

Towards a major methodological shift in depression research by assessing continuous scores of recurrence of illness, lifetime and current suicidal behaviors and phenome features: focus on atherogenicity and adverse childhood experiences

(1-4) Michael Maes, (1,5) Ketsupar Jirakran, (1) Asara Vasupanrajit, (6) Patchaya Boonchaya-Anant, (1,2) Chavit Tunvirachaisakul,

(1) Department of Psychiatry, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, Bangkok, Thailand

(2) Cognitive Impairment and Dementia Research Unit, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

(3) IMPACT Strategic Research Center, Barwon Health, Geelong, Australia

(4) Department of Psychiatry, Medical University of Plovdiv, Plovdiv, Bulgaria

(5) Center of Excellence for Maximizing Children's Developmental Potential, Department of Pediatric, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

(6) Division of Endocrinology and Metabolism, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

ESF, Table 1. Demographic and clinical data of the major depression patients (MDD) and healthy controls (HC) included in the present study.

Variables	HC (n=67)	MDD (n=66)	F/X²/FEPT	df	p
Sex (Male / Female)	9/58	18/48	3.94	1	0.055
Age (years)	37.9 (9.2)	36.9 (11.5)	0.263	1/131	0.609
Education (years)	14.1 (3.4)	14.8 (2.8)	1.72	1/131	0.193
Income (baht/month)	21500 (7269)	23770 (19203)	0.817	1/131	0.368
Single/married/widower/divorced	35/26/3/3	36/22/4/4	FHHET		0.877
Employed / unemployed	66/1	47/19	19.388	1	<0.001
TUD (No/Yes)	62/5	54/12	3.43	1	0.074
BMI (kg/m ²)	27.4 (6.1)	26.9 (5.5)	0.266	1/130	0.607
Waist Circumference (cm)	88.8 (14.9)	89.7 (15.0)	0.142	1/130	0.707
Systolic Blood Pressure (mmHg)	127.9 (15.3)	129.9 (17.8)	0.475	1/131	0.492
Diastolic Blood Pressure (mmHg)	79.2 (11.3)	77.9 (12.4)	0.420	1/131	0.518
Metabolic syndrome (MetS) (No/Yes)	34/33	35/31	0.069	1	0.863
Neuroticism	18.3 (5.0)	27.2 (6.4)	80.332	1/131	<0.001
Total BDI	5.6 (6.5)	26.9 (13.8)	129.518	1/131	<0.001
Total HAMD	2.3 (3.0)	18.1 (6.4)	330.943	1/131	<0.001
Total STAI	38.2 (7.8)	51.9 (10.4)	73.623	1/131	<0.001
PC HAMD + BDI + STAI	-0.758 (0.421)	0.770 (0.810)	187.443	1/131	<0.001
PC HAMD + BDI + STAI + Current SB	-0.754 (0.352)	0.765 (0.850)	182.045	1/131	<0.001

Variables	HC (n=67)	MDD (n=66)	F/X ² /FEPT	df	p
Current suicidal ideation (SI)	-0.489 (0.0)	0.493 (1.248)	KWT	-	<0.001
Current suicidal attempts (SA)	-0.245 (0.0)	0.256 (1.390)	KWT	-	0.004
Current Suicidal behaviors (SI and SA)	-0.420 (0.0)	0.426 (1.290)	KWT	-	<0.001
HR_QoL, Physical domain	26.9 (3.4)	21.5 (4.5)	61.92	1/131	<0.001
HR_QoL, mental health	23.0 (3.6)	17.3 (5.6)	46.65	1/131	<0.001
HR_QoL, social	11.6 (2.0)	9.2 (2.5)	37.02	1/131	<0.001
HR_QoL, environment	28.4 (4.9)	25.4 (5.8)	10.32	1/131	0.002
Previous Covid-19 infection (No/Yes)	62/5	62/4	0.104	1	1.000
T2DM (No/Yes)	61/6	61/5	0.083	1	1.000
Dyslipidemia (No/Yes)	58/9	55/11	0.272	1	0.635
Drugs targeting MetS-related conditions (No/Yes)	50/17	52/14	0.322	1	0.682

Results are shown as mean $\pm$ SD. F: results of analysis of variance; X²: analysis of contingency tables, FFHT: Fisher-Freeman-Halton Exact Test; KWT: Kruskal-Wallis test.

