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Prevalence and correlates of dementia and mild cognitive impairment classified with different versions of Telephone Interview for Cognitive Status-modified (TICS-m)

Short running title: Evaluation of different TICS-m versions

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Data sharing: Due to the consent given by study participants and the high degree of identifiability, data cannot be made publicly available. Data are available through the Institute for Molecular Medicine Finland (FIMM) Data Access Committee (DAC) for authorized researchers who have IRB/ethics approval and an institutionally approved study plan. For more details, please contact the FIMM DAC (fimm-dac@helsinki.fi).

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ABSTRACT

Objectives: The Telephone Interview for Cognitive Status modified (TICS-m) is an efficient and cost-effective screening instrument of dementia, but there is less support for its utility in the detection of mild cognitive impairment (MCI). We undertook a comprehensive evaluation of the utility of different TICS-m versions with or without an education-adjusted scoring method to classify dementia and MCI in a large population-based sample.

Methods: Cross-sectional assessment of cognition (TICS-m), depressive symptoms (CES-D) and apolipoprotein E (APOE) ε4 status was performed on 1772 older adults (aged 71–78 y, education 5–16 y, 50% female) from the population-based older Finnish Twin Cohort. TICS-m classification methods with and without education adjustment were used to classify individuals with normal cognition, MCI or dementia.

Results: The prevalence of dementia and MCI varied between education-adjusted (dementia=3.7%, MCI=9.3%) and unadjusted classifications (dementia=8.5–11%, MCI=22.3–41.3%). APOE ε4 status was associated with dementia irrespective of education adjustment, but with MCI only when education adjustment was used. Regardless of the version, poorer continuous TICS-m scores were associated with higher age, lower education, more depressive symptoms, male sex and being an APOE ε4 carrier.

Conclusions: We showed that demographic factors, APOE ε4 status and depressive symptoms were similarly related to continuous TICS-m scores and dementia classifications with different versions. However, education-adjusted classification resulted in a lower prevalence of dementia and MCI and in a higher proportion of APOE ε4 allele carriers among those identified as having MCI. Our

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results support the use of education-adjusted classification especially in the context of MCI.

Keywords: Mild cognitive impairment; Cognitive Status; Dementia; Cognition; Telephone screening; Education; Sex differences; Memory and learning tests; Depressive symptoms; APOE genotype

Key-points:

- There exists variation in the usage of TICS-m resulting from the application of different instrument versions and approaches used to classify cognitive status with and without adjusting cut-off values for education.
- There were considerable differences in the prevalence of dementia and MCI across the TICS-m classification methods with and without education adjustment.
- Having an APOE ε4 allele was related to dementia regardless of the classification method, whereas APOE ε4 carriers had higher prevalence of MCI only when education adjustment was applied.
- The education-adjusted scoring of TICS-m potentially increases the accuracy of identifying MCI. Adjustment for age and sex may increase the accuracy further.

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INTRODUCTION

The modified Telephone interview for Cognitive Status (TICS-m) is a frequently used (available in several languages) self-report telephone-administered instrument for screening cognition in older adults (for a review, see[1]). The TICS-m is intended for research and clinical practice. The administration of TICS-m typically lasts less than 10 minutes. It has been used in clinical trials,[2–4] and in several cross-sectional and longitudinal epidemiological studies that have used the TICS-m either for classifying the cognitive status of individuals,[5–8] or as a continuous measure.[9–11] There exists considerable variation in the usage of TICS-m resulting from the application of different versions which have maximum scores ranging from 27 to 50 and distinct approaches used to classify cognitive status: for example, it is unclear whether to adjust cut-off values for education or not. The utility of different methodologies has not been compared in the same population prior to this study.

Mild cognitive impairment (MCI) and related terms, such as cognitively impaired no dementia (CIND), are used to describe individuals who are in the intermediate stage between normal cognition and dementia.[12] In addition to being a sensitive and specific indicator of dementia,[13,14] the TICS-m has been suggested to be useful for identifying MCI.[15–17] Due to the more normal-shaped distribution of TICS-m compared to Mini Mental State Examination (MMSE), it has been suggested that the TICS-m is less limited by a ceiling effect which usually limits the utility of screening tests to detect MCI.[16] However, most studies have indicated that the TICS-m, like other cognitive screening instruments,[18] performs only fairly in discriminating MCI from healthy cognition.[2,3,19–21] The TICS-m has been reported to have sensitivities ranging from 71 to 82% and specificities from 67 to 87% for discriminating MCI from

