



# Physiological Predictors of Cognitive Functions in Patients with Chronic Diseases

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## INTRODUCTION

- Chronic diseases pose cognitive risk via complex physiological mechanisms, especially in aging societies.
- While the Montreal Cognitive Assessment (MoCA) is a validated screening tool for cognitive risk, it is not scalable due to time and staffing needs.

### How Chronic Disease Complexities May Exacerbate Age-Related Cognitive Decline

- Multimorbidity Burden
- Hydration Imbalance
- Systematic Inflammation

Research Gap: Studies examine these mechanisms in isolation

### Research Objective:

This study proposed an integrative, data-driven approach to identify key physiological predictors of cognitive function in patients with chronic diseases.

## MATERIALS

### Participant Recruitment (Jan. 2023 - June 2024) :

#### Eligibility Criteria:

#### ✓ Inclusion ✗ Exclusion

- Age 20–75 years
- Chronic disease with follow-up for >1 year
- ≥ 1 visit every 6 months

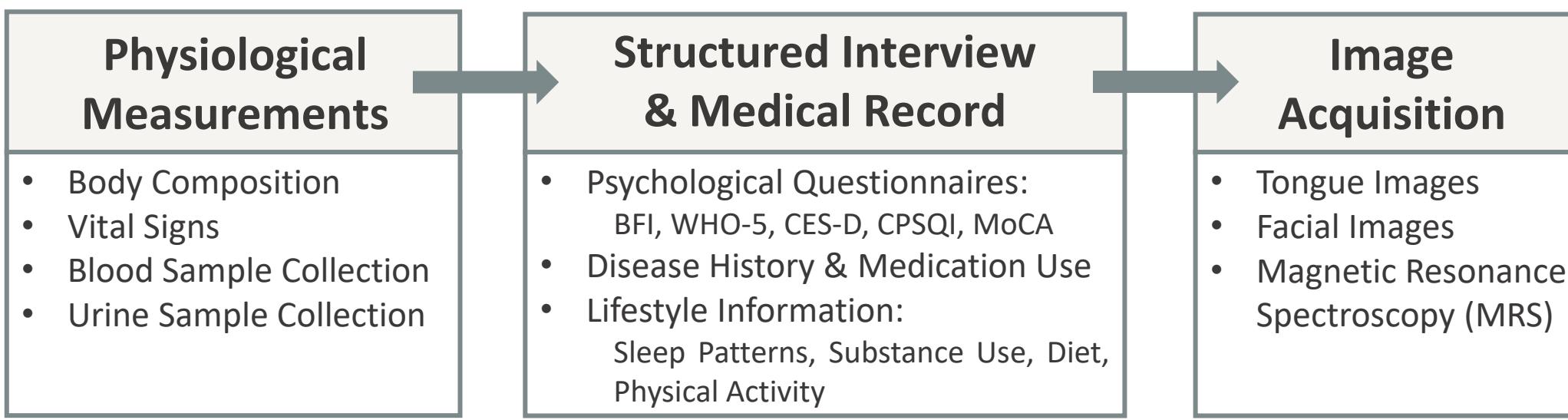
- Unable to consent or make decisions
- Acute infectious diseases (in 2 weeks) / Recent hospitalization (in 1 month)
- Pregnancy or lactation
- Olanzapine doses (lithium salts/antipsychotics) > 20 mg/day

#### Study Site:

National Taiwan University Hospital, Family Medicine Dept.

#### Multimodal Data collection: A cross-sectional study

Each participant completed the following procedures in one day under fasting conditions.

