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RESEARCH ARTICLE

Toward digitally screening and profiling AD: A GAMLSS approach of MemTrax in China

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Abstract

PURPOSES: To establish a normative range of MemTrax (MTx) metrics in the Chinese population.

METHODS: The correct response percentage (MTx-%C) and mean response time (MTx-RT) were obtained and the composite scores (MTx-Cp) calculated. Generalized additive models for location, shape and scale (GAMLSS) were applied to create percentile curves and evaluate goodness of fit, and the speed-accuracy trade-off was investigated.

RESULTS: 26,633 subjects, including 13,771 (51.71%) men participated in this study. Age- and education-specific percentiles of the metrics were generated. Q tests and worm plots indicated adequate fit for models of MTx-RT and MTx-Cp. Models of MTx-%C for the low and intermediate education fit acceptably, but not well enough for a high level of education. A significant speed-accuracy trade-off was observed for MTx-%C from 72 to 94.

CONCLUSIONS: GAMLSS is a reliable method to generate smoothed age- and education-specific percentile curves of MTx metrics, which may be adopted for mass screening and follow-ups addressing Alzheimer's disease or other cognitive diseases.

KEYWORDS
Alzheimer's disease, cognitive screening, digital biomarkers, GAMLSS, norms

Highlights

- GAMLSS was applied to establish nonlinear percentile curves of cognitive decline.
- Subjects with a high level of education demonstrate a later onset and slower decline of cognition.
- Speed-accuracy trade-off effects were observed in a subgroup with moderate accuracy.
- MemTrax can be used as a mass-screen instrument for active cognition health management advice.

Wanwan Liu and Qun Xu authors are contributing equally to this work.

1 | INTRODUCTION

Alzheimer's disease (AD) has become one of the deadliest diseases and has no cure or effective therapies. Alarmingly, 50 million people worldwide were living with dementia in 2018, and this number is expected to more than triple to 152 million by 2050.[1] Early detection of mild cognitive impairment (MCI) or preclinical AD stages, coupled with timely initiation of disease-modifying treatments, is the preferred path to successfully combat the medical threat and social burden of AD.[2] One of the greatest challenges has been the lack of an objective, quantifiable, precise, and simple tool to identify individuals at high risk of AD by monitoring the subtle changes caused by early AD pathology. Accordingly, computerized online mass-screening tools[3] suitable either for self-evaluation or assessment by public healthcare personnel have been shown to be urgently needed as never before in the face of an increasingly aging society.

MemTrax is a picture-based online adaptation of the continuous recognition task paradigm with a variable *N*-back design. Taking less than 2 min to administer, MemTrax challenges attention/executive function and specifically measures episodic memory with the index of percentage of correct responses (in %, MTx-%C) and processing speed with the index of mean response time (in seconds, MTx-RT) of all responses.[4] Participants can take the test repeatedly with minimal learning effect because MemTrax has a library of distinct pictures that can produce over 600 unique tests, which allows long-term, frequent follow-up.[5] MemTrax effectively detects both clinically diagnosed MCI[5,6] and AD[5] with similar or better accuracy compared to the Montreal Cognitive Assessment (MoCA).[5,6] We therefore performed this MemTrax analysis and normative metrics determination investigation to validate the practical utility of MemTrax for large-scale cognitive health screening.

AD in its sporadic form is a neurodegenerative disease, with aging being the greatest risk factor.[7,8] Importantly, distinct types of changes in cognition are expected as part of normal aging, in contrast to those changes that might suggest the onset of brain disease.[9] Rate of deterioration from a baseline level can be used to assist in effectively making this distinction between normal and pathological aging. However, this requires a practical assessment tool that can identify and track cognitive decline sensitively and, at the same time, does not have inherent learning effects, thereby allowing for ongoing follow-up in individuals. Researchers have tried to develop cognition trajectory assessments to identify individuals at high risk of AD. For example, Boyle's team used a shape-invariant model to develop a cognitive clock that assumed cognitive change over time following a standard pattern; but this approach did not take education into account.[10] Ashford and colleagues developed a so-called time index for assessing change over time.[11,12] However, abundant studies suggest cognition change over time including interaction with education.[13,14] Therefore, it is warranted to develop education-specific reference norms of tests that may be adopted during mass screening for early detection and monitoring of AD or other cognitive impairment-associated diseases. Reference norms of MemTrax in a French population have been generated by assuming a linear and quadratic age-cognition relation; however, these were not corrected by education.[15] During its early development, MemTrax was tested in community centers using projectors. Using only MTx-%C,[16] education was found to affect performance. Moreover, individuals with a college education and higher outperformed those with no more than a high school education. Given that there is no study of reference norms of MemTrax tests in the Chinese population and the trajectory of cognition is likely to be nonlinear, as suggested by previous studies,[17,18] our primary objective was to establish age- and education-specific reference percentile curves (ie, reference norms) of MemTrax metrics in China using the generalized additive models for location, shape and scale (GAMLSS) method.[19] Anticipated results would lend support to the validity and practical utility of MemTrax as an affordable cognitive mass screening tool for the early detection of AD in China and globally.

RESEARCH IN CONTEXT

1. **Systematic Review**: The literature was reviewed using PubMed, Wangfang Data, and CNKI. Though the 2.5-min online MemTrax test for continuous cognitive assessment under different settings was published, its potential contribution to cognitive research and clinical practice is emerging and education-corrected reference norms are lacking.
2. **Interpretation**: MemTrax metrics (accuracy/speed) demonstrated nonlinear cognition reference norms and declined with age. Our cross-sectional results provided direct evidence that higher levels of education has protective effects on age-associated cognitive decline. A subgroup demonstrated speed-accuracy trade-off effects. Our results are consistent with the cognitive reserve hypothesis.
3. **Future Directions**: The manuscript proposes a viable instrument for cognitive research and calls for additional studies, eg, (1) longitudinal studies to verify these cross-sectional results and investigate the cognitive decline trajectories of normal and cognitive diseases, (2) extending our findings to wider age ranges and different test settings, and (3) predictive values for the early detection of cognitive diseases.