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healthy cognition.[15,19,20] Word list test, particularly delayed free recall, has been suggested to be the most important measure of TICS-m for detecting MCI.[2,3]

In order to yield a better understanding of TICS-m instrument in screening of cognitive impairment, we applied the commonly used versions of TICS-m and approaches used to classify cognitive status (dementia, MCI, healthy cognition) in a large population-based sample of 1772 older adults. First, we examined the distribution of total and item scores from different TICS-m versions. Secondly, the prevalence of MCI and dementia were calculated with education-adjusted and unadjusted classification methods and associations of demographic factors, APOE ε4 carrier status and depressive symptoms with MCI and dementia were examined. Thirdly, we examined the relationship of education, sex, age, depressive symptoms, APOE ε4 carrier status and interactions of both age, APOE ε4, and depressive symptoms with sex on the TICS-m and word list recall performance.

METHODS

Participants

The participants were twin individuals born in 1938−1944 from the older Finnish Twin Cohort (FTC) study,[22] who participated in questionnaire surveys in 1975 and 1981 and in a cognitive assessment and collection of saliva samples for DNA extraction and genotyping in 2013−2017 (1817 participants, participation rate 61%). A flowchart showing participation and inclusion/exclusion of individuals is shown in Supplementary Figure 1.

The study was conducted in compliance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland.

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The questionnaire studies were approved by the National Board of Health. Informed consent was obtained from individuals: answering the questionnaire was considered as consent, oral consent was obtained in the beginning of the interview and written consent was obtained for saliva samples.

Cognitive measures

The interview protocol in 2013−2017 was based on the earlier FTC data collection during 1999−2007.[23] The new protocol included the previously validated telephone interview for cognition,[24] but a few questions were added to the original TICS to form the TICS-m.[13] TICS-m data without any missing items was available for 1802 twins.

The TICS-m (50-point scale) included the following items: (1) name (2 points); (2) age (1 point); (3) telephone number (1 point); (4) date (5 points); (5) current president (2 points); (6) previous president (substitute for vice president in the Finnish version) (2 points); (7) counting backwards (2 points); (8) immediate recall of a 10-word list (10 points); (9) subtracting by sevens (5 points); (10) responsive naming (4 points); (11) repetition of phrases (2 points); (12) finger tapping (2 points); (13) word opposites (2 points); (13) delayed recall of the 10-word list (10 points).

Three different scoring protocols were used. First, the total score of the original TICS-m (0−50 points) was used as a continuous variable and as a categorical variable (normal, MCI, dementia) according to the procedure published by Knopman et al.[19] The procedure includes an education adjustment: 5 points are added to the score of individuals with less than 8 years of education, 2 points are added to individuals with 8−10 years of education, no points are added to individuals with 11−15 years of education, and 2 points are subtracted from individuals with 16 or

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more years of education. The cut-off score ≤27 is used for identifying individuals with dementia and scores 28−31 for individuals with MCI.

The second version of TICS-m was a 27-point scale developed by Langa and Weir[21] and was used as a continuous score and as a categorical variable to indicate cognitive status. It included the following items: immediate recall of 10-word list (10 points); delayed recall of 10-word list (10 points); subtracting by sevens (5 points); and counting backwards (2 points). We followed the published approach without adjusting for education and employing the cut-off scores of ≤6 for dementia and 7−11 for CIND.[21] CIND corresponds very closely to MCI.

The third abbreviated 35-point scale version of TICS-m[21,25] was used as a continuous score and included the following items: immediate recall of 10-word list (10 points); delayed recall of 10-word list (10 points); subtracting by sevens (5 points); counting backwards (2 points); date (4 points); responsive naming (2 points); current president (1 point); and previous president (1 point). This TICS-m version was not used as a categorical variable as there was no proposed classification method in literature that included an MCI category.

