Biomarkers and Cognition Study, Singapore (BIOCIS) : Protocol, Study Design, and Preliminary Findings

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INTRODUCTION

The Biomarkers and Cognition Study, Singapore (BIOCIS) is situated within the context of a significant shift in medical focus from treatment to prevention, particularly concerning dementia and Alzheimer's disease (AD). Research indicates that biomarkers for these conditions can manifest decades before any observable symptoms appear, highlighting the critical window for early intervention. Despite advancements in understanding modifiable risk factors and treatment options, there remains a notable gap in research specifically addressing the epidemiology and clinical characteristics of cognitive diseases within Asian populations. This study aims to fill that gap by exploring the pathobiology of cognitive impairment through a longitudinal approach that incorporates diverse methodologies such as fluid biomarker profiling, neuroimaging, and neuropsychological assessments in a multi-ethnic Southeast Asian context.

METHODS

The Biomarkers and Cognition Study, Singapore (BIOCIS) is a 5-year longitudinal study aimed at investigating cognitive impairment and dementia among a diverse Southeast Asian population. The study plans to recruit 2,500 participants aged 30 to 95, assessing them annually. Key methodologies include fluid biomarker profiling through blood samples, neuroimaging techniques like MRI, and comprehensive neuropsychological assessments to evaluate cognitive functions. Additionally, behavioral and lifestyle questionnaires, retinal imaging, and microbiome analysis will be utilized to explore correlations with cognitive health. The primary hypothesis of the BIOCIS study is to characterize the underlying mechanisms of cognitive impairment and dementia through the identification of fluid biomarker profiles, neuroimaging changes, and neuropsychological outcomes in individuals from diverse ethnic backgrounds within Southeast Asia.

RESULTS

Analysis of Fluid Biomarkers and Neuroimaging Findings

There was a significantly higher level of biomarkers (i.e. **GFAP, P-tau181, Oaβ, Aβ42 and Aβ40**) in the impaired cohort (CI) compared to the healthy controls (CU), with **GFAP and P-tau181** being possible biomarkers for dementia in Southeast Asians.

There was a slightly higher proportion of the **APOE ε2 allele** in the **healthy control groups**, indicating that it may confer some protection against the development of dementia.

APOE ε4 has higher proportions in the **MCI and dementia group** which is associated with earlier onset and higher likelihood of developing dementia.

Table 2. Fluid Biomarkers and Neuroimaging Visual Ratings

	CN n=257	SCD n=151	MCI n=308	Dementia n=8	Overall n=724
Fluid Biomarkers					
APOE ε2 gene*,**	45 (15.0%)	19 (10.4%)	39 (11.0%)	0 (0%)	103 (12.2%)
APOE ε3/ε3 genotype**	210 (69.8%)	132 (72.5%)	246 (69.7%)	7 (87.5%)	595 (70.5%)
APOE ε4 gene*,**	46 (15.3%)	31 (17.0%)	68 (19.3%)	1 (12.5%)	146 (17.3%)
Oaβ†	0.53 ± 0.41	0.48 ± 0.28	0.55 ± 0.38	0.69 ± 0.46	0.53 ± 0.37
NfL†	16.31 ± 9.45	14.83 ± 12.04	18.14 ± 7.93	35.70 ± 22.20	17.11 ± 9.42
Aβ42†	5.16 ± 1.56	5.01 ± 1.68	5.32 ± 1.52	5.99 ± 2.43	5.22 ± 1.56
Aβ40†	87.61 ± 24.72	84.68 ± 31.14	96.88 ± 22.32	118.50± 17.68	91.91±25.14
GFAP†	82.14 ± 46.23	69.04 ± 36.17	100.07 ±49.24	201.50±135.06	89.75 ± 49.07
P-tau181	19.72 ± 7.10	19.25 ± 9.25	19.73 ± 6.60	34.10 ± 15.98	19.75 ± 7.33
Neuroimaging Visual Ratings					
	CN n=270	**SCD n=152**	**MCI n=287**	**Dementia n=6**	**Overall n=715**
Total Fazekas†	3.62 ± 2.70	3.95 ± 2.74	4.49 ± 2.89	10.33 ± 2.34	4.10 ± 2.86
Low Fazekas(0-4)**	190 (70.4%)	94 (61.8%)	162 (56.4%)	0 (0%)	446 (62.4%)
Med Fazekas(5-8)**	64 (23.7%)	49 (32.2%)	95 (33.1%)	1 (16.7%)	209(29.2%)
High Fazekas(9-12)**	16 (5.9%)	9 (5.9%)	30 (10.5%)	5 (83.3%)	60 (8.4%)
Confluent WMH**	12 (4.4%)	6 (3.9%)	22 (7.7%)	4 (66.7%)	44 (6.2%)
Staals†	0.88 ± 0.96	1.04 ± 1.00	1.32 ± 1.11	2.33 ± 1.03	1.10 ± 1.06
MTA†	2.64 ± 1.00	2.62 ± 1.05	2.90 ± 1.10	5.17 ± 1.72	2.76 ± 1.09
MB count†	0.19 ± 0.53	0.18 ± 0.51	0.25 ± 0.69	6.00 ± 13.73	0.26 ± 1.40
Lacunes Total†	0.51 ± 1.19	0.74 ± 2.50	1.03 ± 2.14	4.00 ± 8.85	0.80 ± 2.09
PVS Total†	2.05 ± 0.88	2.28 ± 0.97	2.43 ± 0.95	2.67 ± 1.63	2.26 ± 0.95

