

Supplementary Material

Estimating Likelihood of Dementia in the Absence of Diagnostic Data: A Latent Dementia Index in 10 Genetically Informed Studies

MEASURES

Sweden

HARMONY

In the HARMONY LDI, we included four cognitive variables, three memory variables, and one functional ability variable. The four cognitive variables were Block Design, a spatial processing task that requires participants to use two-color blocks to reproduce drawings of increasing complexity, from the Swedish version of the WAIS [1]; Information, a verbal task designed to measure general knowledge, also from the Swedish WAIS [1]; Symbol Digit, a perceptual speed and accuracy task that requires respondents to state out loud as rapidly as possible the digit assigned to one of nine two-dimensional geometric symbols that are presented in a series of rows of symbols [2]; and Semantic Fluency, a verbal task that requires participants to generate as many names of animals as possible in 60 seconds, from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [3,4].

The memory task was Word List from CERAD, that asks participants to read aloud 10 unrelated words during three presentations of the words, recalling as many words as possible after each presentation and then after a delay of ~5 minutes. From Word List, we included three variables: Immediate Recall, the sum of all words recalled immediately after each of the initial three presentations; Delayed Recall, the number of words recalled after the delay; and Delayed Recognition, the number of words correctly identified from a list of 10 original words plus 10 new distractor words.

The functional ability variable was based on informant rating of seven tasks that were related to daily living tasks requiring cognitive function and were not specific to memory decline or to physical impairment (e.g., shopping, household chores, finding one's way, finances) taken from the interview used to score the Clinical Dementia Rating (CDR) [5].

SATSA

In the SATSA LDI, we included nine cognitive variables, four memory variables, and a functional ability variable. The cognitive tasks were Kohs Block Design [6]; Information; Symbol Digit; Digits Forward, a short-term memory task asking the respondent to repeat strings of digits in the order as administered; Digits Backward, a working memory task asking the respondent to repeat strings of digits in the reverse order as administered; Figure Identification, a perceptual speed task that requires participants to decide which of five figures is identical to a given figure (Form A only) [7,8]; Figure Rotation, a spatial task where figures must be recognized as the same despite different rotations [9]; Synonyms, a vocabulary test requiring the respondent to select the word that provided the best synonym to a target word from a set of five alternatives[7.8]; and Analogies, a verbal task that requires understanding how a pair of words is alike and applying the rule to a second pair of words [10]. The four memory variables were the same three CERAD Word List variables as in HARMONY plus Picture Memory, a visual recognition task that presents a series of pictures sequentially then immediately requires participants to identify each previously presented drawing from among four pictures [11]. The functional ability variable was created from eight self-report items similar to those in HARMONY.

OCTO-Twin

In the OCTO-Twin LDI, we included seven cognitive variables, two memory variables, and a self-reported functional ability variable. The cognitive tasks were Block Design, Information, Symbol Digit, Digits Forward, Digits Backward, Figure Identification, and Synonyms. The memory variables were Picture Memory and Prose Recall Immediate, a verbal episodic memory task that required participants to recall a paragraph story immediately after it was read aloud [12]. The functional ability variable was created from seven self-report items tapping instrumental activities of daily living.

GENDER

In the GENDER LDI, we included five cognitive variables, four memory variables, and a self-reported functional ability variable, with the battery overlapping substantially with the other Swedish studies. The cognitive tasks were Block Design, Symbol Digit, Figure Identification, Figure Rotation, and Synonyms. The memory variables were the same three CERAD Word List

variables as in HARMONY and SATSA and the same Picture Memory variable as in SATSA and OCTO-Twin. The functional ability variable was the same as in OCTO-Twin.

Mental Status. HARMONY gave the MMSE from the Canadian Study of Health and Aging [13] where the mental reversal score uses points for spelling backwards (the Swedish word “KONST”). Serial 7s was used in the scoring of SATSA, OCTO-Twin, and GENDER.

Clinical Dementia Diagnosis. For HARMONY and for SATSA through IPT 4, the clinical workup included physical and neurological examination by a physician; a complete medical history based on medical record review and informant interview, including onset and sequence of memory and cognitive symptoms; neuropsychological assessment; collection of blood for laboratory tests; and referral for computed tomography imaging [14]. For SATSA after IPT4, OCTO-Twin, and GENDER, diagnostic workups relied on the IPT cognitive assessment battery, brief physical and neurological evaluation, blood panel, and medical records [15]. Final dementia diagnosis for all Swedish studies was made at multidisciplinary consensus conferences according to DSM-III-R or DSM-IV criteria [16,17] for dementia, with subtypes according to their respective criteria. Anyone diagnosed as “questionable” dementia (cognitively impaired not dementia) was considered non-demented in our dichotomous clinically demented variable. This dichotomous variable was coded 1=demented; 0=non-demented.