Other variables

Depressive symptoms were evaluated at the same time as cognition with the 20-item Center for Epidemiologic Studies Depression Scale (CES-D).[26] The CES-D score was calculated by multiplying the mean score of completed items (each item scored 0 to 3) by 20. The total scores range from 0 to 60 and higher scores indicate more depressive symptoms. We excluded 29 individuals who had more than 4 missing items in CES-D. Education information was collected with self-report postal questionnaires in 1975 and 1981 when most individuals had achieved the highest

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educational attainment of their life. Education was reported in 8 categories and this information was transformed into years of education. Education information was missing for 1 individual. APOE genotype was determined from saliva samples. DNA was extracted and genotyped on Illumina HumanCoreExome array. The two single nucleotide polymorphisms (rs429358 and rs7412) were not directly available on the array. Genotype imputation was done using Haplotype Reference Consortium release 1.1 reference panel.[27] APOE genotype was classified into APOE ε4 carriers (ε3/ε4, ε4/ε4, n=476) versus non-carriers (ε3/ε3, ε2/ε3, ε2/ε2, n=1093). APOE ε4 status and did not differ by sex.

Statistical analysis

After the cognitive status classification of Knopman et al.[19] or Langa & Weir[21] was employed, multinomial logistic regression was used to examine the association between the cognitive status (normal, MCI, dementia) and age, sex, CES-D score, APOE ε4 status, and education (with Langa & Weir). The results were reported using relative risk ratios (RRR) with 95% confidence intervals (CI) and p-values.

Linear regression analysis was carried out to examine the association of sex (men as reference group), age (in years), education (in years), depressive symptoms (continuous CES-D score), APOE ε4 status (all non-carriers as reference group) on the continuous total TICS-m score or on the immediate word list recall score (i.e. the sum of immediately recalled words); ε2/ε4 carriers and individuals with unknown genotype formed their own category. Interactions of age, APOE ε4 status and depressive symptoms with sex were analyzed. If a statistically significant interaction ($p<0.05$) was found, separate regression models were performed for men and women. The association of variables with the delayed word list recall performance

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(i.e. the sum of recalled words after a delay) was examined in a similar manner with negative binomial regression. The results were reported using unstandardized regression coefficients with 95% CI and two-tailed p-values.

The analyses included 1772 individuals (891 men and 881 women) without missing information in the telephone interview, CES-D or education. Family structure of the data was considered in all analyses by using robust standard errors adjusted for family relatedness.[28] Years of age and CES-D score were centered at their mean values to avoid multicollinearity.

RESULTS

Sample demographics

The included individuals (n=1772) were more often men (p=0.007) and more educated (p<0.001) compared to excluded individuals (individuals who declined or for other reasons did not participate in the study, n=1178, or who had missing information, n=45). The characteristics and descriptive statistics of individuals included in analyses are shown by sex in Table 1.

Properties of the TICS-m and difficulty of the items

The TICS-m scores of all versions followed approximately a normal distribution. The normal distribution of TICS-m scores (50-, 35-, and 27-point scale) was due to the free immediate and delayed recall of a 10-word list, as the scores from all other measures of TICS-m were negatively skewed (Figure 1 A, B). Closer examination of word list recall revealed that the immediate recall scores exhibited a normal distribution, and the delayed recall scores had a strong positively skewed distribution, with zero being the most frequent score (24.0%) (Figure 1 C). One third

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of individuals with low education (≤6 years) recalled zero words after a delay, whereas every tenth of individuals with high education (≥13 years) recalled zero words ($F(2.00, 2473.80)=35.82$, $p<0.001$) (Figure 2 B).

The most difficult item of the TICS-m was the word list recall, followed by the serial subtraction by sevens, repetition of phrases, word opposites and naming the previous president (Supplementary Table 1).

Cognitive status classifications and their association with sex, education, age, depressive symptoms, and APOE ε4

Following the published cut-off values by Knopman for education-adjusted TICS-m scores, 3.7% of individuals were classified with dementia and 9.3% with MCI. Without adjusting for education and using the same cut-off values, 11.0% of individuals would have been classified as demented and 22.3% as mildly impaired. Based on the classification by Langa & Weir that does not correct for education, 8.5% of individuals had dementia and 41.3% had CIND. The numbers of individuals are given in Supplementary Table 2. The distribution of individuals into cognitive status categories based on the different classification methods and according to education level is shown in Figure 3.

Multinomial logistic regression models were used to examine the association of age, sex, education, CES-D and APOE ε4 with cognitive status classified according to Knopman or to Langa & Weir (Table 2). The association of higher age with MCI and dementia showed similar effect sizes and statistical significance irrespective of the classification method used. Higher CES-D score had a statistically significant association with dementia but not with MCI according to both classification methods.

