascular Health Score (Panel B), and Relative Risk (RR) of Dementia Evaluated Using Penalized Splines With 4 Degrees of Freedom in a Cox Proportional Hazard Model



Cox proportional Hazard models used delayed entry and age as a time scale, were stratified for study center and adjusted for sex, educational level, and APOE ϵ 4 carrier status. The plot was centered on 0 (reference value) for the number of optimal metrics and on 1 for the global cardiovascular health score (no zero value for the global score in the sample).

$P(\text{linear})$ is the P-value for the test of a linear association against a null association. $P(\text{non-linear})$ is the P-value for the test of a non-linear association against a linear association.

eFigure 2. Dose-Response Relationships Between Number of Recommended Optimal Metrics (Panel A), Global Cardiovascular Health Score (Panel B), and the Trajectory of Global Cognitive Change Evaluated Using Natural Cubic Splines in a Linear Mixed Model With Splines Functions of Time

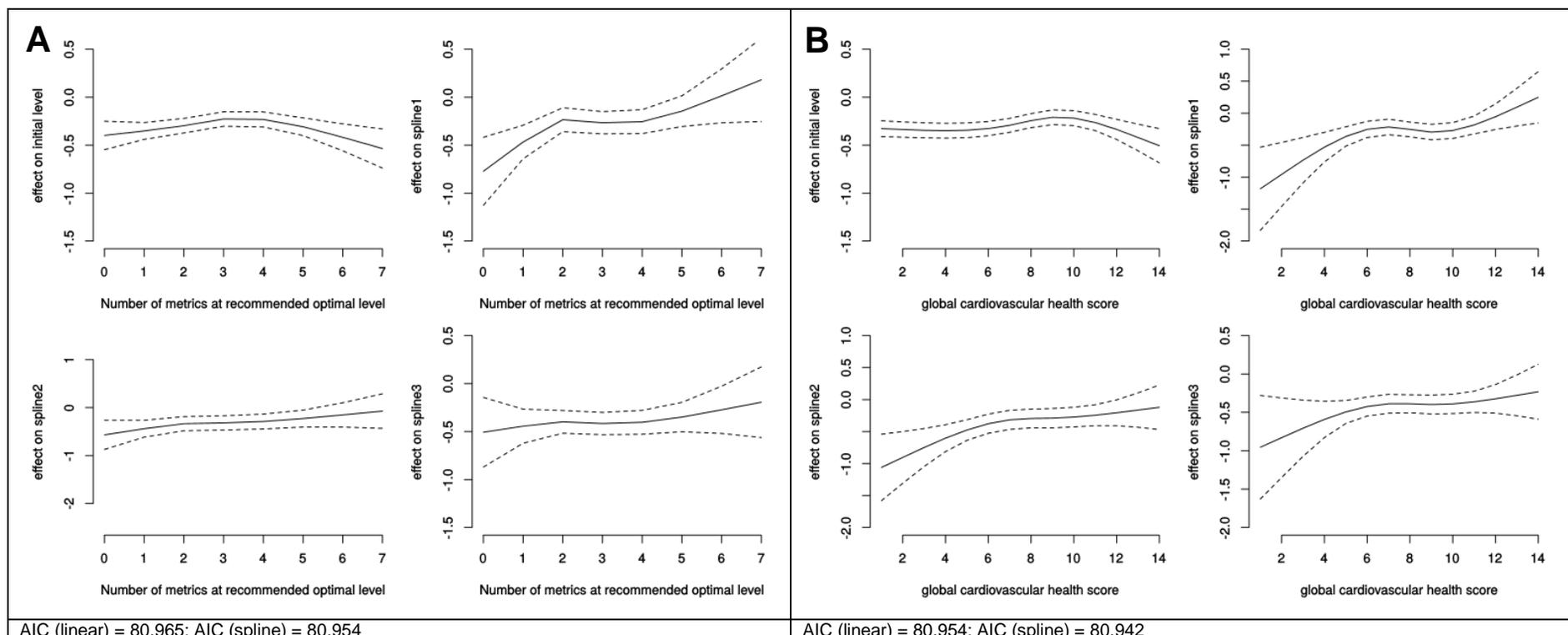


Trajectories of change in global cognition were estimated using mixed models, which included splines functions of time (natural cubic splines with 2 internal knots placed at the tertiles of measurement times) and corresponding random effects; cardiovascular health level variable (number of recommended optimal cardiovascular health metrics [panel A] or higher total cardiovascular health score [panel B]) and its interactions with splines functions of time; age, study center, educational level, APOE ϵ 4 carrier status, and their interactions with time.

