

Geraldo F. Busatto¹, Pedro Bacchi², Anderson M. Winkler³, Marcio A. Almeida³, Paula Squarzon², Tania CTF Alves², Jaqueline H. Tamashiro-Duran², Salma RI Ribeiz¹, Sharon Sanz Simon⁴, Luiz K. Ferreira⁵, Fabio Porto², Artur Coutinho⁶, Debora Bassit², Tibor R. Perroco², Margarete Klein², Mario HR Louzã², Ricardo Nitri⁷, Stevin Zung⁸, Homero Vallada¹, Claudia da Costa Leite⁶, Orestes Forlenza¹, Daniele de Paula Faria⁶, Sonia Brucki⁷, Carlos Alberto Buchpiguel⁶, Fabio LS Duran².

¹Department of Psychiatry, Faculdade de Medicina, Universidade de São Paulo, Brazil, ²Instituto de Psiquiatria, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, Brazil, ³University of Texas Rio Grande Valley, Edinburg, TX, USA, ⁴Krieger Klein Alzheimer's Research Center, Brain Health Institute, Rutgers University, Newark, NJ, USA, ⁵Division of Clinical Geriatrics, Department of Neurobiology, Karolinska Institutet, Sweden, ⁶Instituto de Radiologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, Brazil, ⁷Department of Neurology, Faculdade de Medicina, Universidade de São Paulo, Brazil, ⁸Medical Division, Aché Laboratórios Farmacêuticos, Brazil

Background

- Women account for nearly two thirds of Alzheimer’s disease (AD) cases and may differ from men in resilience to AD pathology. Women with unimpaired cognition (UC) show greater preservation of cortical thickness (CT) than men despite the presence of AD pathology,¹ whereas women with mild cognitive impairment (MCI) may exhibit faster cognitive decline, suggesting that sex differences in resilience may change across the AD continuum.²
- Cognitive reserve has been associated with better cognitive performance despite age-related brain changes and may contribute to resilience mechanisms³. However, most AD studies have been based on samples with high levels of education (the commonest cognitive reserve proxy), limiting the generalizability of findings.
- Little is known about whether relationships among CT, cognition, and education differ between sexes across stages of the aging–AD continuum.
- We investigated these associations using pooled data from nine Brazilian studies including older adults with UC, amnesic MCI, and dementia clinically compatible with AD.

Methods

- Table 1 shows data from adults (≥ 58 years) with UC, amnesic MCI, or dementia. Samples from two studies (A and D) were drawn from epidemiological investigations in socially disadvantaged census sectors of São Paulo^{4,5}, whereas all others used convenience sampling.^{6,7,8,9,10,11,12} Amnesic MCI and dementia were diagnosed using syndrome-based criteria^{13,14}. Global cognition was assessed with the Mini-Mental State Examination (MMSE); in Study A⁴, scores on a composite cognitive measure (COGSCORE) were converted to MMSE-equivalent values using equipercentile equating.
- Years of education were used as a proxy for cognitive reserve. A substantial proportion of subjects had five or less years of educational attainment, including 56.8% of UC subjects, 24.0% of MCI patients and 46.7% of dementia patients.
- We processed T1-weighted MRI data with FreeSurfer 7.4.1. CT measures were harmonized using NeuroComBat. A CT signature was calculated from 9 AD-vulnerable regions.¹⁵
- Linear regression models examined associations between CT, MMSE scores, sex, and education, adjusted for age and intracranial volume. Separate moderation analyses in each group tested whether education modified the relationship between brain structure and cognition differently in women and men (CT $\times$ education $\times$ sex interaction).