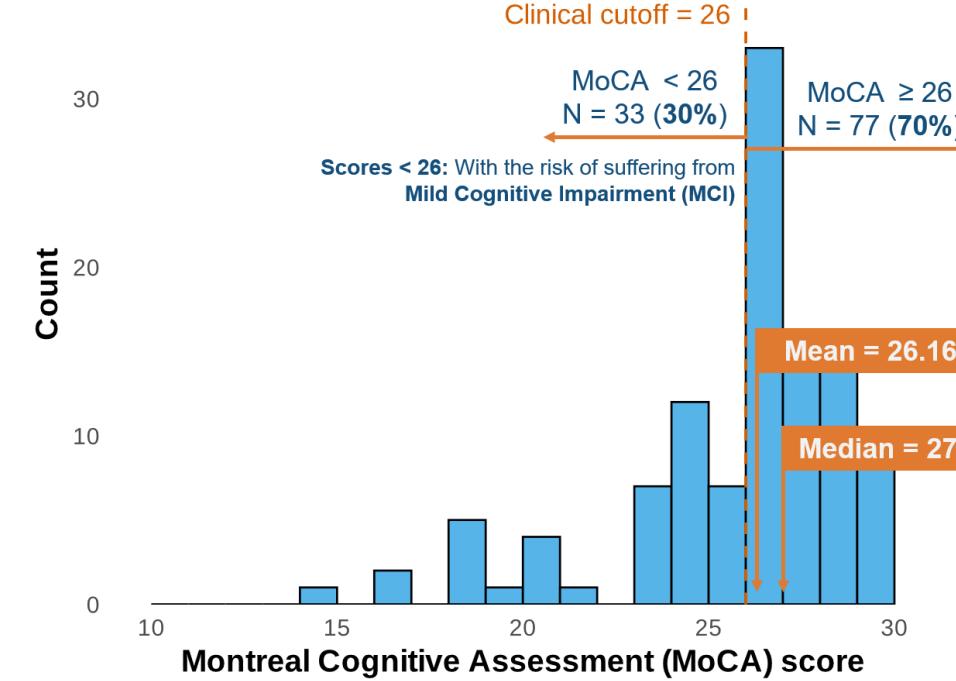


## METHODS

### Study Variables:

#### Outcome (Y):

#### Montreal Cognitive Assessment Score



#### Predictors (X):

##### 1. Physiological Indicators:

###### Domain I. Biochemical Tests (Invasive)

###### Domain II. Physical Measurements (Non-Invasive)

Categories	Variables	Unit
Renal	Creatinine (Cr)	mg/dL
	Estimated Glomerular Filtration Rate (eGFR)	ml/min/1.73m <sup>2</sup>
	Urinary Albumin-to-Creatinine Ratio (UACR)	mg/g
Uric Acid (UA)	mg/dL	
Aldosterone	ng/dL	
Aspartate Aminotransferase (AST, SGOT)	U/L	
Total Bilirubin (T-Bil)	mg/dL	
Direct Bilirubin (D-Bil)	mg/dL	
Total Cholesterol (TC)	mg/dL	
Low-Density Lipoprotein (LDL)	mg/dL	
High-Density Lipoprotein (HDL)	mg/dL	
Triglycerides (TG)	mg/dL	
HbA1c	%	
Fasting Glucose (GluAC)	mg/dL	
Hb	g/dL	
Hemoglobin (Hb)	mg/dL	
Insulin	mU/L	
High-sensitivity C-Reactive Protein (hsCRP)	mg/dL	
Iron	mg/dL	
Ferritin	mg/dL	

###### Domain III. Psychological & Behavioral Questionnaire

Questionnaires	Definition and Scoring
Chinese Pittsburgh Sleep Quality Index (CPSQI)	>6: sleep disorders.
Center for Epidemiologic Studies Depression Scale (CES-D)	≥16: depressive tendencies.
World Health Organization-Five Well-Being Index (WHO-5)	<13: low well-being/depression.
Item-ten Personality Inventory (TIPI-BS)	Extraversion, Agreeableness, Conscientiousness, Neuroticism, Openness. Items are rated on a scale of 1–7.