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There was no statistically significant sex difference in dementia risk, but female sex was associated with lower risk of CIND according to Langa & Weir classification.

APOE ε4 status was associated with higher risk of dementia according to both classifications but with higher risk of MCI only when the classification by Knopman was used (Table 2). According to education-adjusted classification, 43.8% of demented, 41.7% of MCI and 28.7% of cognitively healthy individuals were APOE ε4 carriers whereas no difference between MCI and cognitively healthy individuals in APOE ε4 carrier status was evident when using classifications without adjustment for education (see Supplementary Table 3 for the number of APOE ε4 carriers by different classifications). Knopman classification with and without adjusting for education yielded APOE ε4 status-dementia associations with a relative risk ratio (RRR)=1.95, 95% CI 1.08 to 3.52 and RRR=1.89, 95% CI 1.30 to 2.73, respectively. However, APOE ε4 status was associated with MCI only in Knopman classification with education adjustment (RRR=1.78, 95% CI 1.23 to 2.56) but not without education adjustment (RRR=1.21, 95% CI 0.91 to 1.61).

Associations of continuous TICS-m score with sex, education, age, depressive symptoms and APOE ε4

Main effects. Higher age (unstandardized regression coefficient beta (B)=-0.60 per year, 95% CI -0.75 to -0.45), lower education (B=0.53 per year, 95% CI 0.46 to 0.60), male sex (B=0.98, 95% CI 0.51 to 1.45), higher CES-D score (B=-0.06 per unit, 95% CI -0.10 to -0.03) and APOE ε4 status (B=-0.79, 95% CI -1.34 to -0.25) were associated with poorer TICS-m score (50-point scale). Women had higher TICS-m scores than men due to higher scores in word list recall (Supplementary

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Figure 2). The associations were similar for the 35- or 27-point scale versions of TICS-m (Supplementary Table 4).

Interaction effects. The interaction effect between sex and age was statistically significant (p=0.007), indicating a stronger effect of age on cognition for females than for males (Figure 4); the coefficient of age was -0.83 (95% CI -1.08 to -0.58) for women, and -0.42 (95% CI -0.60 to -0.24) for men. We did not detect any interaction of either APOE ε4 (p=0.74) or CES-D (p=0.73) with sex. The results were similar for the abbreviated versions of TICS-m.

Associations of immediate and delayed word list recall performance with sex, education, age, depressive symptoms, and APOE ε4

Higher age (B=-0.16, 95% CI -0.21 to -0.11), lower education (B=0.12, 95% CI 0.09 to 0.15), male sex (B=0.52, 95% CI 0.35 to 0.68), higher CES-D score (B=-0.01, 95% CI -0.02 to -0.001) but not APOE ε4 carrier status (B=-0.11, 95% CI -0.30 to 0.07) were statistically significantly associated with poorer immediate recall performance. The interaction between age and sex was statistically significant (p=0.01), such that the coefficient of age was -0.23 (95% CI -0.31 to -0.15) for women and -0.10 (95% CI -0.16 to -0.04) for men. The interactions of both APOE ε4 (p=0.41) and CES-D (p=0.75) with sex were not statistically significant.

Higher age (B=-0.09, 95% CI -0.12 to -0.06), lower education (B=0.06, 95% CI 0.05 to 0.07), male sex (B=0.29, 95% CI 0.20 to 0.38), CES-D (B=-0.01, 95% CI -0.02 to -0.004) and having an APOE ε4 allele (B=-0.12, 95% CI -0.23 to -0.01) were associated with worse delayed recall performance. For delayed recall performance,

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we did not detect an interaction of age (p=0.32), APOE ε4 (p=0.68) or CES-D (p=0.45) with sex.

DISCUSSION

Total scores of commonly used TICS-m versions followed approximately a normal distribution even without adjusting for education. Closer examination showed that immediate word list recall was the only measure with a normal distribution. Delayed recall performance had a notable floor effect in individuals with low education: over third of those with less than 6 years of education did not recall any words after a delay. Our findings together with earlier findings[20] indicate that discrepancies in the utility of TICS-m to detect MCI may be partly explained by differences in the educational background of participants across studies. Instead of using a single repetition of 10-word list in TICS-m, multiple learning trials could improve the properties of delayed recall measure as also suggested before.[19,29] Typically, the word list is presented only once during the TICS-m. One study consisting of a highly educated sample in which the TICS-m was modified by presenting the word list three times found that the delayed word list recall task was useful in detecting cognitive impairment (dementia and MCI combined).[30]

