Supplementary Material

Mild Cognitive Impairment, Reversion Rates, and Associated Factors: Comparison of Two Diagnostic Approaches

Calculation of the Normative Sample for the Cognitive Tests

Study population

The data used to estimate the expected values for the different cognitive tests was obtained from the "The Swedish National Study on Aging and Care" (SNAC) and the study's sites SNAC-Kungsholmen and SNAC-Blekinge [1]. Participants with dementia were excluded since the objective was to reflect cognitive test results of a cognitively normal population. The data were collected between 2001 and 2004.

Supplementary Table 1. Characteristics of the normative population

Variables		SNAC-Kungsholmen	SNAC-Blekinge
Sex, n [%]	Female	1,690 [62.0]	774 [58.1]
	Male	1,036 [38.0]	557 [41.8]
Age (y), mean [std, min-max]		72.7, [10.2, 58-102]	76.2, [10.1, 60-96]
Formal education (y) mean [std, min-max]		12.1, [4.2, 1.5-37.5]	7.8, [2.8, 1-26]

Statistical methods

Quantile regression was used to calculate the expected quantiles for the different test scores [2] corrected for age, level of education, and sex. The calculations were done in python 7.19.0 and validated using IBM-SPSS statistics package 27.

Effect of Categorization of Self-Reported Alcohol Consumption at First MCI Diagnosis on the Risk of Reversion

In the primary model, alcohol consumption was categorized as:

- Low consumption: Never or at most once a month
- Moderate consumption: 2-4 times a month
- High consumption: At least 2-3 times a week

To investigate whether non-consumers and low-consumers had the same risk of reversion, alcohol consumption was categorized as the following in a sensitivity analysis.

- No alcohol consumption
- Low consumption: At most once a month

- Moderate consumption: 2-4 times a month
- High consumption: At least 2-3 times a week

Results

No significant differences were detected between no consumers and low consumers on the risk of reversion when applying the Petersen criteria (Supplementary Table 2).

Supplementary Table 2. Summary of the Poisson regression models with incident rate ratios for reversion using the Petersen criteria. A comparison between the primary model used in the manuscript and a sensitivity model stratifying alcohol into four categories.

	Primary model		**Sensitivity analysis**	
	Incidence rate ratio (person/year) (95% CI)	**p**	**Incidence rate ratio (person/year) (95% CI)**	**p**
Living alone (cohabitant reference)	0.86 (0.71; 1.05)	0.14	0.86 (0.71; 1.04)	0.128
Low alcohol consumption (no/low reference in primary analysis) (no reference in sensitivity analysis)	N/A	N/A	1.28 (0.90;1.82)	0.167
Moderate alcohol consumption (no/low reference in primary analysis) (no reference in sensitivity analysis)	1.44 (1.20; 1.81)	<0.001***	1.74 (1.25; 2.40)	<0.001***
High alcohol consumption (no/low reference in primary analysis) (no reference in sensitivity analysis)	1.40 (1.08; 1.82)	0.01**	1.66 (1.15; 2.39)	0.01**
Female sex (male reference)	0.91 (0.75; 1.09)	0.29	0.91 (0.76; 1.09)	0.322
Age (y)	1.02 (1.01; 1.03)	<0.001***	1.02 (1.01; 1.03)	<0.001***
BMI (kg^2/m)	0.98 (0.96; 1.01)	0.14	0.98 (0.96;1.01)	0.152
Depressive symptoms	1.01 (0.99; 1.03)	0.39	1.01 (0.99; 1.03)	0.356
Cardiovascular disease (no disease reference)	0.89 (0.74; 1.08)	0.24	0.89 (0.73; 1.07)	0.216
Smoker (non-smoker reference)	0.98 (0.82; 1.18)	0.87	0.97 (0.81; 1.17)	0.776
Sleeping disturbances (no disturbances reference)	0.98 (0.81; 1.15)	0.74	0.98 (0.81; 1.17)	0.806
Physically active (sedentary reference)	1.14 (0.60; 2.16)	0.69	1.15 (0.60; 2.18)	0.673
Two or more impaired cognitive domains (one impaired domain is reference)	0.37 (0.27; 0.49)	<0.001***	0.37 (0.28; 0.50)	<0.001***
Years of formal education	0.99 (0.96; 1.01)	0.23	0.98 (0.96; 1.00)	0.229

BMI, body max index; N/A, not applicable. *p<0.05, **p<0.01, ***p<0.001

Comparison of Reversion Rates when Using the Same Participants

As the Neuropsychological (NP) criteria requires more cognitive data (two cognitive tests per domain) fewer participants were eligible for the NP criteria classification in comparison to the Petersen criteria which requires less cognitive data (one cognitive test per domain). In the original analyses, there were 1,785 and 987 participants who fulfilled the MCI criteria according to Petersen and the NP criteria, respectively. We performed a sensitivity analysis which included the same participants that fulfilled both MCI criteria at first diagnosis.

Results

The overlap between the participants was:

- 911 participants fulfilled both MCI criteria in at least one study visit. Of those, 334 had follow-up visits with enough data for MCI classification or reversion, irrespective of applied criteria.
- 874 participants only fulfilled the Petersen criteria
- 76 participants only fulfilled the NP criteria

The number of cognitive domains affected was similar for both definitions, with one affected cognitive domain as the most common impairment in both criteria (Supplementary Table 3).

Supplementary Table 3. Comparison of affected cognitive domains for MCI participants that fulfilled both Petersen and Neuropsychological criteria at first diagnosis and with follow-up data.