### Analysis Framework

#### 01 Data Preprocessing

Standardize variables (Z-score) to remove scale differences

#### 02 Best Subset Regression

Select the most optimal combination of physiological predictors

#### 03 Mediation Analysis

Assess whether age influences cognition via physiological predictors

#### 04 Robustness Analysis

Validate the model consistency Of the Best Subset Predictors

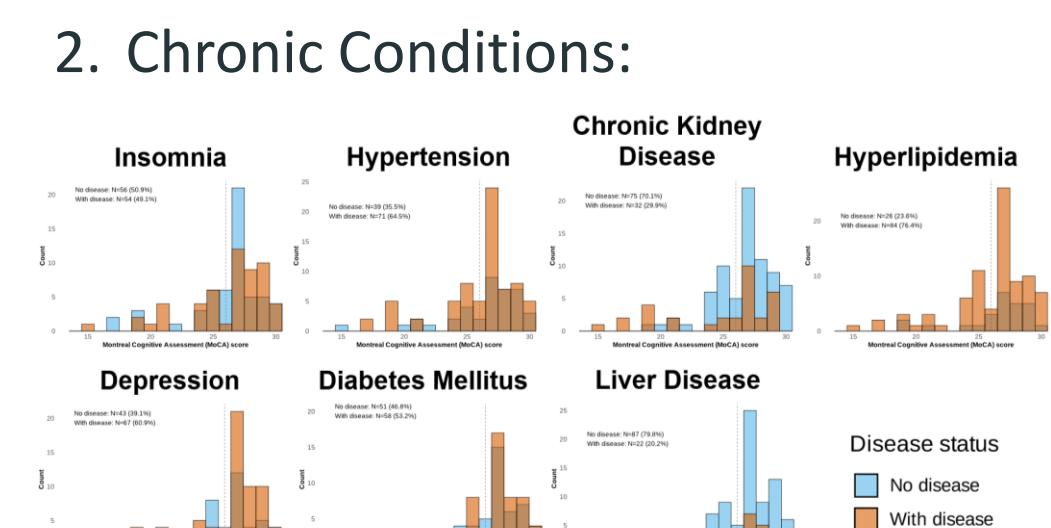
##### 04-1 Lasso Regression

Linear Framework

##### 04-2 Neural Network with SHAP

Nonlinear Framework

### 2. Chronic Conditions:



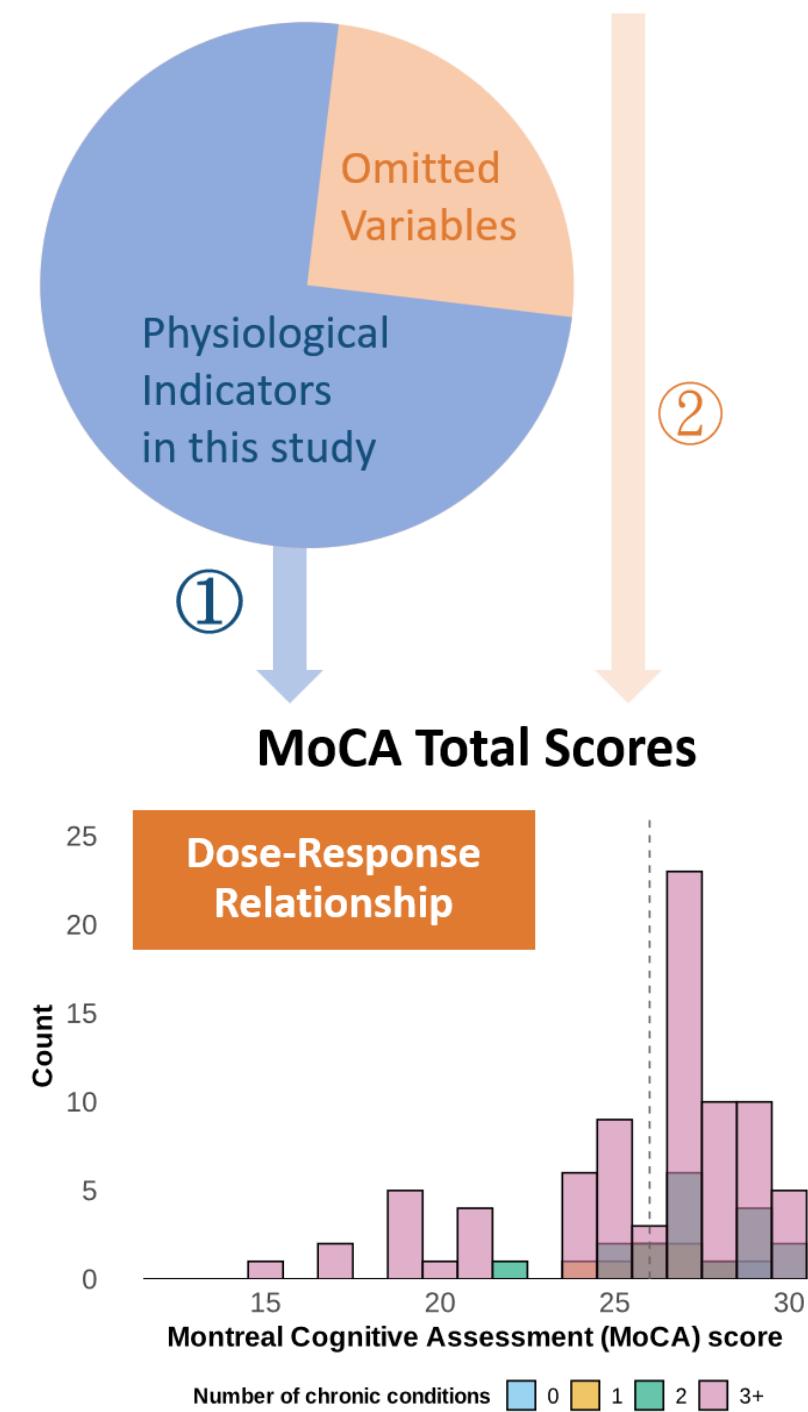
## RESULTS

### Best Subset Regression

#### Predicting MoCA Total Scores with Different Sets of X:

If route ② has better predictive power than route ①, then there must be omitted variables related to the Chronic Disease Condition.

#### Chronic Disease Condition



#### Route ①

Adjusted-R <sup>2</sup> =0.3763*** Set for Choosing X: Physiological Indicators			
Predictors	Estimate	Standard Error	p-value