By comparing previously published approaches to classify cognitive status, we saw considerable differences in the frequency of individuals classified as having dementia or MCI/CIND. The prevalence of MCI/CIND was 9.5% according to the classification by Knopman et al.[19] that includes an education adjustment and 41.4% according to the classification by Langa & Weir[21] that does not adjust for education. The estimated frequency of MCI according to the Knopman classification is in-line with the MCI prevalence estimates in this age group (10.1% for ages 70−74 and

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14.8% for ages 75−79).[12] As the total score is mostly affected by the word list recall, TICS-m is more likely to identify amnestic MCI compared to nonamnestic presentations.

The reasoning for correcting cut-off values for education is that cognitively normal individuals with more years of education are expected to have better cognitive test performance due to better premorbid cognitive abilities compared to cognitively normal individuals with fewer years of education. Adjusting for premorbid cognitive ability has also been previously shown to affect the prevalence of MCI.[31] Receiving more years of education may delay the onset of dementia by increasing cognitive reserve that helps to tolerate brain pathology.[32] For example, high-educated Alzheimer's disease (AD) patients have been shown to have more advanced pathological and functional brain changes compared to low-educated patients with similar clinical disease severity.[33]

APOE ε4 status was associated with dementia irrespective of the classification method but with MCI only when education adjustment was applied. The finding of a relationship between the most important single risk gene for AD and education-adjusted MCI classification may suggest that education adjustment increased the accuracy of identifying individuals with increased risk of future dementia. In addition, we found poorer total TICS-m score and delayed free recall of 10-word list learning score to associate with APOE ε4 carrier status. To our knowledge, this is the first study to show that the association of APOE ε4 with baseline cognition can be detected with the TICS-m. Previously, greater cognitive decline in APOE ε4 carriers has been detected using the TICS-m.[11]

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Sex may modulate the prevalence of risk factors for cognitive impairment and AD but also the susceptibility to the effects of risk factors (for a review, see[34,35]). We found that poorer TICS-m score was associated with male sex while there was no sex difference in education, age or APOE ε4 status. Only a few studies have examined sex differences in TICS-m. Previously, sex difference in TICS-m performance has been detected in studies with over 500 individuals,[36,37] but not in smaller studies.[16,37] Women tend to outperform men in verbal episodic memory tests.[38] In line with this, we found that lower mean TICS-m score in men was due to poorer immediate and delayed word list recall performance in men than in women.[36] Importantly, we saw that the sex difference in TICS-m and immediate recall scores was dependent on years of age: the negative effect of age was twice as strong in women compared to men during their 70's indicating that the magnitude of sex difference attenuated as a function of older age. Depressive symptoms did not affect this relationship. In a previous large population-based study, the female advantage in TICS-m was less clear with increasing age.[36] We replicated an earlier finding of a diminishing sex difference with increasing age for immediate recall but not for delayed recall performance of TICS-m.[39] We did not detect interaction of either APOE ε4 status or depressive symptoms with sex.

In addition to APOE ε4 status and male sex, poorer TICS-m score was expectedly associated with higher age, lower education and more depressive symptoms as measured by CES-D. We detected similar associations with different TICS-m versions. Previous studies have consistently detected a negative association between age and TICS-m.[16,29,36,37,40] Most studies have also seen a positive association between education and TICS-m,[29,36,37,40] except one study.[16] Previously, depressive symptoms as measured by Geriatric Depression Scale have shown a

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negative association with total TICS-m scores.[29,37] Poorer immediate and delayed word list recall were also associated with higher age, lower education, higher CES-D score and male sex.

A limitation of this cross-sectional study is the lack of comparison with classifications based on clinical diagnostic criteria. With longitudinal data, it would be possible to evaluate if MCI classification done based on education-adjusted scores identifies better the individuals who show future cognitive decline. The participants were asked about their hearing, to find a quiet place and not to use any external memory aids. Nevertheless, the telephone interview is limited by severe hearing loss and the restricted control over motivation and external distractors. An objective hearing test and an assessment of motivation could be useful additions to the interview. Our results are generalizable only to adults in their 70's, which is nonetheless an important period from the point of brain aging.[41]

CONCLUSION

We showed that the prevalence of dementia and MCI differs with different scoring and education adjustment. The overall prevalence of dementia was lower when using education-adjusted classification. Demographic factors, depression and APOE genotype were similarly associated with dementia classification and continuous total scores regardless of the TICS-m version. Delayed word list recall test which is often considered as the most important measure of TICS-m had a notable floor effect in low-educated individuals. The overall prevalence of MCI was considerably lower when using education-adjusted approach. Further, APOE ε4 status was associated with MCI only when education adjustment was applied. Our findings support the use

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of education-adjusted scoring for more accurate classification of MCI in research and clinical practice.

