TWO PSYCHOLOGICAL SURVEY STUDIES:

(1) UNDERSTANDING THE STIGMA TOWARD LUNG CANCER

(2) USING RESEARCH DOMAIN CRITERIA PROJECT (RDOC) TO PREDICT REMISSION RATES OF MAJOR DEPRESSIVE DISORDER PATIENTS

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DEDICATION

I would like to thank both of my mentors, Drs. Yang Xie and Guanghua Xiao. Their mentoring and help over the past few years is the key element of all my accomplishments during my PhD study at UT Southwestern. My appreciation also extends to my thesis committee members, Drs. Joan Schiller, Adi Gazdar and Xiaowei Zhan, who provided me with very insightful suggestions on my current research and future directions. Further, I am very lucky to have the opportunities to collaborate with excellent scientists both on-campus and in other research institutes on my projects. Last but not least, I am really thankful for my parents, husband, families, friends and lab mates, who continue to support and encourage me during my research and life in Dallas.

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by

TSUNG-WEI MA

DISSERTATION

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TWO PSYCHOLOGICAL SURVEY STUDIES:

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The University of Texas Southwestern Medical Center at Dallas, 2017

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Abstract

This dissertation is composed of two psychological survey studies. In the first study, people's negative attitudes toward lung cancer are assessed and discussed. The second topic is about predicting the remission rates of major depressive disorder patients with patients' self-reported questionnaires.

In the first topic, I analyzed data from *The Lung Cancer Project*, an online survey study, to assess both explicit and implicit attitudes expressed by the four participant groups: health care professionals, cancer patients, caregivers and the general public. Negative attitudes toward lung cancer were detected among all these participant groups. I also discovered several demographic factors significantly associated with negative attitudes toward lung cancer. Furthermore, I investigated the association between state-level perceptions of lung cancer (including both explicit and implicit attitudes) and rates of treatment (drug treatment rates or total treatment rates, including surgery, chemotherapy, radiation, and immunotherapy) for lung cancer patients in the corresponding states.

In the second topic, existing data from the *Combining Medications to Enhance Depression Outcomes (CO-MED)* trial were utilized to develop a data-driven method for mapping the behavioral factors to the constructs defined in *Research Domain Criteria (RDoC)*. And I used the defined behavioral factors from *CO-MED* to discover patient subgroups. In further analysis, I found that the discovered patient subgroups have significantly different remission rates to the antidepressant treatment, which indicates that there are three endo-phenotypes in major depression disorder.

Keywords:

Lung cancer stigma, implicit association test, implicit attitudes, explicit attitudes, regression analysis, major depressive disorder, factor analysis, cluster analysis, endo-phenotype

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LIST OF ABBREVIATIONS

IAT: Implicit association test

AIC: Akaike information criterion

LC: Lung cancer

BC: Breast cancer

SHA: Source healthcare analytics

DT: Drug treatment

SEER: Surveillance, epidemiology, and end results

CDC: Centers for disease control and prevention

MDD: Major depressive disorder

RDoC: Research domain criteria project

CO-MED: Combining medications to enhance depression outcomes

EFA: Exploratory factor analysis

DSM-IV: Diagnostic and statistical manual of mental disorders, 4th edition

ICD9: International classification of diseases, 9th revision

HAM-D: Hamilton depression rating scale

IDS-C: The 30-item inventory of depressive symptomatology, clinician version

QIDS-C: The 16-item quick inventory of depressive symptomatology, clinician version

QIDS-SR: The 16-item quick inventory of depressive symptomatology, self-rated version

Topic I. UNDERSTANDING THE STIGMA TOWARD LUNG CANCER

CHAPTER ONE. The Demographic Predictors of Explicit and Implicit Attitudes Against Lung Cancer