Age	-0.378	0.093	<.001 ***
Body Height (BH)	0.427	0.206	0.041 *
Systolic Blood Pressure (SBP)	0.096	0.084	0.257
Fat-Free Mass (FFM)	-1.673	0.474	0.001 **
Conscientiousness	0.162	0.088	0.068 •
Well-Being Index (WHO-5)	-0.109	0.088	0.219
Total Body Water (TBW)	1.31	0.374	0.001 **
Total Cholesterol (TC)	0.146	0.096	0.132
Triglycerides (TG)	-0.133	0.095	0.167
High-Density Lipoprotein (HDL)	-0.215	0.11	0.053 •
Hemoglobin (Hb)	0.117	0.103	0.256
Platelet Count (Plt)	0.244	0.091	0.009 **
Fasting Glucose (GluAC)	0.134	0.089	0.136

Significance code: \*\*\* p<0. \*\* p<.001. \* p<.01. • p<.05. • p<1.

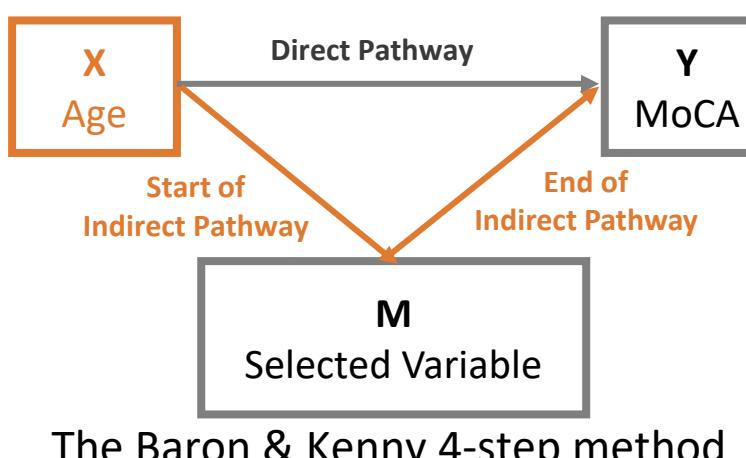
#### Route ②

Adjusted-R <sup>2</sup> =0.05964* Set for Choosing X: Multimorbidity Count (continuous) & Each Chronic Disease Condition (dummy)			
Predictors	Estimate	Standard Error	p-value
Chronic Kidney Disease	-0.4924	0.1757	0.00605
Liver Disease	0.3263	0.2223	0.14509

Significance code: \*\*\* p<0. \*\* p<.001. \* p<.01. • p<.05. • p<1.