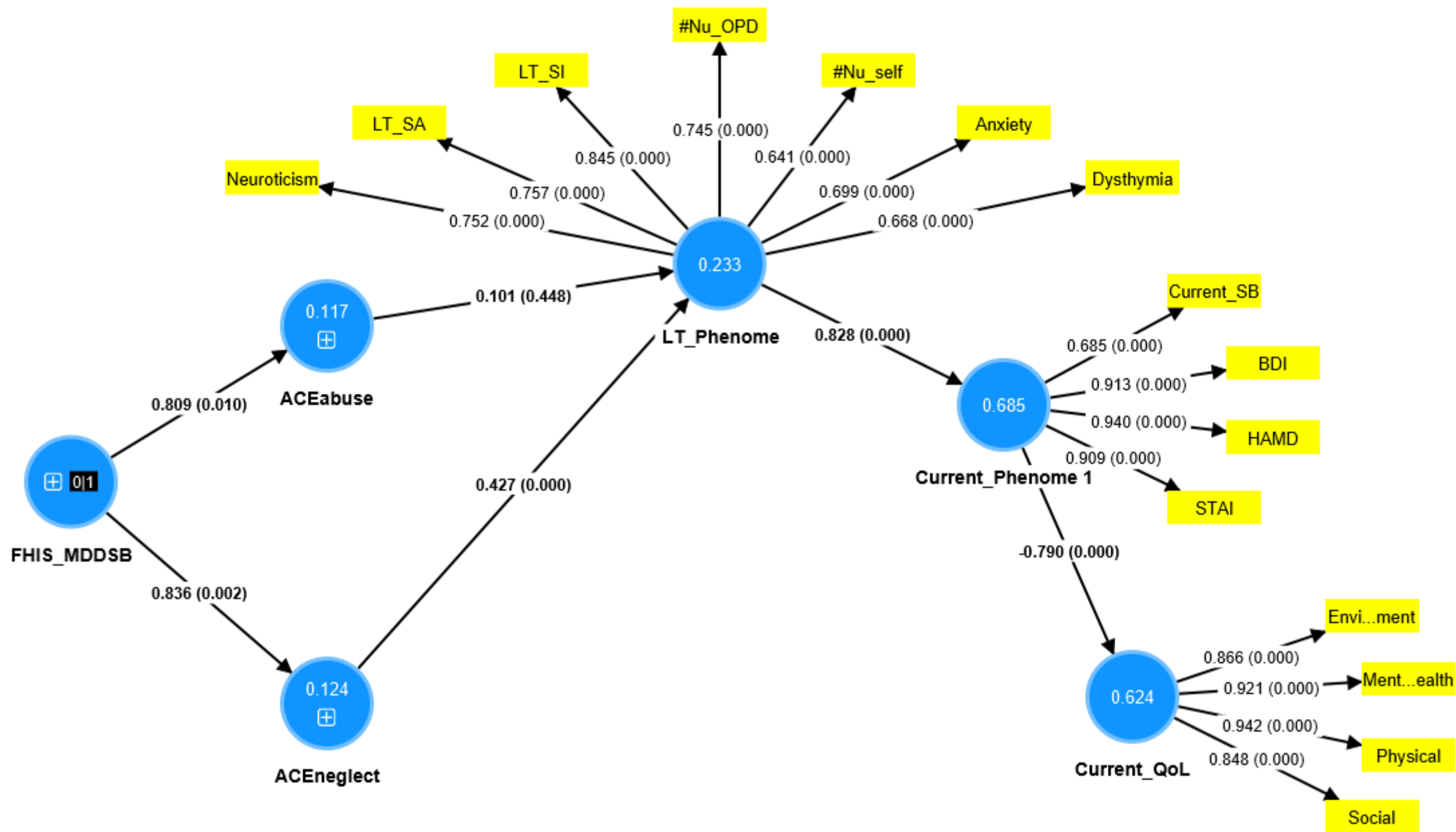
BMI: body mass index; TUD: Tobacco use disorder; BDI: Beck Depression Inventory; HAMD: Hamilton Depression Rating Scale; STAI: State and Trait Anxiety Inventory; PC: principal component; SB: suicidal behaviors, that is ideation (SI) and attempts (SA); T2DM: type 2 diabetes mellitus; PC HAMD + BDI + STAI: first PC score extracted from these three rating scales; PC HAMD + BDI + STAI + Current SB: first PC score extracted from these three rating scales and suicidal behaviors; HR_QoL: health-related quality of life, T2DM: type 2 diabetes mellitus. Adapted from Jirakran et al., 2023 [14]

ESF, Table 2. Biomarker data of the major depression patients (MDD) and healthy controls (HC) without metabolic syndrome.

Variables	HC (n=34)	MDD (n=35)	F	df	p
Free Cholesterol (FC) (mg/dL)	51.7 (3.2)	62.0 (3.2)	5.00	1/62	0.029
Cholesteryl esters (mg/dL)	138.3 (5.6)	140.8 (5.6)	0.10	1/62	0.756
Cholesterol esterification rate (CER)	72.8 (1.5)	69.2 (1.5)	2.72	1/62	0.104
HDLc (mg/dL)	64.3 (2.4)	56.8 (2.4)	4.83	1/62	0.032
Triglycerides (TG) (mg/dL) *	84.1 (8.9)	123.1 (8.9)	9.71	1/62	0.003
LDLc (mg/dL)	118.2 (6.2)	132.3 (6.2)	2.52	1/62	0.118
Apolipoprotein A (ApoA) (mg/mL)	149.8 (5.0)	135.2 (5.0)	4.14	1/62	0.046
ApoB (mg/mL)	80.6 (3.6)	91.5 (3.6)	4.39	1/62	0.040
ApoB/ApoA ratio *	0.56 (0.03)	0.70 (0.03)	10.34	1/62	0.002
TG/HDLc	1.37 (0.22)	2.39 (0.22)	10.75	1/62	0.002
PRO_AI (z scores)	-0.308 (0.170)	0.325 (0.170)	6.73	1/62	0.012
ANTI_AI (z scores)	0.308 (0.165)	-0.286 (0.165)	6.29	1/62	0.015
PRO/ANTI_AI (z scores)	-0.392 (0.163)	0.384 (0.163)	11.00	1/62	0.002