2 | MATERIALS AND METHODS

2.1 | Study population

All subjects were recruited from the Health Management Center, Renji Hospital of Shanghai Jiaotong University School of Medicine (ie, Renji Hospital), from May 2020 to October 2021. Individuals voluntarily (with voluntary informed consent) took the MemTrax tests during their routine annual exams at the center. The inclusion criteria were (1) age

from 25 to 75 years, (2) scheduled to have upcoming health check-ups in Renji Hospital, (3) would be taking MemTrax for the first time, and (4) a willingness and ability to provide a signed informed consent to participate in this study. The exclusion criteria were (1) younger than 25 years or older than 75 years; (2) having a diagnosis of AD or diseases causing cognitive impairment (eg, Parkinson's disease, stroke, major depression disorders, or current systemic diseases such as hypothyroidism or vitamin B12 deficiency); and (3) physical impairments (eg, impairments of visual or relevant movement abilities) that would prevent normal completion of the MemTrax test. The study protocol was reviewed and approved by the ethics committee of Renji Hospital.

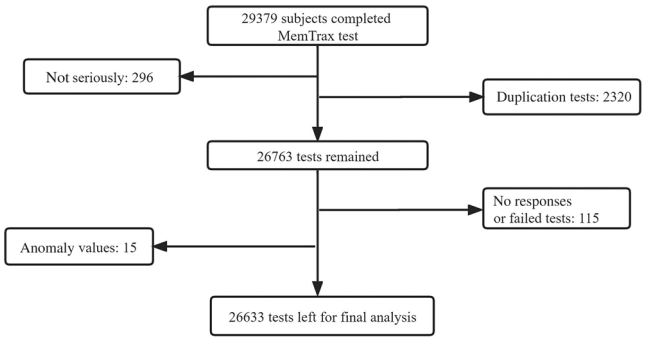

FIGURE 1 Flow chart of recruitment.

2.2 | MemTrax test procedures and output metrics

A detailed description of the MemTrax theory, design, and user engagement was published previously.[15] Briefly, with each MemTrax test, a series of 50 images was shown: 25 new images and 25 repeated images. Each image was shown for 3 s or until a behavioral response (touch screen or hit the space bar) was recorded. The users were instructed to respond and touch the screen or hit the space bar as quickly as possible only when repeated images were shown. At the end of the test, the program calculated and displayed MTx-RT and MTx-%C. The MemTrax composite score (MTx-Cp) was derived by multiplying the numbers in MTx-%C by the reciprocal of MTx-RT.[5]

Before taking the MemTrax test, subjects were asked to complete a questionnaire about their medical background to ensure they met the established study criteria. The test was administered by trained raters, and all subjects took the test on a computer. Each subject was asked to read the instructions carefully and was reminded of common mistakes. Several key points were emphasized by the rater: (1) responses should be to an exact duplicate image, not a similar one; (2) the space bar should be hit as quickly as possible when a repeated image appeared. Then subjects took the test while the rater stayed silent at a comfortable distance from the very beginning to judge whether the subjects were taking the test attentively and uninterrupted (eg, half-heartedly or while using their phone) and understood the test procedures correctly.

MTx-RT > 1.4 s[20] or MTx-%C < 81% indicates possible cognitive impairment, according to previous study results.[21] Therefore, if MTx-RT was longer than 1.4 s or MTx-%C was lower than 81%, the rater would ascertain whether the subject completely understood the test instructions. If a subject did not understand the test instructions completely or did not seem to be taking the test seriously, the subject would have two more opportunities to take the test again with a new set of pictures. For a subject who refused to try a second test, raters would record the circumstances. Results with MTx-RT less than 300 ms or longer than 2900 ms were considered non-responses (responses less than 300 ms would not represent a physiological response to a perceived stimulus and correct recognition responses nearly always occurred in less than 2000 ms, and 2900 ms was used as a cutoff to be safe[15]). MTx-%C less than 60% was considered a failed test, given its proximity to chance (the average random percentage being 50%).

2.3 | Selection of subjects for detailed analyses

The investigation included a total of 29,379 completed tests. Two hundred ninety-six tests were removed from analyses because the subjects did not seem to be taking the test seriously and refused to take a second one, and 2320 duplicate tests were removed because of multiple trials. No responses or failed tests led to the exclusion of 115 tests. To eliminate the effect of outliers on percentile curves, any observed value that was $>(\bar{X}+5\times SD)$ or $<(\bar{X}-5\times SD)$ was removed. This evaluation process was repeated three times, leading to 15 tests with anomaly values being deleted. Finally, 26,633 tests, each from a unique individual, were left for detailed analyses (Figure 1).

2.4 | Statistical methods for constructing the reference norms of cognition

2.4.1 | Education category generation

Multivariate linear regression analysis was performed using SPSS version 22.0 software to generate education categories. The dependent variables were MTx-%C, MTx-RT, and MTx-Cp. The independent variables were age (dummy variable), sex, and education (dummy variable). Education was added as a hierarchical variable and classified into four levels: high school and below, associate degree, bachelor's degree, master's degree and above, with high school and below as the reference point.