Note. *=heterozygote or homozygote, †=mean ± Standard Deviation, **=Frequency (percentages); Abbreviations: CN=Cognitively Normal, MCI=Mild Cognitive Impairment, SCD=Subjective Cognitive Decline, APOE=Apolipoprotein E, Oaβ = Aβ oligomers, NFL=Neurofilament Light Chain, Aβ=Amyloid Peptides, GFAP=Glial fibrillary acidic protein, P-tau181=Phosphorylated Tau at position 181, WMH=White Matter Hyperintensity, MTA=Medial Temporal Atrophy, MB=Cerebral Microbleeds, PVS=Perivascular Spaces

MRI scans revealed increasing **white matter disease** and **progressive atrophy in the hippocampus** as the diseased group progressed. A correlation between **confluent WMH** and cognitive impairment suggests **white matter abnormalities** can potentially be used for early detection and interventions for dementia.

Differences in Neuropsychological and Behavioral Findings

Table 3. Neuropsychological, Mood, Behavioural and Lifestyle Assessments/Questionnaires

	CN n=385	SCD n=239	MCI n=510	Dementia n=14	Overall n=1148
Neuropsychological Assessments					
Global cognition					
CDR 0	385 (100%)	115 (48.1%)	203 (39.8%)	0 (0%)	703 (61.2%)
CDR 0.5	0 (0%)	124 (51.9%)	306 (60%)	0 (0%)	430 (37.5%)
^MoCA	27.7 ± 1.33	25.9 ± 2.39	23.8 ± 3.20	13.2 ± 7.58	25.4 ± 3.41
^VCAT	27.4 ± 2.36	27.7 ± 2.08	25.5 ± 3.62	14.5 ± 8.56	26.4 ± 3.50
Learning/Memory					
^RAVLT Immediate	53.01 ± 8.96	52.07 ± 9.06	43.60 ± 11.09	33.00 ± 22.25	48.43 ± 11.15
^RAVLT Delayed	14.20 ± 1.09	14.18 ± 1.20	13.65 ± 1.66	13.00 ± 3.35	13.94 ± 1.43
^Logical Immediate	18.15 ± 2.95	18.53 ± 2.36	15.16 ± 3.98	9.08 ± 7.43	16.81 ± 3.83
^Logical Delayed	20.06 ± 3.02	20.56 ± 2.38	16.72 ± 4.66	8.08 ± 8.62	18.56 ± 4.34
^RCFT Delayed	21.85 ± 6.69	23.37 ± 5.58	17.20 ± 7.57	14.33 ± 10.63	20.05 ± 7.41
^FCSRT Immediate	35.33 ± 4.63	35.06 ± 4.74	30.73 ± 7.28	33.00 ± 5.89	33.22 ± 6.37
^FCSRT Delayed	13.13 ± 2.00	12.84 ± 2.01	11.54 ± 2.72	13.00 ± 0.82	12.37 ± 2.46
Executive Function					
˅TMT-B	65.70 ± 29.36	57.28 ± 18.18	89.75 ± 58.18	214.99 ± 156.15	75.28 ± 47.24
^TOP-J	17.17 ± 4.03	17.03 ± 3.97	15.37 ± 4.20	10.14 ± 5.49	16.28 ± 4.22
˅CT2	86.04 ± 28.43	81.01 ± 29.88	107.32 ± 45.44	253.40±172.94	95.48 ± 42.46
Processing speed					
˅CT1	44.17 ± 17.30	38.86 ± 11.66	55.04 ± 29.71	120.50 ± 111.68	48.35 ± 25.64
^SDMT	72.62 ± 15.65	76.59 ± 16.43	62.04 ± 31.92	22.00 ± 18.53	68.23 ± 25.57
Language Animal fluency (MoCA)	19.90 ± 4.92	19.46 ± 4.26	16.42 ± 5.10	8.23 ± 5.09	18.13 ± 5.25
Visuospatial skills					
^Block Design	37.88 ± 7.69	39.19 ± 7.04	34.54 ± 8.21	21.14 ± 10.76	36.58 ± 8.14
^RCFT Copy	33.16 ± 3.01	33.81 ± 1.92	31.57 ± 4.11	24.07 ± 12.00	32.53 ± 3.66
Attention					
^DS-Forward Span	7.16 ± 1.32	7.08 ± 1.36	6.76 ± 1.31	6.18 ± 1.17	6.96 ± 1.33
^DS-Forward Total	11.29 ± 2.46	11.10 ± 2.36	10.43 ± 2.31	8.82 ± 2.44	10.84 ± 2.41
^DS-Backward Span	5.61 ± 1.40	5.59 ± 1.23	4.81 ± 1.38	4.00 ± 1.27	5.24 ± 1.41
^DS-Backward Total	9.92 ± 2.50	10.08 ± 2.11	8.35 ± 2.33	6.64 ± 2.42	9.22 ± 2.49
Mood, Behavioural and lifestyle Questionnaires					
DASS					
˅Depression†	1.48 ± 2.18	2.25 ± 2.71	2.22 ± 2.95	3.09 ± 3.86	1.98 ± 2.69
˅Anxiety†	1.97 ± 2.17	2.42 ± 2.47	2.46 ± 2.71	4.09 ± 4.42	2.30 ± 2.52
˅Stress†	2.95 ± 2.90	3.87 ± 3.34	3.54 ± 3.41	5.09 ± 4.95	3.42 ± 3.27