Results are shown as estimated marginal means (SEM) after univariate GLM analyses with age, sex, body mass index and waist circumference as covariates; * Processed in Log transformation; HDLc: high density lipoprotein cholesterol; LDLc: low density lipoprotein cholesterol; PRO_AI: composite based on LDLc, TG, ApoB, and FC; ANTI_AI: composite based on HDLc, ApoA and CER; PRO/ANTI_AI: PRO_AI versus ANTI_AI ratio

Adapted from Jirakran et al., 2023 [14]



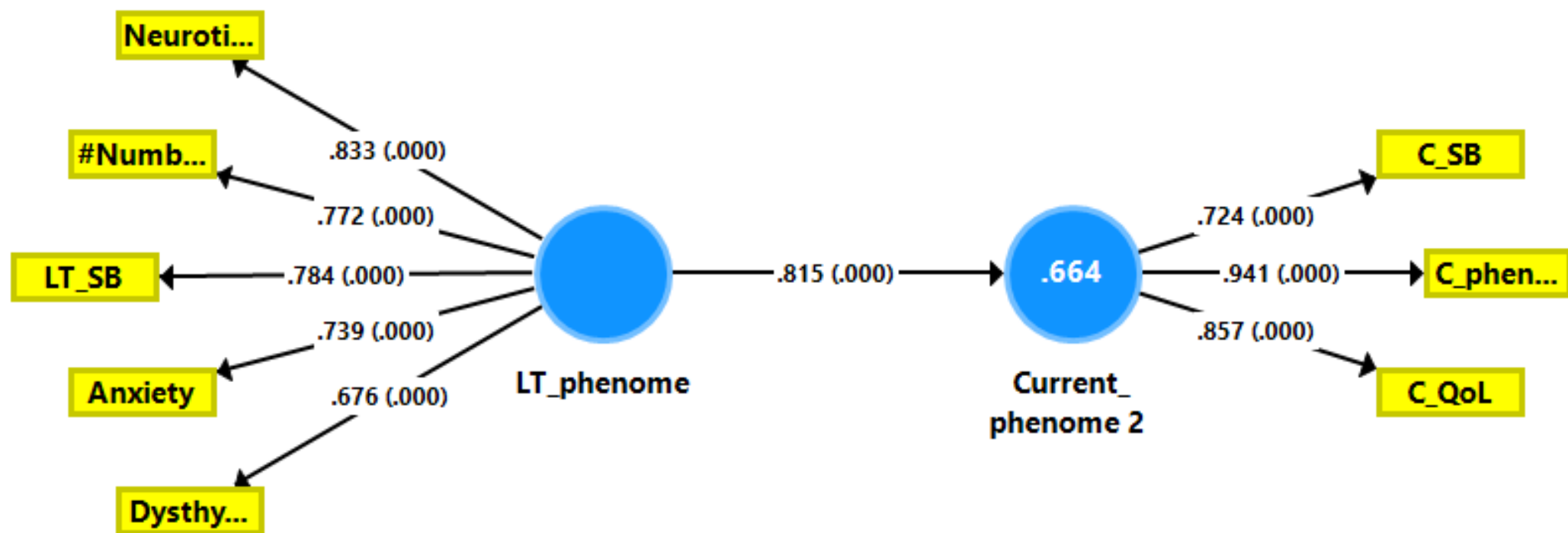
ESF, Figure 1. A second Partial Least Squares model.

Current_QoL: latent vector (LV) extracted from 4 health-related quality of Life (QoL) domains;

Current_phenome: LV extracted from current suicidal behaviors (Current_SB), Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory (BDI), and Spielberger State and Trait Anxiety;

LT_phenome: a LV extracted from lifetime suicidal ideation (LT_SI) and attempts (LT_SA), and number of episodes, either according to the outpatient files (#Nu_OPD) or self-declared (#Nu_self), and mood disorder traits;

ACE: adverse childhood experiences, either abuse or neglect; FHIS_MDDSB: family history in first-degree relatives of major depression and suicidal attempts.



ESF, Figure 2. A third Partial Least Squares model.

Current_phenome 2: a latent vector (LV) extracted from current suicidal behaviors (C_SB), C_phenome (a LV extracted from the Hamilton Depression Rating Scale, Beck Depression Inventory, and Spielberger State and Trait Anxiety scores) and C_QoL (a LV extracted from the 4 quality of life domains);

LT_phenome: a LV extracted from lifetime (LT) suicidal ideation (LT_SI) and attempts (LT_SA), and number of episodes (#Numb), and mood disorder traits.