2.4.2 | Curve creation and fitting effect evaluation

Smoothed percentile curves were created for the age- and education-specific MTx-%C, MTx-RT, and MTx-Cp based on GAMLSS. An underlying skewed normal distribution of the measurements was assumed, so that a suitable power transformation would render the distribution to be normal. The distribution at each age (t) is summarized by four parameters: location parameter, scale parameter, and two shape parameters (affecting the skewness and kurtosis of the distribution).[22]

Basis spline, cubic spline, polynomial, and fractional polynomial smoothing were assessed based on the global deviance (GD), Akaike information criterion (AIC), and Schwartz Bayesian criterion (SBC). The detrended Q-Q plot was used as a global diagnostic and plotted the quantiles of the theoretical distribution (on the horizontal axis) against those of the empirical distribution (on the vertical axis). Q tests focus on low-order moments of Z-scores. The diagnostics included detrended Q-Q plot[23] and Q test for goodness of fit. The final model was chosen based on GD, AIC, and SBC, along with the results of the model and residual diagnostics as well as visual assessment of the percentiles themselves. The GAMLSS algorithm was implemented using the R3.6.3 software GAMLSS package by Rigby and Stasinopoulos.[19]

2.4.3 | Interaction between education and age

To test whether there was an interaction between education and age, univariate analysis was applied, with MTx-%C, MTx-RT, and MTx-Cp as dependent variables and with education, sex, age, and age * education as independent variables using SPSS 22.0.

2.4.4 | Speed-accuracy trade-off

To determine whether there was a speed-accuracy trade-off, a set of self-administered online MemTrax tests was introduced in the study (see supplementary file). Before registering on the MemTrax website, subjects signed a user agreement (including informed consent) with SJN Biomed LTD, Kunming, China. Subjects voluntarily took MemTrax tests online following the screen instructions. The inclusion and exclusion criteria were the same as those described in this study. Multivariate linear regression was used to examine the difference of MTx-RT corresponding to identical MTx-%C between the two different test settings using SPSS 22.0.

3 | RESULTS

3.1 | Population characteristics

There were a total of 26,633 subjects, with 12,862 (48.29%) women. The numbers of subjects with different education levels were 3705 (13.91%) for high school and below, 3624 (13.61%) for associate degree, 13,540 (50.84%) for bachelor's degree, and 5,764 (21.64%) for master's degree and above. The mean age of the subjects was 43.0 ± 12.1 years old.

3.2 | Education categories

Multivariate linear regression was undertaken, with MTx-RT, MTx-%C, and MTx-Cp as dependent variables and sex, education (dummy variable), and age (dummy variable) as independent variables. When subjects with a high school education and below were taken as the reference point, for MTx-RT, the regression coefficients for subjects with associate degree, bachelor's degree, and master's degree and above were $b = -0.062$, $b = -0.081$, $b = -0.080$ (all $P < .05$); for MTx-%C, the regression coefficients were $b = 2.0160$, $b = 3.363$, $b = 3.693$ (all $P < .05$); and for MTx-Cp, the regression coefficients were $b = 6.729$, $b = 9.817$, $b = 10.01$ (all $P < .05$), respectively. There was no statistical difference between the bachelor's degree and master's degree and above; however, there was a statistical difference (all $P < .05$) between all education levels (except master's and bachelor's). Therefore, education was further integrated into the following three categories: low education category with high school and below (3705, 13.91%), intermediate education category with associate degree (3624, 13.61%), and high education category with bachelor's degree and above (19,304, 72.4%) (Figure 2). The percentile norms were then established by these three education categories.

3.3 | Education specific percentile curves for MemTrax metrics

After the assessment of smoothing and transformation parameters, the best fit model was Box-Cox power exponential (BCPE) distribution for the calculation of the MTx-RT, MTx-%C, and MTx-Cp percentiles except MTx-RT of low education, for which the best fit model was a Box-Cox-t (BCT) distribution. GD, SBC, and AIC of the final models are shown in Table A.1. percentile threshold values according to gestational age are reported in Table 1. The final MTx-RT, MTx-%C, and MTx-Cp against age percentile curves of the different education categories are shown in Figure 3.

By visual assessment, both MTx-RT and MTx-%C stayed nearly stable until the decade of the 40s for subjects with high and intermediate education, whereas the values for these measures declined earlier and more steeply for subjects with low education. For MTx-RT, when (high education * age) was taken as the reference, β of (intermediate education * age) was 0.002 ($P < .05$) and β of (low education * age) was 0.004 ($P < .05$). For MTx-%C, β of (intermediate education * age) was −0.061 ($P < .05$) and β of (low education*age) was −0.101 ($P < .05$). These findings suggested a significant interaction between the effects of education and age, that is, the lower the education, the faster the deterioration of episodic memory and executive function. Likewise, MTx-Cp for high and intermediate education also remained stable until the mid-40s, then declined with age. However, for subjects with low education, MTx-Cp steadily declined from the beginning recruitment age of 25, as shown by the curve, and the lower the education, the faster the MTx-Cp decreased. When (high education*age) was taken as the reference, the β values of (intermediate education * age) and (low education * age) were −0.174 ($P < .05$) and −0.268 ($P < .05$), respectively.