Furthermore, nonlinear relationships between cardiovascular health level variables and the trajectory constituents (intercept and splines functions) were explored using natural cubic splines with two internal knots placed at the tertiles (plain lines: estimated association; dashed lines: 95% confidence bands obtained by the Delta-method).

The comparison of the AIC values between the linear and the spline-based models indicates that the assumption of a linear relationship between cardiovascular health level and trajectory of cognitive change is acceptable.

eFigure 3. Dose-Response Relationships Between Number of Recommended Optimal Metrics (Panel A), Global Cardiovascular Health Score (Panel B), and the Trajectory of Memory Change Evaluated Using Natural Cubic Splines in a Linear Mixed Model With Splines Functions of Time



Trajectories of change in memory were estimated using mixed models, which included splines functions of time (natural cubic splines with 2 internal knots placed at the tertiles of measurement times) and corresponding random effects; cardiovascular health level variable (number of recommended optimal cardiovascular health metrics [panel A] or higher total cardiovascular health score [panel B]) and its interactions with splines functions of time; age, study center, educational level, APOEε4 carrier status, and their interactions with time.

Furthermore, nonlinear relationships between cardiovascular health level variables and the trajectory constituents (intercept and splines functions) were explored using natural cubic splines with two internal knots placed at the tertiles (plain lines: estimated association; dashed lines: 95% confidence bands obtained by the Delta-method).

The comparison of the AIC values between the linear and the spline-based models indicates that the assumption of a linear relationship between cardiovascular health level and trajectory of cognitive change is acceptable.

eTable 1. Comparison of Baseline Characteristics Between Included and Excluded Participants

		Included (N=6,626)	Excluded ^a (N=904)	P-value
Study center, No. (%)	Bordeaux	1,284 (19.4)	137 (15.2)	<0.001
	Dijon	3,702 (55.9)	421 (46.6)	
	Montpellier	1,640 (24.8)	346 (38.3)	
Age, mean (SD), y		73.7 (5.2)	75.4 (6.6)	<0.001
Female, No. (%)		4,200 (63.4)	557 (61.6)	0.30
Education, No. (%)	No or primary	1,566 (23.6)	264 (29.6)	<0.001
	Secondary	2,450 (37.0)	313 (35.1)	
	High School	1,351 (20.4)	175 (19.6)	
	University	1,259 (19.0)	140 (15.7)	
APOEε4 carrier, No. (%)		1,304 (19.7)	182 (21.1)	0.31
Current smoker, No. (%)		368 (5.6)	67 (7.4)	0.02
Body mass index, mean (SD), kg/m ²		25.6 (4.0)	25.6 (4.1)	0.91
Fish ≥ 2 portions per week, No. (%)		3,349 (50.5)	440 (49.0)	0.38
Fruit and vegetables ≥ 3 portions per day, No. (%)		2,343 (35.4)	271 (30.3)	0.003
Regular exercise, No. (%)		1,671 (25.2)	135 (22.4)	0.13
Total cholesterol, mean (SD), mg/dL		225.7 (37.3)	228.4 (42.1)	0.07
Triglycerides, mean (SD), mg/dL		109.4 (52.6)	115.5 (56.4)	0.002
Systolic blood pressure, mean (SD), mmHg		146.5 (21.5)	146.7 (21.8)	0.79
Lipid-lowering medication, No. (%)		1,957 (29.5)	220 (24.3)	0.001
Antihypertensive medication, No. (%)		3,064 (46.2)	446 (49.3)	0.08
Diabetes, No. (%)		552 (8.3)	100 (11.4)	0.002

^a mean (SD) and percentages were calculated among those with non-missing values. Values were missing for < n=50 participants for all variables except physical activity, for which data were missing for n=302 individuals.

eTable 2. Baseline Characteristics Across Increasing Number of Cardiovascular Health Metrics at Recommended Optimal Level (n=6,626)