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Table 1. Characteristics and descriptive statistics of study sample (n=1,772)

	Women (*n* = 881)			**Men (*n* = 891)**			P for difference in means by sex
	Mean (SD)	Median (IQR)	Range	Mean (SD)	Median (IQR)	Range	
Age, y	73.7 (1.4)	73.6 (2.2)	71−78	73.9 (1.6)	73.8 (2.4)	71−78	0.06†
Education, y	8.6 (3.1)	7 (4)	5−16	8.5 (3.2)	7 (4)	5−16	0.49†
CES-D	8.5 (7.9)	6.3 (10)	0−55	7.0 (6.7)	5 (9)	0−38	0.001†
TICS-m (0−50)	33.9 (5.4)	34 (7)	13−50	32.8 (4.9)	33 (6)	14−50	<0.001‡
TICS-m (0−35)	19.7 (4.7)	20 (6)	2−35	18.8 (4.2)	19 (5)	6−35	<0.001‡
TICS-m (0−27)	12.2 (4.4)	12 (6)	0−27	11.5 (3.8)	11 (4)	2−27	0.001‡
Immediate recall	4.4 (1.8)	4 (3)	0−10	3.9 (1.6)	4 (2)	0−10	<0.001‡
Delayed recall	2.4 (2.1)	2 (2)	0−10	1.8 (1.8)	1 (3)	0−10	<0.001§

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Abbreviations: IQR, interquartile range; TICS-m, Modified Telephone interview for Cognitive Status; CES-D, Center for Epidemiologic Studies Depression Scale. Note. Immediate recall is the sum of immediately recalled words and delayed recall is the sum of recalled words after a delay in the word list test of TICS-m. †Statistical significance tested with adjusted Wald test. ‡Statistical significance tested with linear regression adjusted for age, sex, education, CES-D, APOE ε4 status and for clustering of twins. §Statistical significance tested with negative binomial regression adjusted for age, sex, education, CES-D, APOE ε4 status and for clustering of twins.

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Table 2. Association of sex, age, education, CES-D, and APOE ε4 with cognitive impairment according to the previously published cognitive status classification by Knopman or Langa & Weir

	Dementia				**Mild cognitive impairment**			
	Knopman		**Langa & Weir**		**Knopman**		**Langa & Weir**	
Variables	**RRR (95% CI)**	**P**	**RRR (95% CI)**	**P**	**RRR (95% CI)**	**P**	**RRR (95% CI)**	**P**
Sex								
Female	0.84 (0.49, 1.44)	0.528	0.80 (0.55, 1.15)	0.228	0.73 (0.52, 1.02)	0.068	0.74 (0.60, 0.91)	**0.004**
Age†	1.24 (1.09, 1.42)	**0.001**	1.30 (1.16, 1.45)	**<0.001**	1.29 (1.17, 1.42)	**<0.001**	1.25 (1.16, 1.35)	**<0.001**
Education†	-		0.63 (0.55, 0.73)	**<0.001**	-		0.87 (0.84, 0.90)	**<0.001**
CES-D	1.05 (1.02, 1.08)	**<0.001**	1.03 (1.00, 1.05)	**0.037**	1.02 (1.00, 1.04)	0.089	1.01 (0.99, 1.02)	0.211
APOE ε4‡	1.95 (1.08, 3.52)	**0.027**	2.13 (1.41, 3.21)	**<0.001**	1.78 (1.23, 2.56)	**0.002**	1.23 (0.96, 1.56)	0.096

Abbreviations: RRR, relative risk ratio; CES-D, Center for Epidemiologic Studies Depression Scale. Notes. The reference group is healthy cognition. Because the

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classification by Knopman includes an education adjustment, education was not included in the multinomial regression model. †Age and education as years. ‡APOE ε4: non-carriers (ε2/ε2, ε2/ε3, ε3/ε3) = 0, APOE ε4 carriers (ε4/ε3, ε4/ε4) = 1.