3.4 | Fitting effect evaluation

Owing to scarce data, the interval becomes broader toward the extremes, so large differences between theoretical and empirical

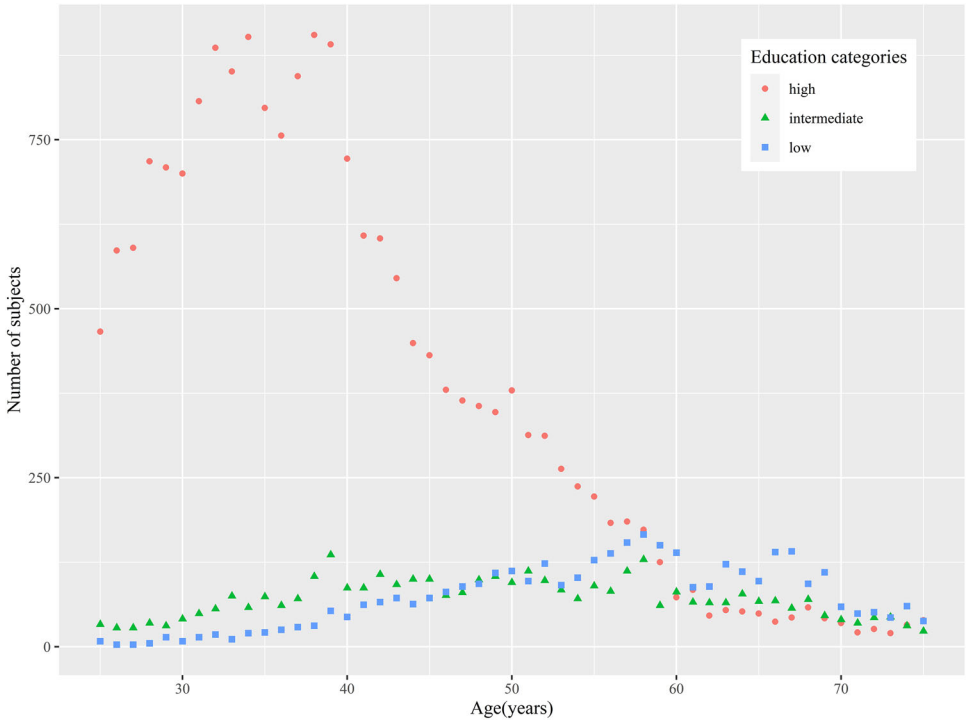

FIGURE 2 Distribution of subjects by age and education category.

quantiles in the tails are tolerated. Detrended Q-Q plots of MTx-RT and MTx-Cp showed that residuals were normally distributed around zero and the worms (plots visualizing differences in distribution) were located almost in the 95% confidence interval of overall residuals, indicating that the empirical and theoretical distributions generally agreed and the models for all three education categories fit quite well (Figure 4). However, a larger number of empirical quantile points in the detrended Q-Q plot of MTx-%C were located away from the main diagonal, especially for subjects with high education. This analysis indicated a modest fit of the model for MTx-%C.

The Q test results indicated that the residual skewness in less than two out of 20 age groups in each model with overall Q-test *p* value was non-significant at the 5% level. Thus, it was considered that the residual distribution of mean, variance, and skewness of the fit curve had no statistical difference with the standard normal distribution, indicating an adequate fit in each model (Tables A.2 to A.10).

3.5 | Speed-accuracy trade-off

For the online, self-administered data, a total of 8113 subjects, with 3527 (43.47%) men and 4586 (56.53%) women, produced data that fit our selection criteria. The average age was 39.73 ± 11.48 years. The numbers of subjects with the education levels of high school and below, associate degree, bachelor's degree, and master's degree and above were respectively 1253 (15.44%), 1142 (14.08%), 3253 (40.10%), and 2465 (30.38%). There were statistical differences in sex, age, and education between the two populations from different test settings (Table A.11). For head-to-head comparison, when MTx-%C was within the interval of 62 to 70 or 96 to 98, there was no significant difference between provider- and self-administered MTx-RT with an identical MTx-%C score. However, when MTx-%C was within the interval of 72 to 94, self-administered MTx-RT was significantly longer than that of provider-administered MTx-RT. For those tests for which MTx-%C reached the maximal level of 100, provider-administered MTx-RT was longer (Table A.12).

4 | DISCUSSION

In recognition of an imminent greater widespread impact and social/financial burden from AD, numerous computerized cognitive assessment tools continue to be developed. Primarily developed to specifically measure episodic memory, which is associated with early AD, MemTrax has been implemented and utilized online in various countries for the general population.[7,15,24,25] In this study, MemTrax tests were performed on a large annual exam population to generate reference norms in China.

4.1 | MemTrax metrics

As an extension of the original study with the projector version of MemTrax, where the recognition memory was found to correlate with education,[16] our current study found that the performance of subjects with an associate degree fell between high school- and college-educated subjects. Further, the percentile curve of MTx-RT against age fitted quite well for all education categories. This

TABLE 1 MTx-RT, MTx-%C, and MTx-Cp percentile for reference standard of three education levels.