INTRODUCTION

1.1 Introduction

Around 85% of lung cancer cases, a leading cause of death nationally, are believed to result from smoking. This association has created a perception that lung cancer is a self-inflicted disease[1]. Such negative social attitudes toward lung cancer[1] affect not only lung cancer patients with a history of smoking but also those who have never smoked[2,3]. This kind of perception impedes lung cancer patients' qualify of life[4]. To develop strategies for removing these misconceptions, it is important to understand the factors associated with these attitudes. There are limitations to most existing studies on the stigma of lung cancer since they assessed only conscious attitudes (explicit attitudes) but not unconscious attitudes (implicit attitudes). To gain a better understanding of lung cancer stigma, I studied the characteristics associated with both explicit and implicit attitudes. I used both the explicit measures tests and the Implicit Association Test (IAT), which measures implicit attitudes and beliefs that may exist outside of conscious awareness, to study people's attitudes toward lung cancer.

MATERIALS AND METHODS

1.2 The Lung Cancer Project Data

In our study, we analyzed attitudes data from *The Lung Cancer Project* survey study. *The Lung Cancer Project* test includes two parts – an explicit attitude test and an implicit association test (Implicit Association Test, IAT). *The Lung Cancer Project* is an online survey study hosted at www.TheLungCancerProject.org, using software services provided by Project Implicit[5]. Participants in this survey completed items focused on both lung and breast cancer to assess explicit attitudes; implicit attitudes were measured by the Implicit Association Test (IAT), a well-established tool. More detailed information about *The Lung Cancer Project*, its methods, and general attitudinal results are published by Sriram[6].

1.2.1 Explicit Attitude Test

To compare participants' explicit attitudes regarding breast cancer patients and lung cancer patients, participants were asked to complete a survey consisting of five descriptive and five normative statements each for both lung and breast cancer. Participants rated their agreement with each statement on a five point Likert scale, with a higher score indicating greater agreement. The five descriptive statements for each cancer type began with "People with lung/breast cancer are…", while the normative statements began with "In my opinion, people with lung/breast cancer ought to be/feel…" These statements were completed with the phrases: "ashamed about their disease," "embarrassed to tell others about their disease," "feel that their own behavior contributed to their disease," "are likely to die from their disease in a few years," and "are hopeful about their future." For each pair of comparable statements for lung and breast cancer, the score for the breast cancer statement was subtracted from the score for the corresponding lung cancer statement to generate a score representing the difference in participant's attitudes toward lung cancer and breast cancer. The average of scores representing difference between attitudes toward lung cancer vs. breast cancer for the statements ending with "ashamed about their disease" and "embarrassed to tell other about their disease" were then used to generate a summary score for explicit normative attitudes and explicit descriptive attitudes, using the corresponding statements.

1.2.2 Implicit Attitude Test (Implicit-Association Test, IAT)

Following the explicit attitudes test, participants were asked to complete the implicit attitudes test. Their implicit attitudes were assessed by the implicit association test. The implicit association test is a well-established method of inferring subconscious attitudes and stereotypes from participants' reaction times to visual cues[7-9]. The goal of this test is to measure the strength of associations between concepts and evaluations or stereotypes. The presupposition is that making a response is easier when closely related items in the participants' memory share the same response key.