		0 n=34	1 n=564	2 n=1814	3 n=2369	4 n=1412	5 n=370	6 to 7 ^a n=63
Study center, No. (%)	Bordeaux	5 (14.7)	131 (23.2)	378 (20.8)	428 (18.1)	263 (18.6)	64 (17.3)	15 (23.8)
	Dijon	21 (61.8)	330 (58.5)	1,052 (58.0)	1,364 (57.6)	725 (51.4)	183 (49.5)	27 (42.9)
	Montpellier	8 (23.5)	103 (18.3)	384 (21.2)	577 (24.4)	424 (30.0)	123 (33.2)	21 (33.3)
Age, mean (SD), y		71.7 (5.3)	73.6 (5.0)	73.9 (5.1)	73.8 (5.3)	73.5 (5.3)	72.8 (4.9)	71.8 (5.0)
Female, No. (%)		9 (26.5)	274 (48.6)	1,059 (58.4)	1,597 (67.4)	963 (68.2)	253 (68.4)	45 (71.4)
Education, No. (%)	No or primary	6 (17.7)	154 (27.3)	495 (27.3)	558 (23.6)	286 (20.3)	58 (15.7)	9 (14.3)
	Secondary	11 (32.4)	203 (36.0)	691 (38.1)	934 (39.4)	472 (33.4)	125 (33.8)	14 (22.2)
	High School	8 (23.5)	98 (17.4)	336 (18.5)	466 (19.7)	341 (24.2)	80 (21.6)	22 (34.9)
	University	9 (26.5)	109 (19.3)	292 (16.1)	411 (17.4)	313 (22.2)	107 (28.9)	18 (28.6)
APOEε4 carrier, No. (%)		8 (23.5)	120 (21.3)	356 (19.6)	445 (18.8)	279 (19.8)	85 (23.0)	11 (17.5)
Current smoker, No. (%)		29 (85.3)	95 (16.8)	130 (7.2)	92 (3.9)	20 (1.4)	1 (0.3)	1 (1.6)
Body mass index, mean (SD), kg/m ²		29.5 (4.0)	29.1 (3.8)	27.8 (3.5)	24.9 (3.8)	23.4 (2.9)	22.6 (2.4)	22.3 (1.9)
Fish ≥ 2 portions per week, No. (%)		15 (44.1)	201 (35.6)	731 (40.3)	1,142 (48.2)	910 (64.5)	292 (78.9)	58 (92.1)
Fruit and vegetables ≥ 3 portions per day, No. (%)		4 (11.8)	111 (19.7)	422 (23.3)	773 (32.6)	713 (50.5)	262 (70.8)	58 (92.1)
Regular exercise ^b , No. (%)		0 (0)	8 (1.4)	143 (7.9)	504 (21.3)	675 (47.8)	282 (76.2)	59 (93.7)
Total cholesterol, mean (SD), mg/dL		229.6 (37.0)	226.3 (36.3)	228.3 (36.2)	228.1 (37.9)	222.0 (37.3)	214.4 (37.1)	204.7 (31.0)
Triglycerides, mean (SD), mg/dL		156.2 (96.1)	138.3 (66.1)	120.2 (53.8)	106.1 (50.3)	95.2 (42.1)	88.1 (34.2)	79.5 (33.4)
Systolic blood pressure, mean (SD), mmHg		154.2 (21.7)	153.5 (20.6)	150.3 (20.2)	146.7 (20.5)	142.5 (22.0)	135.0 (22.2)	125.2 (28.8)
Lipid-lowering medication, No. (%)		12 (35.3)	231 (41.0)	622 (34.3)	688 (29.0)	315 (22.3)	79 (21.4)	10 (15.9)
Antihypertensive medication, No. (%)		18 (52.9)	367 (65.1)	1,007 (55.5)	1,061 (44.8)	508 (36.0)	93 (25.1)	10 (15.9)
Diabetes ^c , No. (%)		13 (38.2)	206 (36.5)	201 (11.1)	86 (3.6)	40 (2.8)	5 (1.4)	1 (1.6)
MMSE score (range 0-30) ^d , mean (SD)		27.2 (1.9)	27.4 (1.9)	27.4 (1.9)	27.5 (1.9)	27.4 (1.9)	27.5 (1.8)	27.5 (1.9)
Episodic memory MMSE sub-score (range 0-8) ^d , mean (SD)		6.6 (0.9)	6.6 (0.9)	6.6 (0.9)	6.7 (1.0)	6.7 (0.9)	6.7 (0.9)	6.6 (1.1)
BVRT score (range 0-12) ^d , mean (SD)		11.0 (2.2)	11.4 (2.0)	11.4 (2.0)	11.6 (2.0)	11.7 (2.0)	11.9 (1.9)	11.6 (2.1)
IST score ^e , mean (SD)		32.0 (6.6)	31.8 (6.7)	32.0 (6.7)	32.5 (6.9)	32.8 (6.7)	33.1 (7.0)	32.9 (7.5)
TMT-A score ^e , mean (SD)		26.6 (7.3)	28.4 (10.1)	29.4 (10.3)	29.5 (10.4)	30.1 (10.3)	32.1 (10.4)	30.5 (9.8)

Data are % or mean (SD) of non-missing values (values were missing at baseline for 0.3% for MMSE, 1.2% for both BVRT and IST, and 2.5% for TMT-A).