Table 1. Pooled studies, sociodemographic data and image acquisition parameters

Study	N	Diagnostic Groups	Age (M±SD)	% Female	Education (M±SD)	Sequence/weighted	Equipment and Field Strength	Voxel Size (mm3)	TI (ms)	TE (ms)	TR (ms)	Flip Angle
Study A	243	UC (243)	70.9 ± 2.9	53.5%	4.3 ± 3.5	3D T1-FSPGR-IR	1.5T GE Signa	0.94x0.94x1.5	400	4.2	12.1	15
Study B	25	UC (25)	68.4 ± 3.3	56.0%	17.2 ± 3.1	3D T1-TFE	3T scanner Philips Achieva	1x1x1	900	3.2	7.0	8
Study C	30	MCI (30)	72.2 ± 6.2	80.0%	12.1 ± 4.1	3D T1-TFE	3T scanner Philips Achieva	1x1x1	900	3.2	7.0	8
Study D	21	UC (21)	70.9 ± 4.5	42.9%	5.5 ± 4.3	3D T1-TFE	3T scanner Philips Achieva	1x1x1	900	3.2	7.0	8
Study E	38	UC (21), dementia (17)	72.1 ± 5.7	68.4%	8.7 ± 4.5	3D T1-fSPGR-IR	1.5T GE Signa	0.85x0.85x1.6	400	4.2	12.1	15
Study F	119	UC (33), dementia (39), MCI (47)	72.5 ± 6.4	74.8%	10.5 ± 5.1	3D T1-TFE	3T scanner Philips Achieva	1x1x1	900	3.2	7.0	8
Study G	86	UC (25), dementia (34), MCI (27)	73.1 ± 7.2	68.6%	9.2 ± 5.3	3D T1-TFE	3T scanner Philips Achieva	1x1x1	900	3.2	7.0	8
Study H	34	UC (34)	68.9 ± 4.1	82.4%	14.6 ± 3.7	3D T1-MPRAGE	1.5T Siemens Espree	1.25x1.25x1.2	1000	3.65	2400	8
Study I	24	UC (24)	68.6 ± 6.8	70.8%	2.8 ± 1.6	3D T1-EFGRE	1.5T GE Signa	0.85x0.85x1.5	NA	5.2	21.7	20
Total	620		71.4 ± 5.3	63.9%	7.9 ± 5.7							

UC: : unimpaired cognition; MCI: mild cognitive impairment; TI: time inversion; TE: time echo; TR: time repetition, TFE: turbo field echo; FSPGR-IR: fast spoiled gradient recalled echo with inversion recovery; EFGRE: enhanced fast gradient recalled echo; MPRAGE: magnetization prepared rapid gradient echo.

References

1. Akinci et al, *JAMA Netw Open* 2026; 2. Arenaza-Urquijo et al, *Alzheimers Dement* 2024; 3. Arenaza-Urquijo & Vemuri, *Neurology* 2018; 4. de Toledo Ferraz Alves et al, *J Alzheimers Dis* 2011; 5. Ferreira et al, *Cereb Cortex* 2016; 6. Simon SS et al, *Alzheimers Dement (N Y)* 2020; 7. Alexandrino-Silva et al, *Arch Clin Psychiatry* 2019; 8. Ferreira et al, *Braz J Psychiatry* 2017; 9. Busatto et al, *Alzheimers Dement (Amst)* 2020; 10. Coutinho et al, *Dement Neuropsychol* 2015; 11. Klein et al, *J Atten Disord* 2021; 12. Zung et al, *Transl Psychiatry* 2016; 13. Albert et al, *Alzheimer's Dement* 2011; 14. McKhann et al, *Alzheimer's Dement* 2011; 15. Dickerson et al, *Cereb Cortex* 2009; 16. Maurer J, *Demography* 2017; 17. Stern Y, *Neuropsychologia* 2009.

Results

- | Variable | UC (n = 426) | | MCI (n = 104) | | Dementia (n = 90) | | Group Effect
p | Overall sample
Female |
|-----------------------|--------------|------------|---------------|------------|--------------------|--------------------|-------------------|--------------------------|
| | Female | Male | Female | Male | Female | Male | | |
| Demographics | (n = 261) | (n = 165) | (n = 77) | (n = 27) | (n = 58) | (n = 32) | | (n = 396) |
| Age, years | 70.3 (4.4) | 70.3 (3.7) | 72.8 (6.2) | 72.4 (6.3) | 74.6 (6.6) | 75.5 (6.8) | <.001 | 71.4 (5.4) |
| Education, years | 7.6 (6.1) | 6.9 (5.6) | 10.0 (4.7) | 10.0 (5.3) | 7.6 (4.5) | 8.8 (4.7) | <.001 | 8.1 (5.7) |
| Neuroimaging | | | | | | | | |
| AD cortical thickness | 21.5 (1.0) | 21.6 (1.0) | 21.5 (1.0) | 21.6 (1.0) | 20.7 (1.3)* | 19.8 (1.6)* | <.001 | 21.4 (1.1) |
| signature, mm | | | | | | | | |
| ICV, cm ³ | 1396 (131) | 1571 (138) | 1410 (128) | 1585 (143) | 1380 (119) | 1559 (131) | 0.053 | 1395 (129) |

