

Appendix 3 Multiple imputation analysis [posted as supplied by author]

To replace missing values (see Table A) we carried out multiple imputation analysis using all non-magnetic resonance imaging variables and the outcome variable. The procedure used was multivariate imputation by chained equations. Ten imputed datasets were created and the results combined using Rubin's rules.

Table B shows the pooled results from the Cox proportional hazards regression analysis for the conventional model, with and without magnetic resonance imaging variables. The models were similar to those identified in the complete-case analysis.

Table C shows the discrimination performance of the models in each of the imputed datasets (n=10). Similar results were obtained to those found in the complete-case analysis (Note: we did not attempt to combine the concordance statistic estimates across the imputed datasets due to lack of robust or agreed methods to undertake results pooling).

Table A Description of variables and pattern of missingness

Variable	Type	Description	N (% missing)
Age at baseline	Categorical	0: 65 to 74 years; 1: 75 to 79 years & 2: 80+ years	0 (0%)
Sex	Categorical	0: Male & 1: Female	0 (0%)
Education	Categorical	0: High; 1: Intermediate & 2: Low	0 (0%)
Impairment in Activities of Daily Living	Categorical	0: Not Impaired & 1: Impaired (Age & Education Adjusted)	15 (0.87%)
Mini Mental State Examination	Categorical	0: Not Impaired & 1: Impaired (Age & Education Adjusted)	3 (0.17%)
Benton Visual Retention Test	Categorical	0: Not Impaired & 1: Impaired (Age & Education Adjusted)	13 (0.76%)
Digit Span	Categorical	0: Not Impaired & 1: Impaired (Age & Education Adjusted)	6 (0.35%)
Smoking	Categorical	0: Never & 1: Past or Current Smoker	0 (0.0%)
Alcohol	Categorical	0: None/Ex Drinker; 1: Low (≤ 12 grams); 2: Moderate (12-24 grams) & 3: High (> 25 grams)	41 (2.38%)
Diabetes	Categorical	0: Not Diabetic & 1: Diabetic	15 (0.87%)
Cardiovascular Disease	Categorical	0: No History of CVD & 1: A History of CVD	0 (0%)
Systolic Blood Pressure	Continuous	N/A	0 (0%)
Apolipoprotein	Categorical	0: APOE $\epsilon 4$ negative & 1: APOE $\epsilon 4$ positive	11 (0.64%)
Hippocampal Volume	Continuous	N/A	0 (0%)
White Matter Lesion Volume	Continuous	N/A	0 (0%)
Whole Brain Volume	Continuous	N/A	0 (0%)

Table B Pooled results from the Cox proportional hazards analyses with and without magnetic resonance imaging variables added to the risk prediction model incorporating conventional risk variables only (outcome = all-cause dementia; n=1,721)

	Model 1 (M1)*		M1 + all 3 Magnetic Resonance Imaging Variables		M1 + Hippocampal Volume		M1 + White Matter Lesion Volume		M1 + Whole Brain Volume	
	Hazard Ratio	95%CI	Hazard Ratio	95%CI	Hazard Ratio	95%CI	Hazard Ratio	95%CI	Hazard Ratio	95%CI
Age	2.8	(2.1 to 3.7)	2.2	(1.6 to 3.1)	2.0	(1.5 to 2.7)	2.9	(2.1 to 3.8)	2.5	(1.8 to 3.4)
Sex	0.8	(0.5 to 1.4)	0.8	(0.5 to 1.3)	0.8	(0.5 to 1.4)	0.8	(0.5 to 1.3)	0.9	(0.5 to 1.4)
Education	1.3	(1.0 to 1.6)	1.3	(1.0 to 1.6)	1.3	(1.0 to 1.6)	1.3	(1.0 to 1.6)	1.3	(1.0 to 1.6)
Impairment in Activities of Daily Living	3.1	(1.7 to 5.4)	2.7	(1.5 to 4.9)	2.7	(1.5 to 4.9)	2.9	(1.7 to 5.2)	3.0	(1.7 to 5.3)
Mini Mental State Examination	2.4	(1.5 to 4.0)	2.3	(1.4 to 3.9)	2.5	(1.5 to 4.1)	2.3	(1.4 to 3.8)	2.6	(1.6 to 4.2)
Benton Visual Retention Test	2.4	(1.5 to 3.9)	2.4	(1.5 to 3.9)	2.4	(1.5 to 3.8)	2.4	(1.5 to 3.8)	2.4	(1.5 to 3.8)
Digit Span	2.1	(1.3 to 3.5)	1.9	(1.2 to 3.2)	2.0	(1.2 to 3.3)	2.0	(1.2 to 3.4)	2.1	(1.3 to 3.5)
Smoking	1.2	(0.8 to 1.9)	1.1	(0.7 to 1.7)	1.1	(0.7 to 1.8)	1.2	(0.7 to 1.9)	1.2	(0.8 to 1.9)
Alcohol	0.9	(0.7 to 1.2)	0.9	(0.7 to 1.1)	0.9	(0.7 to 1.1)	0.9	(0.7 to 1.1)	0.9	(0.7 to 1.1)
Diabetes	1.4	(0.7 to 2.5)	1.5	(0.8 to 2.7)	1.4	(0.8 to 2.6)	1.4	(0.8 to 2.5)	1.3	(0.7 to 2.4)
Cardiovascular Disease	0.8	(0.4 to 1.7)	0.8	(0.4 to 1.7)	0.8	(0.4 to 1.7)	0.8	(0.4 to 1.6)	0.8	(0.4 to 1.7)
Systolic Blood Pressure	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)	1.0	(1.0 to 1.0)
APOE	2.1	(1.4 to 3.2)	2.1	(1.4 to 3.1)	2.1	(1.4 to 3.1)	2.2	(1.5 to 3.2)	2.1	(1.5 to 3.2)
Hippocampal Volume			4.3e ⁻⁶	(5.3e ⁻⁸ to 3.5e ⁻⁴)	2.2e ⁻⁵	(5.8e ⁻⁷ to 8.2e ⁻⁴)				
White Matter Lesion Volume			1.1	(0.9 to 1.5)			1.4	(1.1 to 1.8)		
Whole Brain Atrophy			1.1	(1.0 to 1.2)					0.9	(0.9 to 1.0)