		High education								Intermediate education								Low education							
	Age	Number of subjects	P_3	P_{10}	P_{25}	P_{50}	P_{75}	P_{90}	P_{97}	No. of subjects	P_3	P_{10}	P_{25}	P_{50}	P_{75}	P_{90}	P_{97}	Number of subjects	P_3	P_{10}	P_{25}	P_{50}	P_{75}	P_{90}	P_{97}
MTx-RT(s)	25 to 29	3069	1.209	1.081	0.974	0.873	0.79	0.725	0.67	155	1.206	1.085	0.98	0.879	0.792	0.723	0.664	33	1.189	1.087	0.993	0.901	0.818	0.751	0.691
	30 to 34	4145	1.225	1.093	0.982	0.879	0.793	0.728	0.671	279	1.228	1.104	0.995	0.89	0.801	0.731	0.67	71	1.248	1.133	1.03	0.927	0.837	0.764	0.7
	35 to 39	4191	1.234	1.1	0.987	0.883	0.797	0.73	0.674	445	1.247	1.119	1.007	0.9	0.809	0.738	0.676	159	1.303	1.175	1.06	0.948	0.85	0.772	0.702
	40 to 44	2925	1.254	1.114	0.997	0.89	0.801	0.733	0.675	473	1.269	1.135	1.018	0.908	0.813	0.74	0.676	307	1.347	1.206	1.081	0.96	0.855	0.771	0.698
	45 to 49	1877	1.292	1.142	1.018	0.905	0.811	0.74	0.68	459	1.317	1.171	1.045	0.926	0.825	0.748	0.681	444	1.394	1.241	1.106	0.976	0.863	0.775	0.698
	50 to 54	1502	1.346	1.185	1.052	0.932	0.833	0.758	0.695	460	1.377	1.219	1.084	0.958	0.851	0.769	0.698	525	1.458	1.292	1.147	1.008	0.888	0.795	0.714
	55 to 59	886	1.407	1.235	1.094	0.967	0.863	0.785	0.718	474	1.43	1.266	1.125	0.993	0.882	0.797	0.724	736	1.518	1.345	1.193	1.048	0.923	0.826	0.741
	60 to 64	309	1.466	1.284	1.136	1.003	0.894	0.812	0.743	355	1.485	1.314	1.167	1.03	0.914	0.825	0.749	549	1.578	1.398	1.241	1.09	0.961	0.859	0.771
	65 to 69	229	1.519	1.329	1.174	1.035	0.922	0.836	0.764	308	1.539	1.36	1.207	1.064	0.943	0.851	0.772	581	1.636	1.451	1.29	1.134	1.001	0.896	0.805
	70 to 75	171	1.562	1.368	1.209	1.066	0.95	0.863	0.789	216	1.597	1.406	1.245	1.094	0.968	0.871	0.789	300	1.715	1.516	1.342	1.176	1.033	0.922	0.826
MTx-%C(%	25 to 29	3069	78.74	82.18	85.40	88.75	91.76	94.14	96.24	155	76.51	80.71	84.33	87.83	90.92	93.44	95.72	33	71.06	77.05	82.07	86.84	90.99	94.34	97.35
	30 to 34	4145	78.64	82.16	85.45	88.86	91.93	94.34	96.48	279	76.12	80.46	84.19	87.78	90.95	93.52	95.84	71	71.44	77.00	81.72	86.23	90.19	93.39	96.28
	35 to 39	4191	78.39	81.99	85.33	88.80	91.91	94.35	96.51	445	75.80	80.28	84.10	87.77	91.00	93.61	95.97	159	71.78	77.00	81.48	85.78	89.57	92.66	95.45
	40 to 44	2925	77.86	81.59	85.06	88.63	91.82	94.33	96.54	473	75.61	80.16	84.05	87.76	91.03	93.67	96.05	307	71.88	76.92	81.26	85.46	89.16	92.18	94.92
	45 to 49	1877	77.23	81.13	84.71	88.40	91.68	94.24	96.50	459	75.07	79.78	83.77	87.58	90.91	93.59	96.02	444	71.28	76.45	80.87	85.13	88.89	91.95	94.71
	50 to 54	1502	76.05	80.18	83.94	87.78	91.19	93.84	96.16	460	74.08	78.97	83.08	86.98	90.38	93.11	95.57	525	69.68	75.28	80.01	84.51	88.45	91.63	94.51
	55 to 59	886	74.41	78.83	82.82	86.85	90.39	93.14	95.55	474	72.17	77.49	81.89	86.00	89.55	92.40	94.95	736	67.72	73.71	78.69	83.39	87.47	90.75	93.71
	60 to 64	309	72.63	77.41	81.65	85.90	89.60	92.46	94.95	355	69.69	75.62	80.41	84.82	88.59	91.58	94.24	549	66.46	72.66	77.78	82.58	86.73	90.06	93.06
	65 to 69	229	70.64	75.87	80.44	84.95	88.85	91.84	94.43	308	67.21	73.79	78.98	83.68	87.65	90.78	93.56	581	65.28	71.79	77.11	82.06	86.32	89.72	92.78
	70 to 75	171	68.43	74.11	78.98	83.73	87.80	90.90	93.58	216	64.98	72.08	77.57	82.50	86.62	89.84	92.69	300	63.47	70.43	76.03	81.20	85.61	89.12	92.26
MTx-Cp(/s)	25 to 29	3069	70.65	80.38	90.35	101.54	112.83	123.08	133.27	155	70.58	79.58	89.06	100.00	111.35	121.91	132.65	33	63.06	72.17	82.39	95.12	108.38	119.85	130.78
	30 to 34	4145	69.61	79.48	89.60	100.95	112.42	122.83	133.18	279	67.00	77.15	87.39	98.74	110.06	120.22	130.22	71	61.29	70.19	80.19	92.66	105.64	116.87	127.57
	35 to 39	4191	68.94	78.83	88.96	100.34	111.83	122.26	132.63	445	64.22	75.22	86.03	97.70	109.09	119.13	128.86	159	59.70	68.48	78.35	90.66	103.48	114.57	125.14
	40 to 44	2925	67.51	77.55	87.83	99.37	111.03	121.62	132.15	473	62.94	74.14	85.21	97.25	109.05	119.49	129.66	307	58.30	67.06	76.91	89.20	102.01	113.11	123.68
	45 to 49	1877	64.95	75.17	85.64	97.40	109.29	120.08	130.83	459	60.94	71.87	82.94	95.22	107.49	118.52	129.41	444	56.30	65.05	74.91	87.22	100.07	111.20	121.82
	50 to 54	1502	61.58	71.77	82.23	93.98	105.87	116.66	127.41	460	57.92	68.28	78.98	91.08	103.37	114.59	125.80	525	53.04	61.71	71.50	83.75	96.55	107.66	118.26
	55 to 59	886	57.93	67.91	78.16	89.69	101.34	111.93	122.47	474	55.07	64.62	74.70	86.38	98.51	109.80	121.28	736	49.58	58.07	67.65	79.67	92.25	103.18	113.62
	60 to 64	309	54.38	64.16	74.19	85.48	96.89	107.27	117.60	355	52.66	61.19	70.49	81.59	93.51	104.95	116.89	549	46.69	54.95	64.29	76.01	88.29	98.97	109.18
	65 to 69	229	51.01	60.65	70.55	81.69	92.97	103.23	113.43	308	50.67	58.43	67.07	77.65	89.29	100.74	112.97	581	44.35	52.27	61.24	72.49	84.29	94.55	104.35
	70 to 75	171	48.06	57.45	67.10	77.96	88.96	98.96	108.92	216	48.39	55.77	64.06	74.30	85.70	97.01	109.21	300	41.60	49.35	58.15	69.21	80.83	90.93	100.60