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259

SI conversion factor: To convert triglycerides to millimoles per liter, multiply by 0.0113

Abbreviations: APOEε4: Epsilon 4 allele of the apolipoprotein E gene; BVRT: Benton Visual Retention Test; IST: Isaacs's set test; MMSE: Mini Mental State Examination; TMT: Trail Making Test.

^a n=62 participants with 6 optimal metrics and n=1 participant with 7 metrics at optimal level.

^b Defined as recreational walking ≥2 hours per day or practicing sport ≥2 times per week in Montpellier and Dijon study centers, and as recreational walking ≥8 hours per week or having ≥4 hours of sport or intensive leisure activity per week in Bordeaux center.

^c Fasting glycemia ≥7 mmol/L or antidiabetic medication.

^d higher scores indicates better performance.

^e no theoretical superior limit; higher scores indicates better performance.

eTable 3. Multivariable Associations^a Between Cardiovascular Health Level and the Incidence of Dementia Over 10 Years Adjusting for Incident Stroke (N=6,620^b)

	Hazard Ratio	95% CI	P
Number of recommended optimal cardiovascular health metrics (0 to 7), ordinal (for each additional metric)	0.88	0.81, 0.95	0.002
Global cardiovascular health score (0 to 14), ordinal (for each additional point)	0.91	0.88, 0.96	<0.001

^a Estimated using Cox proportional Hazard models with delayed entry and age as a time scale, stratified for study center and adjusted for sex, educational level, APOEε4 carrier status and incident stroke (the 93 stroke cases adjudicated after age of dementia onset [over a total of 212 incident stroke events] were censored in the analysis).

^b From the 6,626 participants of the main study sample, 6 participants without follow-up for dementia until the 10-year follow-up visit were excluded from these analyses.

eTable 4. Multivariable Associations^a Between Cardiovascular Health Level and the Incidence of Dementia Over 10 Years Excluding Incident Stroke Events From Study Sample (N=6,408^b)

	Hazard Ratio	95% CI	P
Number of recommended optimal cardiovascular health metrics (0 to 7), ordinal (for each additional metric)	0.91	0.84, 0.99	0.03
Global cardiovascular health score (0 to 14), ordinal (for each additional point)	0.94	0.89, 0.98	0.009

^a Estimated using Cox proportional Hazard models with delayed entry and age as a time scale, stratified for study center and adjusted for sex, educational level, APOEε4 carrier status.

^b From the 6,626 participants of the main study sample, 6 participants without follow-up for dementia until the 10-year follow-up visit and 212 incident stroke events were excluded from these analyses.

eTable 5. Multivariable Associations Between Cardiovascular Health Level and the Incidence of Dementia Over 10 Years Taking Into Account Age-Specific Mortality Rates Using Illness-Death Models^a (n=6,620)

	Hazard Ratio	95% CI	P
Number of recommended optimal cardiovascular health metrics (0 to 7), ordinal (for each additional metric)	0.87	0.80, 0.94	<0.001
Global cardiovascular health score (0 to 14), ordinal (for each additional point)	0.91	0.87, 0.95	<0.001

^a Illness-death models are multi-state models which take into account interval censoring of age at dementia (owing to the fact that dementia is assessed only at the follow-up visits), competing risk of death, right censoring, and left truncation (due to the selection of subjects alive and non-demented at inclusion). We used illness-death models based on a Weibull distribution, with age as a time scale and adjusted for study center, sex, educational level and APOEε4 carrier status.

eTable 6. Multivariable Associations Between Cardiovascular Health Level and the Incidence of Dementia With Imputation of Missing Values for Covariates and the Outcome Under Various Scenarios

	n incident cases / N (%)	Hazard Ratio	95% CI	P
Multiple imputation^a of both covariates and dementia outcome	862-888 ^b /7530			
Number of recommended optimal cardiovascular health metrics (0 to 7), ordinal (for each additional metric)		0.90	0.84,0.96	0.002
Global cardiovascular health score (0 to 14), ordinal (for each additional point)		0.92	0.88,0.96	<0.001
Multiple imputation^a of covariates and imputation of dementia under worst-case scenario^c	1340/7530			
Number of recommended optimal cardiovascular health metrics (0 to 7), ordinal (for each additional metric)		0.90	0.86,0.95	<0.001
Global cardiovascular health score (0 to 14), ordinal (for each additional point)		0.92	0.89,0.95	<0.001

^a Multiple Imputation by Chained Equations with fully conditional specification method (M=10 imputations).

^b Range of number of incident dementia events across the M=10 imputations.

^c Assuming all dropouts as incident dementia cases.