Registry Dementia Diagnostic Codes. For all Swedish studies, the National Patient Register (NPR), Out Patient Register (OPR), Cause of Death Register (CDR), and Prescribed Drug Register (PDR) were used to obtain registry diagnostic codes of dementia. All registers were updated through 2016, except the PDR, which was updated through 2017. Using data from the three Swedish Twin Register longitudinal studies, it was estimated that a record with a dementia ICD code appears in the NPR on average 5.5 years after first clinical diagnosis [18,19]. Thus, in our analyses, registry classification of dementia was based on whether the participant had an ICD code for dementia within 5 years after the assessment wave used in the analyses.

Denmark

In the combined Danish LDI, we included four cognitive variables, one memory variable,

and a functional ability variable. Cognitive variables included Symbol Digit, Digits Forward, Digits Backward, and Semantic Fluency. The memory task was a list of 12 unrelated words selected from the Rey Auditory Verbal Learning Test (RAVLT) [20] read aloud in a single administration, after which the individual was asked to repeat as many words as possible, followed by an additional reading of the list, and an ~10-minute delay before the delayed-recall trial. The task generated two variables: Immediate Recall and Delayed Recall. The functional ability variable was the sum of seven self-reported items obtained from Lawton's self-maintaining and instrumental activities measure [21]. Mental status was assessed with the MMSE with serial 7s, and spelling backwards ("SKOLE") as an alternative if the participant said that they could not calculate [22].

Registry Dementia Diagnostic Codes. Register information was obtained from the National Patient Register (NPR) using ICD codes [23].

Australia

In the OATS LDI, we included eight cognitive variables, five memory variables, and a functional ability variable. Cognitive variables included: Block Design from the WAIS-R [24]; Digits Forward and Digits Backward from the WAIS-III [25]; verbal Semantic Fluency (animals); Letter Fluency ("F", "A", "S"; Controlled Oral Word Association Test) [26,27]; Digit Symbol from the WAIS-III; Trail-Making Test A & B [28]; an Australian version of the Boston Naming Test [29]; and Similarities from the WAIS-R. Memory was assessed with a 15-item word list from the adapted RAVLT [20,30] and WMS-R Logical Memory Story A Recall. Memory variables included: Word List Immediate (sum of five learning trials); Short Delayed Recall after an interference list; Delayed Recall from the adapted RAVLT; and Immediate Recall and Delayed Recall from the WMS-R Story A. The functional ability variable was the 10-item informant-rated Bayer Activities of Daily Living Scale [31]. Mental status was measured with the MMSE.

United States

CAATSA

In the CAATSA LDI, we included four cognitive variables, three memory variables, and one

functional ability variable. The four cognitive variables were Digit Span-Forward, Digit Span-Backward, Digit Symbol from the WAIS-R, and Alpha Span Test, a measure of working memory that requires participants to reorder a list of words into alphabetical order [32]. The three memory variables included Immediate Recall of the 10-item Word List from the TICS [33], and Prose Recall Immediate and Prose Recall Delayed, which was administered after ~10-minute delay, from the WMS Logical Memory. The functional ability variable was created from eight self-reported items. The total score of the TICS (omitting the Word List item) was used as the mental status measure.

MIDUS

MIDUS used the Brief Test of Adult Cognition by Telephone (BTACTION) [34], which provided five cognitive variables and two memory variables for the LDI. The five cognitive variables were: Digit Span-Backward from the WAIS-III; Semantic Fluency; Stop & Go Task, a measure of reaction time and inhibitory control, with the primary score being the mean of the median switch and median non-switch trial latencies [35]; Number Series, a test requiring the respondent to hear a series of numbers with one number missing, determine the numerical pattern and provide the missing number [36]; and Backward Counting, a measure of speed of processing requiring participants to count backward from 100 as quickly as possible for 30 seconds [37]. The two memory variables included Word List of 15 unrelated words from the adapted RAVLT read aloud once with an Immediate Recall and a 15-20-minute Delayed Recall. For the functional ability variable, three items were selected from the Personality in Intellectual Aging Contexts (PIA) [38,39] scale administered to the participant. There was no mental status measure.