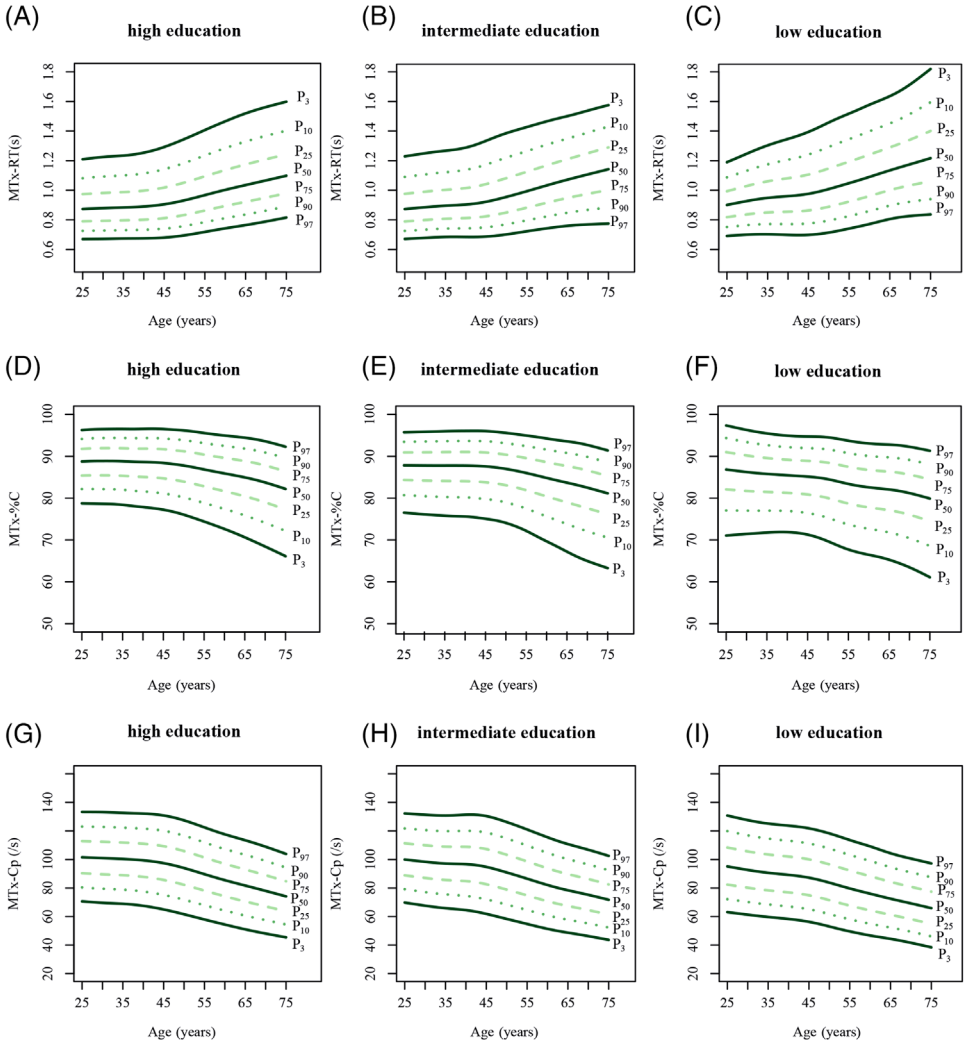

FIGURE 3 Education-specific reference percentiles of MemTrax Metrics. (A-C) MTx-RT percentile curves: (A) high education; (B) intermediate education; (C) low education. (D-F) MTx-%C percentile curves: (D) high education; (E) intermediate education; (F) low education. (G-I) MTx-Cp percentile curves: (G) high education; (H) intermediate education; (I) low education. Px means one's MTx-RT, MTx-%C, or MTx-Cp is better than that of x% users with the same age and education level.

suggests that MTx-RT is an indicator with universality and flexibility in assessing cognition. However, the percentile curve of MTx-%C against age did not fit well, especially for highly educated people. The ceiling effect of MTx-%C found in studies may in part explain these results; however, none of them was stratified by education.[6,15] Therefore, it is essential to establish education-specific percentile reference curves for generating the norms of MemTrax metrics.

Accuracy of recognition reportedly grows at a negatively accelerated rate.[26] We investigated the trade-off of accuracy and recognition time by comparing the metrics from online self-administered tests (Table A.12) with those in this study. Within the MTx-%C interval of 72 to 94 (moderate episodic memory, accounting for 92.51% subjects), self-administered MTx-RT was significantly longer than that of the provider-administered MTx-RT with identical MTx-%C scores. For the in-person, supervised test settings, the rule of hitting the space bar as quickly as possible was emphasized by the rater and therefore may have pressured the trade-off effect toward speed. Interestingly, when MTx-%C was lower than 72 or higher than 94 (poor or good episodic memory, respectively), no significant trade-off effect was observed.