Table 2. Sociodemographic, maging and cognitive data by diagnosis and sex

	UC (n = 426)		MCI (n = 104)		Dementia (n = 90)		Group Effect	Overall sample (n = 620)	
Variable	Female	Male	Female	Male	Female	Male	p	Female	Male
Demographics	(n = 261)	(n = 165)	(n = 77)	(n = 27)	(n = 58)	(n = 32)		(n = 396)	(n = 224)
Age, years	70.3 (4.4)	70.3 (3.7)	72.8 (6.2)	72.4 (6.3)	74.6 (6.6)	75.5 (6.8)	<.001	71.4 (5.4)	71.3 (5.0)
Education, years	7.6 (6.1)	6.9 (5.6)	10.0 (4.7)	10.0 (5.3)	7.6 (4.5)	8.8 (4.7)	<.001	8.1 (5.7)	7.6 (5.6)
Neuroimaging									
AD cortical thickness signature, mm	21.5 (1.0)	21.6 (1.0)	21.5 (1.0)	21.6 (1.0)	20.7 (1.3)*	19.8 (1.6)*	<.001	21.4 (1.1)	21.4 (1.3)
ICV, cm ³	1396 (131)	1571 (138)	1410 (128)	1585 (143)	1380 (119)	1559 (131)	0.053	1395 (129)	1571 (137)
Cognition	(n = 231)	(n = 153)	(n = 58)	(n = 24)	(n = 53)	(n = 31)		(n = 342)	(n = 208)
MMSE scores	28.1 (1.7)*	28.5 (1.5)*	26.6 (2.6)*	28.0 (1.5)*	21.9 (3.6)	22.6 (3.5)	<.001	26.3 (3.6)	26.3 (3.5)

UC: unimpaired cognition; MCI: mild cognitive impairment; ICV: intracranial volume; MMSE: Mini-mental state examination. *Significant difference between women and men

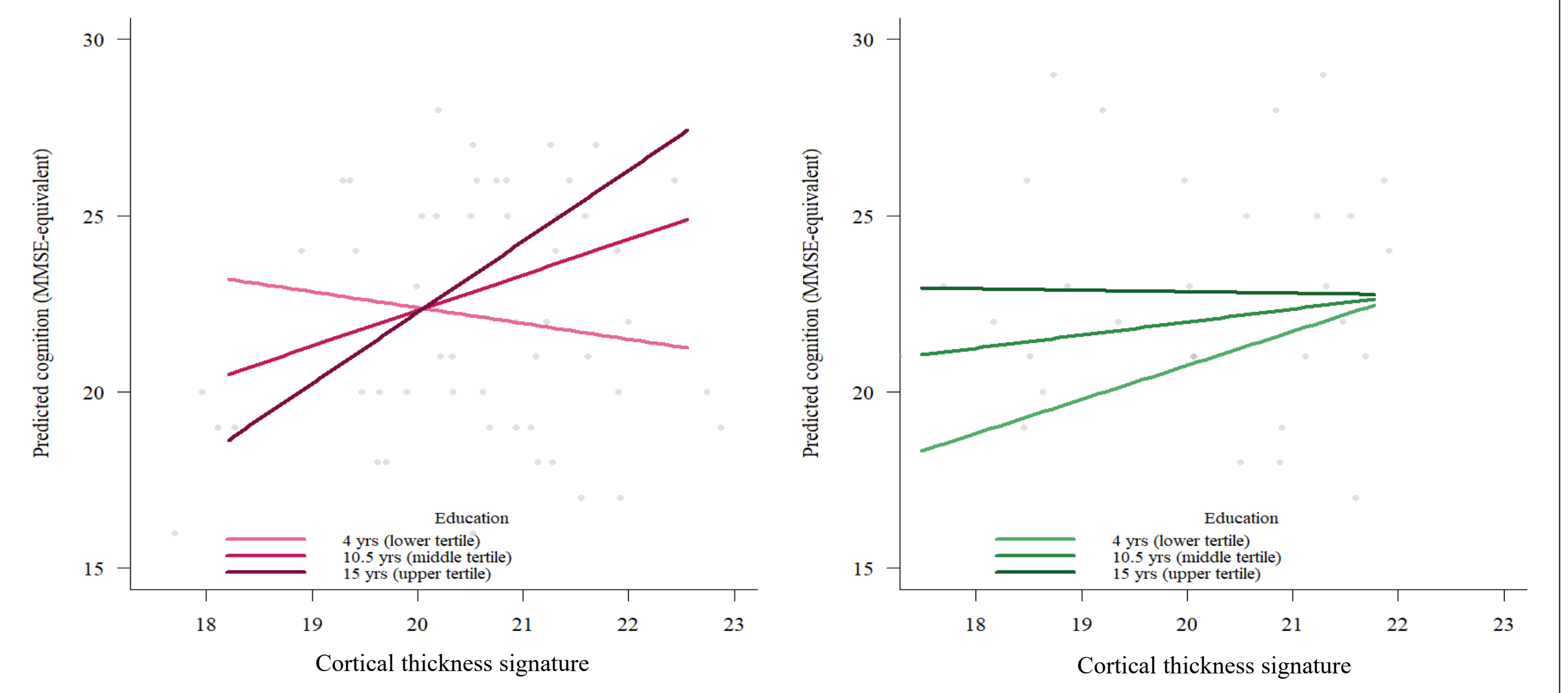
Table 3. Regression models for MMSE scores as outcome, with moderating effects of education