	Cognitive domains affected according to NP criteria				**Total**
Cognitive domains affected according to Petersen criteria	1	2	3	4	
1	176	15	0	0	191
2	59	29	4	0	92
3	17	16	4	2	39
4	2	2	7	1	12
Total	254	62	15	3	334

The reversion rate was 32.9 % (95 % CI: 27.9; 38.3) and 46.4 % (95 % CI: 41.0; 51.9) for the Petersen and the NP criteria, respectively (Supplementary Table 4).

Supplementary Table 4. Comparison of reversion rates for the Petersen and Neuropsychological criteria for participants who fulfilled both MCI criteria at first diagnosis and with follow-up data.

	Neuropsychological criteria		**Total**
Petersen criteria	**Stable MCI**	**Reversion**	
Stable MCI	167 (50.0%)	57 (17.1%)	224 (67.1%)
Reversion	12 (4.0%)	98 (29.3%)	**110 (32.9%)**
Total	179 (53.6%)	**155 (46.4%)**	334 (100.0%)

The observed agreement for both definitions is 79.3 % and the Kappa coefficient is 0.58 (95 % CI: 0.49; 0.66). The agreement between the definitions is considered acceptable given the differences between the MCI criteria regarding the required number of impaired cognitive test scores and the cut-off threshold.

Comparison of Participants that Were Lost to Follow-Up and Further Study Attenders

Petersen criteria

There were 1785 participants who fulfilled the MCI definition according to the Petersen criteria. Of those, 527 did not attend any further re-examinations and 514 attended further re-examinations but were not eligible for MCI classification (e.g., had missing data, were dependent on activities of daily life, no longer reported cognitive complaint). Main baseline characteristics for these participants are contrasted below. As seen in Supplementary Table 5, participants lost to follow-up were somewhat older but otherwise characteristically similar to those remaining in the study.

Supplementary Table 5. Comparison of baseline characteristics for participants ineligible for MCI diagnosis and those lost to follow-up for the Petersen criteria

Characteristics measured at the time of the first MCI diagnosis		**Did not attend any further study visits (n=527)**	**Attended further visits but were not eligible for MCI classification (n=514)**	**Attended further visits with sufficient information for MCI classification (n=744)**
Sex, n [%]	Female	284 [54.0]	295 [57.4]	399 [53.6]
	Male	243 [46.1]	219 [42.6]	345 [46.4]
Age (y), mean [min-max]		72.1 [59.3-96.9]	71.2 [59.3-95.4]	68.3 [59.2-94.0]
Education (y), mean [min-max]		10.8 [1-26]	10.5 [3-25]	10.9 [1-30]
Mini-Mental State Examination, mean [min-max]		25.6 [5-30]	26.1 [1-30]	26.4 [1-30]
Number of impaired cognitive domains, n [%]	1	366 [69.4]	368 [71.6]	524 [70.4]
	2	107 [20.3]	116 [22.6]	151 [20.3]
	3	43 [8.1]	25 [4.9]	54 [7.3]
	4	11 [2.1]	5 [1.0]	15 [2.0]

Neuropsychological criteria

There were 987 participants who fulfilled the MCI definition according to the Neuropsychological criteria. Of those, 324 did not attend any further re-examinations and 288 attended further re-examinations but were ineligible for MCI diagnosis (e.g., had missing data, were dependent on activities of daily life, no longer reported cognitive complaint). Main baseline characteristics for these participants are contrasted below. As seen in Supplementary Table 6, participants lost to follow-up had a 1-point lower average score on the MMSE in comparison to those who further attended study visits and had sufficient information for MCI classification. Participants lost to follow-up were somewhat older but otherwise characteristically similar to those remaining in the study.

Supplementary Table 6. Comparison of baseline characteristics for participants ineligible for MCI diagnosis and those lost to follow-up for Neuropsychological criteria

Characteristics measured at the time of the first MCI classification		**Did not attend any further study visits (n= 324)**	**Attended further visits but were not eligible for MCI classification (n=288)**	**Attended further visits with insufficient information for MCI classification (n=375)**
Sex, n [%]	Female	173 [53.4]	159 [55.2]	194 [51.7]
	Male	151 [46.6]	129 [44.8]	181 [48.3]
Age (y), mean [min-max]		72.3 [59.8-95.8]	70.9 [59.4-95.4]	68.1 [59.4,90.8]
Education (y), mean [min-max]		10.6 [1-26]	10.3 [4-30]	11.0 [4-27]
Mini-Mental State Examination, mean [min-max]		24.9 [1-30]	25.6 [16-30]	26.2 [1-30]
Number of impaired cognitive domains, n [%]	1	234 [72.2]	231 [80.2]	292 [77.9]
	2	64 [20.0]	47 [16.3]	65 [7.3]
	3	23 [7.1]	8 [28.0]	15 [4.0]
	4	3 [0.9]	2 [0.7]	3 [2.9]

REFERENCES

[1] Lagergren M, Fratiglioni L, Hallberg IR, Berglund J, Elmståhl S, Hagberg B, Holst G, Rennemark M, Sjölund BM, Thorslund M, Wiberg I, Winblad B, Wimo A (2004) A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). *Aging Clin Exp Res* **16**, 158–168.

[2] Sherwood B, Zhou AX, Weintraub S, Wang L (2015) Using quantile regression to create baseline norms for neuropsychological tests. *Alzheimers Dement* **2**, 12–18.