Our results further demonstrated that the models for MTx-Cp, the composite metric, fitted much better than those for both MTx-%C and MTx-RT. This likely was because MTx-Cp explained the variation of both MTx-%C and MTx-RT simultaneously. A previous study showed that MTx-Cp has higher sensitivity than MoCA, MTx-%C, and MTx-RT in distinguishing AD from MCI-AD,[6] which was consistent with our findings.

4.2 | Cognition trajectory

The more educated subjects presented with a later onset and slower decline of either processing speed or episodic memory. This corroborates the observation that education is a protective factor for cognition.[14] The results are likewise in line with the predictions of

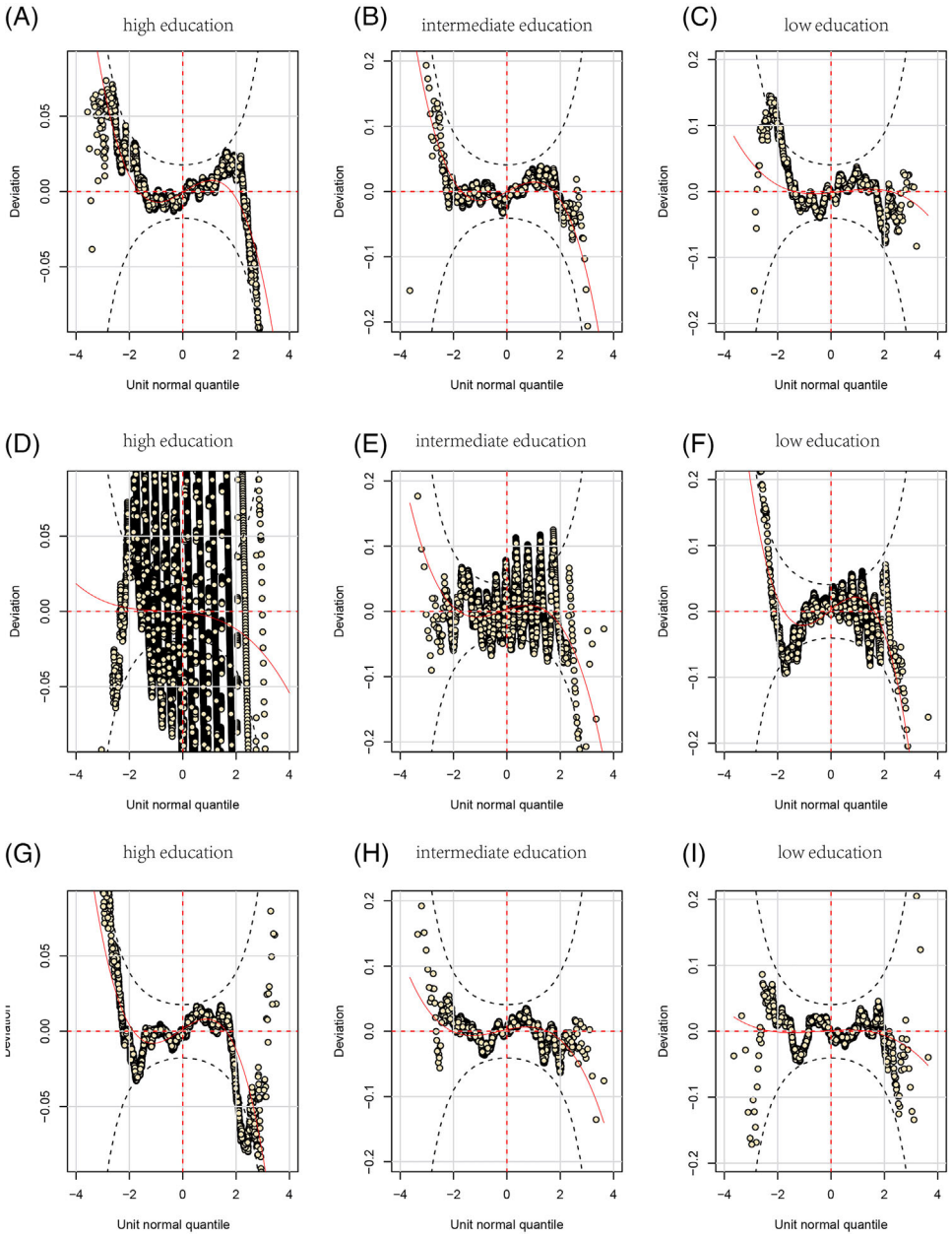

FIGURE 4 Detrended Q-Q plots for fitting effect evaluation. (A) MTx-RT for high education. (B) MTx-RT for intermediate education. (C) MTx-RT for low education. (D) MTx-%C for high education. (E) MTx-%C for intermediate education. (F) MTx-%C for low education. (G) MTx-Cp for high education. (H) MTx-Cp for intermediate education. (I) MTx-Cp for low education.