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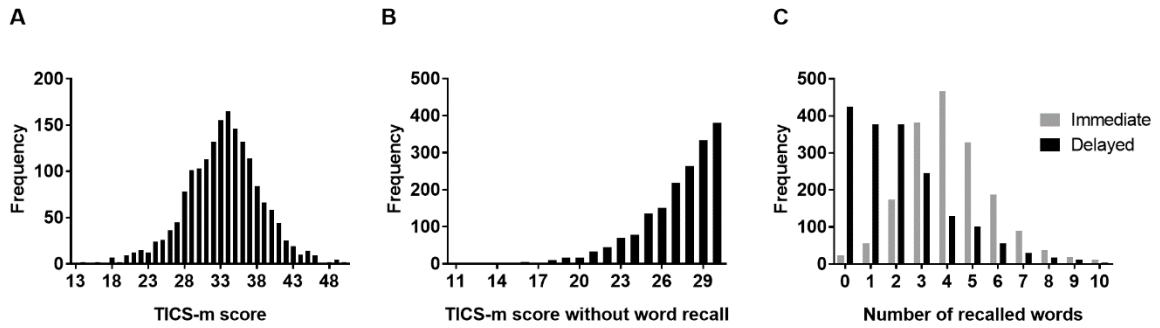

Figure 1. Distribution of TICS-m scores and the memory items of TICS-m (n=1,772). A) The distribution of total scores on the TICS-m version with a maximum score of 50 followed approximately a normal distribution (mean (M)=33.4, SD=5.2, range 13−50, skewness=-0.2, kurtosis=3.7). Also, the total scores on the abbreviated TICS-m versions with maximum scores of 35 and 27 followed approximately a normal distribution (35-point scale: M=19.3, SD=4.5, range 2−35, skewness=0.2, kurtosis=3.6; 27-point scale: M=11.8, SD=4.1, range=0−27, skewness=0.5, kurtosis=3.6). **B)** The distributions of total TICS-m scores without the word list recall score were skewed (50-point scale: M=27.1, SD=2.9, range 11−30, skewness=-1.5; 35-point scale: M=13.0, SD=2.1, range 2−15, skewness=-1.3; 27-point scale: M=5.6, SD=1.6, range=0−7, skewness=-1.1). **C)** The distribution of immediate (M=4.2, SD=1.7, range 0−10, skewness=0.4, kurtosis=3.6) and delayed word list recall scores (M=2.1, SD=2.0, range 0−10, skewness=1.1, kurtosis=4.2).

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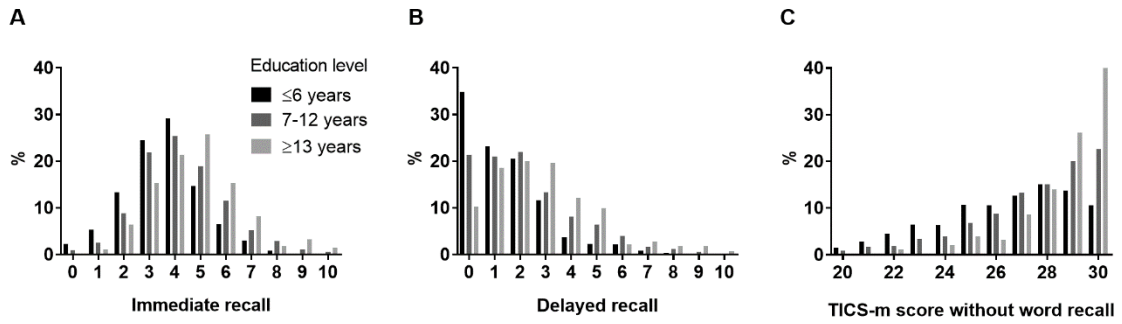

Figure 2. Distribution of TICS-m scores and the memory items of TICS-m stratified by the education level (n=1,772). The black bars represent the percentage of individuals within the category of 6 or less years of education (n=594), the dark gray bars the percentage of those within the category of 7 to 12 years of education (n=900) and the light gray bars the percentage of those within the category of 13 or more years of education (n=278). **A)** The distribution of immediate word-list recall scores. **B)** The distribution of delayed word-list recall scores. 34.7% (206/594) of individuals with 6 or less years of education recalled zero words after a delay, while 9.7% (27/278) of individuals with 13 or more years of education recalled zero words. **C)** The distribution of TICS-m scores without the word list recall according to the education level.