Table 3 (continued). Neuropsychological, Mood, Behavioural and Lifestyle Assessments/Questionnaires

	CN n=385	SCD n=239	MCI n=510	Dementia n=14	Overall n=1148
MBI-C					
˅Total†	1.47 ± 3.01	3.08 ± 4.88	3.00 ± 5.57	9.82 ± 8.55	2.56 ± 4.84
˅Interest†	0.29 ± 0.96	0.76 ± 1.59	0.66 ± 1.67	1.73 ± 1.85	0.57 ± 1.47
˅Mood†	0.45 ± 1.20	0.95 ± 1.81	0.93 ± 1.94	2.00 ± 1.67	0.78 ± 1.71
˅Control†	0.60 ± 1.30	1.20 ± 2.13	1.14 ± 2.17	3.55 ± 4.03	0.99 ± 1.97
˅Social†	0.07 ± 0.34	0.13 ± 0.42	0.18 ± 0.57	0.55 ± 1.04	0.13 ± 0.48
˅Beliefs†	0.05 ± 0.59	0.13 ± 0.54	0.11 ± 0.37	2.00 ± 3.32	0.11 ± 0.61
IPAQ*(high activity)	200 (52.4%)	108 (45.4%)	278 (55.8%)	1 (9.1%)	587 (52.0%)
˅Fried†	0.25 ± 0.50	0.37 ± 0.60	0.41 ± 0.66	1.55 ± 1.13	0.36 ± 0.62
˅PSQI†	4.58 ± 2.59	5.63 ± 3.08	5.54 ± 3.35	6.73 ± 3.58	5.26 ± 3.10
^DemQOL†	100.96±16.05	97.67 ± 12.76	96.55 ±15.63	89.90 ± 9.21	98.18 ± 15.29

Note. †=mean ± Standard Deviation, $=Frequency (percentages), ^=higher value denotes better scores, ˅=lower value denotes better scores; Abbreviations: CN=Cognitively Normal, MCI=Mild Cognitive Impairment, SCD=Subjective Cognitive Decline, CDR=Clinical Dementia Rating, MoCA=The Montreal Cognitive Assessment, VCAT=Visual Cognitive Assessment Test, RAVLT= Rey Auditory Verbal Learning Test, RCFT=Rey Complex Figure Test, FCSRT=Free and Cued Selective Reminding Test, TMT-B= Trial Making Test B, TOP-J=Test of Practical Judgement, CT=Colour Trials, SDMT=Symbol Digit Modalities Test, DS=Digit Span, DASS= Depression Anxiety Stress Scales, MBI-C=Mild Behavioural Impairment-Checklist, IPAQ=International Physical Activity Questionnaire, Fried=Fried Phenotype Frailty, PSQI=Pittsburgh Sleep Quality Index, DemQOL=Dementia-Quality of Life Instrument

Assessments indicated an obvious trend of **worsening cognition and behaviors as the group disease state worsened**. The CI group typically scored lower than the CN group, with neuropsychiatric symptoms more common in the MCI group than CN group. Additionally, the SCD group had higher self-reported behavioral impairments in comparison to the MCI group.

CONCLUSION

The BIOCIS aims to explore dementia's epidemiology, clinical phenotypes, and modifiable risk factors in Southeast Asians. Preliminary findings confirm that impaired groups (e.g., MCI, mild dementia) exhibit lower cognition scores, increased neuropsychiatric symptoms. Notably, biomarkers like GFAP, P-tau181, and APOE-ε4 correlate with disease progression. The ongoing study offers critical insights into early detection and prevention strategies tailored to the Southeast Asian populations, advancing dementia care through public health interventions and precision medicine.

REFERENCES

Leow, Y J, et al. "Biomarkers and Cognition Study, Singapore (BIOCIS): Protocol, Study Design, and Preliminary Findings." The Journal of Prevention of Alzheimer S Disease, 1 Jan. 2024, https://doi.org/10.14283/jpad.2024.89. Accessed 1 Nov. 2024.