Table C Discrimination performance of the conventional risk model with and without the addition of magnetic resonance imaging variables: results from the complete-cases analysis and analysis in each imputed dataset (n=10)

	Model 1 (M1)*		M1 + all 3 Magnetic Resonance Imaging Variables		M1 + Hippocampal Volume		M1 + White Matter Lesion Volume		M1 + Whole Brain Volume	
	c-statistic	95%CI	c-statistic	95%CI	c-statistic	95%CI	c-statistic	95%CI	c-statistic	95%CI
Complete Case Analysis (n=1,634)										
Original	0.7653	(0.7135 to 0.8171)	0.7933	(0.7461 to 0.8405)	0.7915	(0.7433 to 0.8396)	0.7690	(0.7175 to 0.8204)	0.7683	(0.7161 to 0.8205)
Imputation Dataset Number (n=1,721)										
1	0.7710	(0.7233 to 0.8186)	0.7944	(0.7485 to 0.8402)	0.7930	(0.7462 to 0.8397)	0.7761	(0.7286 to 0.8237)	0.7744	(0.7260 to 0.8228)
2	0.7711	(0.7231 to 0.8190)	0.7961	(0.7509 to 0.8414)	0.7949	(0.7486 to 0.8413)	0.7770	(0.7293 to 0.8247)	0.7758	(0.7274 to 0.8241)
3	0.7681	(0.7195 to 0.8166)	0.7919	(0.7457 to 0.8380)	0.7908	(0.7437 to 0.8379)	0.7738	(0.7256 to 0.8219)	0.7715	(0.7223 to 0.8207)
4	0.7697	(0.7215 to 0.8178)	0.7938	(0.7483 to 0.8394)	0.7921	(0.7455 to 0.8387)	0.7754	(0.7276 to 0.8232)	0.7741	(0.7257 to 0.8225)
5	0.7736	(0.7262 to 0.8209)	0.7960	(0.7510 to 0.8409)	0.7946	(0.7488 to 0.8403)	0.7786	(0.7311 to 0.8261)	0.7781	(0.7306 to 0.8255)
6	0.7674	(0.7188 to 0.8161)	0.7922	(0.7460 to 0.8385)	0.7910	(0.7438 to 0.8381)	0.7729	(0.7248 to 0.8210)	0.7712	(0.7220 to 0.8204)
7	0.7678	(0.7188 to 0.8168)	0.7924	(0.7462 to 0.8386)	0.7913	(0.7442 to 0.8384)	0.7730	(0.7248 to 0.8212)	0.7714	(0.7220 to 0.8209)
8	0.7706	(0.7225 to 0.8186)	0.7947	(0.7486 to 0.8407)	0.7928	(0.7458 to 0.8397)	0.7758	(0.7279 to 0.8236)	0.7742	(0.7254 to 0.8230)
9	0.7695	(0.7216 to 0.8174)	0.7930	(0.7471 to 0.8389)	0.7917	(0.7449 to 0.8385)	0.7744	(0.7266 to 0.8222)	0.7728	(0.7241 to 0.8215)
10	0.7690	(0.7209 to 0.8172)	0.7922	(0.7461 to 0.8384)	0.7914	(0.7443 to 0.8385)	0.7739	(0.7259 to 0.8219)	0.7722	(0.7232 to 0.8212)

*Model 1 (M1) includes: age, sex, educational attainment, physical function (impairment in Activities of Daily Living), cognition function (Mini Mental State Examination, Benton Visual Retention Test and Digit Span), health (cardiovascular disease, diabetes and systolic blood pressure), lifestyle (smoking and alcohol use) and apolipoprotein ε4 status