VETSA

VETSA has an extensive assessment battery from which we included 15 cognitive variables and 7 memory variables in the LDI, selecting measures most parallel to other IGEMS studies. The cognitive variables were Digits Forward and Digits Backward from Wechsler Memory Scales-III (WMS-III) [40]; Semantic Fluency-Animals, Semantic Fluency-Boy Names, and Letter Fluency from the Delis-Kaplan Executive Function System (D-KEFS) [41]; Trails Number Sequencing and Trails Switching from the D-KEFS (analogous to Trails A and Trails

B); Gottschaldt Hidden Figures test, which requires the participant to identify a target figure embedded in a more complex two-dimensional design [42]; Letter-Number Sequencing, where participants are read a series of numbers and letters, which must then be repeated back with numbers first in ascending order followed by letters in alphabetical order, from WMS-III; Matrix Reasoning, where participants are asked to complete visually presented patterns of increasing difficulty by selecting from five possible solutions, from the Wechsler Abbreviated Scale of Intelligence (WASI) [43]; Reading Span: Total Score Ascending [44]; Spatial Span-Forward and Spatial Span-Backward from WMS-III; 14) Stroop Interference, where time to read the color in which words are printed while ignoring the color name is compared with reading words or naming colors without interference [45]; and Vocabulary, which requires participants to define a series of increasingly difficult words, from the WASI.

Memory variables included Immediate Recall of a list of 16 words from 4 categories summed across 5 trials, Short Delay Recall after interference list, and 20-minute Delayed Recognition from the California Verbal Learning Test-II [46], and Prose Recall Immediate and 30-minute Prose Recall-Delayed from the WMS-III Logical Memory. The functional ability variable was created from five self-report items. There was no mental status measure.

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Supplementary Table 1. Unstandardized Latent Dementia Indicator Factor Loadings

	Sweden				Australia	Denmark		US		
	HARMONY (n=1,381)	SATSA (n=548)	GENDER (n=479)	OCTO- Twin (n=561)	OATS (n=592)	MADT (n=4,306)	LSADT (n=4,626)	CAATSA (n=675)	MIDUS (n=1,341)	VETSA (n=1,261)
Memory Variables										
Word List Immediate Recall	1.00=	1.00=	1.00=		1.00=	1.00=	1.00=	0.48	1.00=	1.00=
Word List Delayed Recall	1.11	1.46	1.52		1.66	1.36	1.35		1.08	1.78
Word List Delayed Recognition	1.13	0.89	0.60							0.65
Prose Recall-Immediate				1.00=	0.68			1.00=		2.14
Prose Recall-Delayed					0.80			0.80		2.42
Picture Memory		0.86	0.60	0.89						
Cognitive Variables										
Block Design	0.60	0.68	0.51	0.48	0.54					
Digits Forward		0.27		0.30	0.18	0.40	0.55	0.32		0.40
Digits Backward		0.58		0.46	0.36	0.55	0.65	0.44	0.41	0.52
Figure Identification		0.62	0.35	0.50						
Figure Rotation		0.63	0.27							
Fluency-Categorical	0.43				0.27	0.39	0.58		0.20	0.43
Fluency-Letter	0.73	0.80			0.18					0.42
Information		0.62	0.66	0.95						
Synonyms	0.48	0.51	0.42	0.77						
Symbol Digit	0.60	0.68	0.51	0.36	0.33	0.47	0.70	0.48		
Trails A					0.10					0.41
Trails B					0.12					1.02
Functional Ability	-0.79	-0.30	-0.32	-0.14	-0.13	0.07	0.26	-0.09	-0.10	-0.26
LDI mean	5.77	8.16	6.68	5.56	7.24	4.30	3.72	2.48	4.41	4.82
(variance)	(4.28)	(2.56)	(2.82)	(7.68)	(1.85)	(0.94)	(0.62)	(1.40)	(1.88)	(0.30)

Loadings only shown in table for tasks in multiple studies. = indicates loading was fixed to the value shown.

Loadings not displayed in the table by sample include: SATSA: Analogies (0.68); OATS: Naming (0.37), Similarities (0.60), List Immediate Short Delay Recall (1.56); CAATSA: Alphabet Span (0.52); MIDUS: Counting Backward (0.18), Number Series (0.59), Stop-Go Switching (0.07); VETSA: Fluency-Categorical Boy Names (0.38), Hidden Figures (1.03), Letter-Number Sequencing (0.50), Matrix Reasoning (1.06), Reading (0.63), Spatial Span-Forward (0.33), Spatial Span-Backward (0.50), Stroop (0.38), Vocabulary (0.55). All loadings shown for HARMONY, GENDER, and OCTO-Twin.

Fixed loading of Word List Immediate Recall to 1.00 in all studies except OCTO-Twin and CAATSA where we instead fixed Logical Memory Immediate to 1.00. OCTO-Twin did not have Word List and CAATSA, which used TICS 10-item scale, did not have adequate variance on this item.