Stern's model.[27] Our findings are also supported by community studies of Schmand[28] and Staff.[29] In contrast, Amieva's[30] and Scarmeas'[31] studies demonstrated faster recognition decline in highly educated versus less educated AD patients, possibly due to different clinical settings, populations studied, or a "hardy survivor" effect.[14]

Several hypotheses have been put forth to account for the difference in cognitive function decline during aging and diseases. The prevailing hypothesis centers on cognitive reserve (CR), where it is suggested that higher CR is related to better premorbid cognition as well as to delayed onset of cognitive decline. But paradoxically, decline shows a steeper slope thereafter.[27,32,33] Another hypothesis is based on the concept of massive redundancy, which explains survival.[34–36] In a longitudinal biomarker-defined AD continuum study,[37] it was found that education was associated with the rate of cognitive decline. This effect was specific to the disease stage, such that higher education was related to faster cognitive decline among patients with dementia, whereas this relationship was absent (or, in the case of MMSE and visuospatial ability, in the opposite direction) in the pre-dementia group. Baseline age or length of follow-up may also influence the results; that is, studies of middle-aged subjects may require longer follow-up before changes become evident, whereas studies of older subjects may be subject to survival effects.[34] Another finding was that cognition of subjects with a low level of education started to decline from as early as the twenties. This finding was consistent with previous

studies.[38,39] Our results suggest that cognitive health care needs to begin from young adulthood, especially for those with a low level of education. Alternatively, pursuit of education may be a life-long endeavor since education could be a modifiable factor for cognitive health.[40]

4.3 | Application of percentile curves of MemTrax

As a convenient digital biomarker, MemTrax captures intra-individual variability in performance, indicating the earliest changes and subtle health transitions with education- and age-specific reference percentiles. To identify subtle cognitive health transitions or high-risk individuals who will be followed up in our future work, the following considerations are recommended. First, individuals within the third to 10th percentiles in the lower limit of the population performance for age could be at high risk for cognitive impairment. Accordingly, such individuals should take cognitive checkups periodically or have ongoing follow-ups, including MemTrax tests (and of great relevance in the United States for the Medicare Annual Wellness visit mandated cognitive function assessment[41]). Individuals who perform below 3% of the lower limit of the population for their age may have cognitive impairment, so the recommendation is to have a clinical evaluation and intervention as appropriate. The foregoing recommendations are based on the common practice that 3% and 10% are common levels for developing a clinical concern on a laboratory test, though further longitudinal study of the statistical cut-offs for this clinical utility of MemTrax is needed. Second, if one's percentile of cognition drops steadily or significantly during follow-up tests, further clinical cognition evaluation may be recommended. Third, considering the significant speed-accuracy trade-off for those with a MTx-%C interval of 72 to 94, MTx-Cp may be more useful than either MTx-RT or MTx-%C. Fourth, MTx-Cp and MTx-RT may be considered prior to MTx-%C among those individuals with high education due to an unsatisfactory fitting effect. Finally, a standard operating procedure (SOP) for the tests needs to be developed and implemented to minimize the noise and other artifacts of testing. A running average for an individual and a regression model of change could be implemented to allow for a more accurate assessment of cognitive state.

4.4 | Strengths and limitations

This study has several strengths and limitations. GAMLSS is the only method that can model all forms of kurtosis-lepto, platy, and mesokurtosis.[42] With the creative application of this model to cognition, it is possible to model cognition's non-linear relation with advancing age and make precise determination of the time of near optimal MCI onset in specific population groups and then plan strategies to prevent and reverse MCI to the extent possible. In addition, considering that there were no apparent sex effects on cognition[15] and education is one of the most important factors,[43] MTx-Cp, MTx-RT, and MTx-%C against age reference percentiles were established in three education categories. Furthermore, the MemTrax test in our center was administered face to face, and we have subjects' medical information, so there is confidence in the accuracy of information, including performance, sex, age, and education.

Several limitations needed to be mentioned. First, the number of younger subjects with low education was relatively small. Although it is a limitation, it suggests the compulsory education law in China works well. Second, the speed-accuracy trade-off was not investigated using an intra-individual test-retest method. Therefore, we cannot determine whether trade-off effects are an influential factor of model fitness, population sample bias, or device- specific aspect, although the finding that MTx-Cp normalized the speed-accuracy trade-off between the two cohorts at the MTx-%C range of 72 to 94, not in the lower or higher ranges, would argue against device-specific concerns. Third, medication histories were not collected in this study. Drugs for sleep disorders and anxiety, for example, can interfere with visuo-manual abilities as well as with visual attention, without any real cognitive decline. Although extensive care was taken to assess the alertness of the participants as described in the methods section, effects from these types of drugs might still exist but were likely minimized. We will try to collect this information in our follow-up study. Fourth, in this study, age- and education-specific percentile curves of MemTrax metrics are proposed as an initial screen of cognition; other known risk factors beyond education were not considered. We will analyze and try to manage these risk factors in follow-up longitudinal studies. Lastly, the norms still need further verification by multicentric studies to determine whether they can be applied to other populations in other areas of China and globally. However, the large sample size and rigorous methods applied strengthen the potential for more widespread applicability.

5 | CONCLUSIONS

Currently, there are no tests characterized by adequate sensitivity, accessibility, tolerability, and affordability for assessing the transition from cognitively stable to MCI or preclinical changes.[44] Recruitment of patients at an early stage of AD is a key element for clinical trials of various disease-modifying treatments. Reference percentiles of MemTrax may serve as digital biomarkers that can identify and reliably track subtle episodic memory changes in the early detection of AD in a healthcare setting or at home. In addition, this platform may also be used to assess the benefits of intervention trials,[42] as well as following the course of clinical interventions.

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CONFLICTS OF INTEREST STATEMENT

Dr. Ashford developed the MemTrax test and consults with his son, Curtis B. Ashford, to market MemTrax commercially. Dr. Zhou worked with Dr. Ashford and Curtis at MemTrax LLC to develop and implement MemTrax in China, which is marketed commercially by SJN Biomed, where Dr. Zhou was once an executive director. The other authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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