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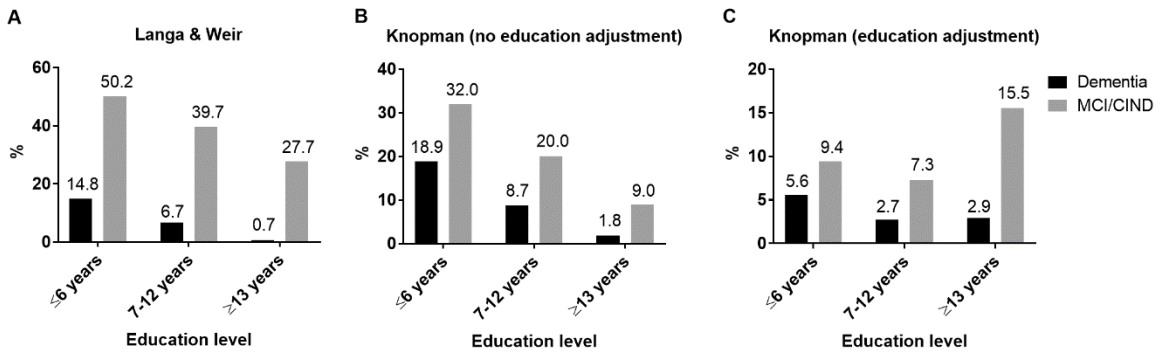

Figure 3. Distribution of participants in the cognitive status categories according to education level (n=1,772). A) The percentage of individuals classified as having dementia or mild cognitive impairment not dementia (CIND) based on the classification of Langa & Weir that does not include an education adjustment. **B)** The percentage of individuals classified with dementia or mild cognitive impairment (MCI) based on the classification by Knopman et al. but without using the education adjustment. **C)** The percentage of participants classified as having dementia or MCI based on the classification of Knopman et al. with education adjustment.

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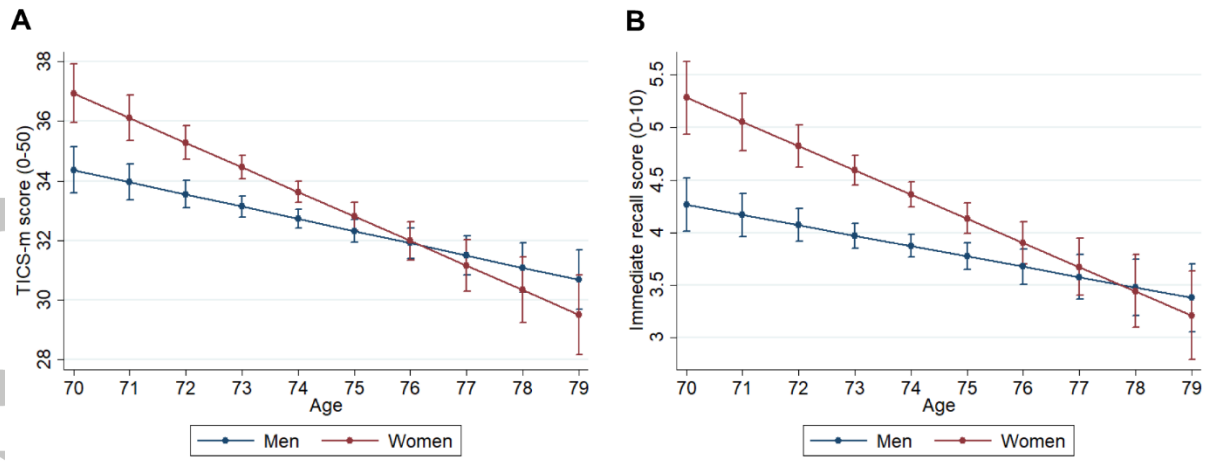

Figure 4. Interaction effect indicating that the relationship between both the TICS-m and the immediate free recall with age differs by sex. A) Predictive margins of sex with 95% confidence intervals for total TICS-m score. **B)** Predictive margins of sex with 95% confidence intervals for immediate recall score (the number of recalled words in immediate free recall of 10-item word list).

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