### Mediation Analysis

- Age is a non-modifiable factor that may influence cognition through modifiable physiological pathways.



#### The Baron & Kenny 4-step method

#### Modifiable Mediator for intervention in cognitive risk management

Mediator (Best Subset Predictor)	Proportion Mediated	Average Causal Mediation Effect	Average Direct Effect	Total Effect
Body Height (BH)	6.34%	-0.0294	-0.3757 ***	-0.4051 ***
Systolic Blood Pressure (SBP)	-1.10%	0.0078	-0.3779 ***	-0.3701 ***
Fat-Free Mass (FFM)	1.17%	-0.0055	-0.3780 ***	-0.3835 ***
Conscientiousness	-2.70%	0.0133	-0.3779 ***	-0.3646 ***
Well-Being Index (WHO-5)	2.96%	-0.0157	-0.3796 ***	-0.3953 ***
Total Body Water (TBW)	1.02%	-0.0047	-0.3793 ***	-0.3839 ***
Total Cholesterol (TC)	6.20%	-0.0290	-0.3800 ***	-0.4090 ***
Triglycerides (TG)	1.25%	-0.0081	-0.3763 ***	-0.3844 ***
High-Density Lipoprotein (HDL)	2.50%	-0.0128	-0.3801 ***	-0.3929 ***
Hemoglobin (Hb)	0.89%	-0.0064	-0.3763 ***	-0.3827 ***
Platelet Count (Plt)	18.24% **	-0.0871 **	-0.3772 ***	-0.4643 ***
Fasting Glucose (GluAC)	8.70%	-0.0394	-0.3781 ***	-0.4175 ***

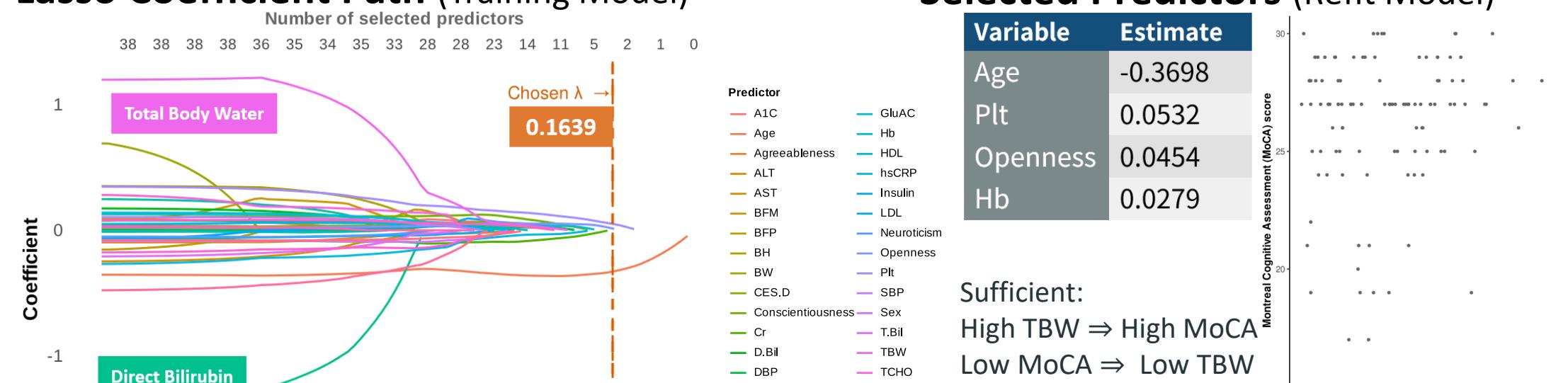
Significance code: \*\*\* p<0. \*\* p<.001. \* p<.01. • p<.05. • p<1.

### Robustness Check

- Y: MoCA Total Scores; Set for Choosing X: Physiological Indicators

### Lasso Regression

#### Lasso Coefficient Path (Training Model)



Variable	Estimate
Age	-0.3698
Plt	0.0532
Openness	0.0454
Hb	