	UC (n=384)		MCI (n=82)		Dementia (n= 84)	
Predictor	β	p	β	p	β	p
Intercept	25.18	<.001	18.99	0.03	2.523	0.77
Cortical thickness	0.145	0.20	0.406	0.20	0.423	0.30
Education (centered)	0.886	0.03	3.071	0.03	-4.497	0.06
Sex (male)	5.431	0.15	3.913	0.73	-4.58	0.70
Age	-0.025	0.25	-0.04	0.38	0.053	0.41
ICV	1.30 ⁻⁶	0.01	1.27 ⁻⁶	0.35	6.02 ⁻⁶	0.01
Cortical thickness $\times$ Education	-0.038	0.05	-0.131	0.04	0.224	<0.05
Cortical thickness $\times$ Sex	-0.243	0.16	-0.127	0.81	0.186	0.75
Education $\times$ Sex	-0.38	0.55	-3.792	0.12	6.515	<0.05
Cortical thickness $\times$ Education $\times$ Sex	0.017	0.56	0.17	0.13	-0.316	<0.05

MMSE: Mini-mental state examination ; UC: unimpaired cognition; MCI: mild cognitive impairment; ICV: intracranial volume.

- Education significantly moderated the relationship CT and MMSE in all three groups (Table 3). While the CT $\times$ education interaction in UC and MCI showed $\beta < 0$ values, in dementia the interaction was positive (higher education associated with greater CT $\times$ cognition coupling).
- A significant CT $\times$ education $\times$ sex interaction was present only in dementia (Table 3). While in men increasing levels of education flattened the slope of the CT $\times$ cognition relationship ($\beta < 0$) (Figure 1), the opposite was seen in women (higher educational associated with steeper slopes, $\beta > 0$).

Figure 1. Moderating effect of education on the relationship between AD cortical thickness signature and predicted MMSE-equivalent scores in women (left) and men (right) with dementia. Lines represent predicted values for the lower, middle, and upper tertiles of years of education. Higher education was associated with stronger CT-cognition coupling in women ($\beta=+0.224$), whereas men showed the opposite pattern ($\beta=-0.091$), consistent with a CT x education x sex interaction ($\beta= -0.316, p < 0.05$).



Discussion and conclusions

- The broad educational range of this Brazilian sample, including many participants with ≤ 5 years of formal education, may have facilitated the detection of education-related effects less apparent in highly educated cohorts. This may also explain the lower MMSE scores observed in women with UC and MCI despite adjustment for age, education, and study of origin, possibly reflecting sex differences in life-course opportunities despite equivalent years of education.¹⁶
- In UC and MCI, higher educational attainment attenuated the relationship between CT and MMSE ($\beta < 0$) with no differences between women and men, consistent with classical cognitive reserve models contributing to resilience, possibly through compensatory recruitment of alternative neural networks to sustain cognitive performance.¹⁷
- In dementia, education showed opposite moderating effects by sex: higher education was associated with weaker CT–cognition coupling in men ($\beta < 0$) but stronger coupling in women ($\beta > 0$). The latter finding is not readily explained by classical cognitive reserve models. One alternative possibility is that higher education in women with dementia may have helped preserve the contribution of the remaining cortical architecture to cognitive performance. This would be consistent with the finding of relatively preserved CT in women with dementia compared to men, and may be compatible with resilience mechanisms related to brain maintenance.³ However, this interpretation should be considered cautiously given the cross-sectional design, and warrants confirmation in longitudinal studies.