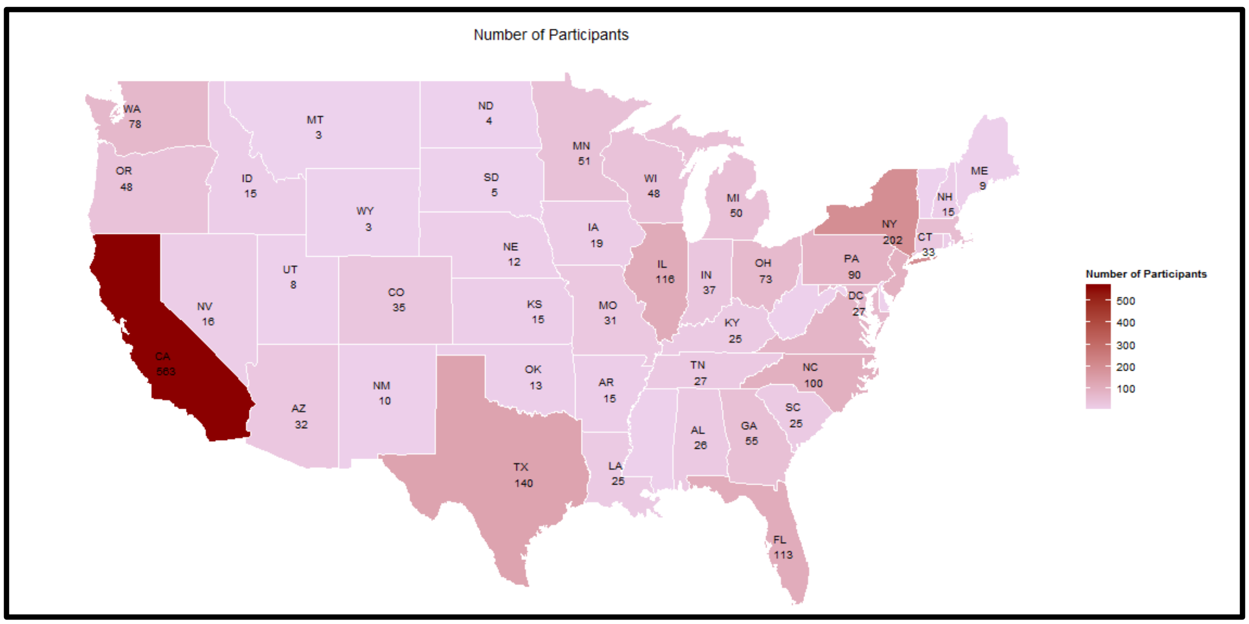
The implicit associations test has two parts. The first section tested participants' automatic association of the concept (lung cancer, breast cancer) with evaluations (bad, good). The second one tested participants' automatic association of the concept (lung cancer or breast cancer) with the stereotypical behaviors (smoking, drinking, or eating). Each participant was randomly prompted to complete one of the three attitudes IATs (lung cancer vs. breast cancer matching with bad vs. good, despair vs. hope or shameful vs. suitable) and one of the three stereotype IATs (lung cancer vs. breast cancer matching with smoking vs. drinking, smoking vs. eating, or eating vs. drinking).

The IAT effect is computed as the D score with the Improved Algorithm[10]. A higher D score indicates stronger associations between lung cancer and negative attributes (bad, shameful, despair) for the attitudes IAT, or between lung cancer and smoking for the stereotype IAT when compared with eating or drinking. The overall implicit attitudes and implicit smoking stereotype measures are summarized from the individual implicit attitudes and smoking-related implicit stereotypes measures, respectively.

1.2.3 Participants

Participants included 3180 individuals who were recruited into *The Lung Cancer Project* between September 2012 and October 2014. These participants were categorized into four groups based on their reported demographics: 493 cancer patients/survivors, 623 health providers, 1332 cancer caregivers, and 1356 members of the general public (individuals who did not report any affiliation with the other three groups). Detailed demographic information (including the state in which they reported) about the participants is provided in Table 1. The geological distribution of participants is illustrated in Figure 1. In the first part of *The Lung Cancer Project* data analysis, I focused on associations between the demographic factors and explicit and implicit attitudes toward lung cancer.

Figure 1. The participant numbers of *The Lung Cancer Project*



The participant numbers of *The Lung Cancer Project* are shown in the US state map. A deeper state map color means a higher number of participants in that state.

Table 1. Demographic characteristics of participants in *The Lung Cancer Project*

Characteristic	No. (%) of Participants (N=3180)
Sex	
Female	2239 (70)
Male	717 (23)
Unknown	224 (7)
Age (Years)	
Median	46 years
<30	520 (16)
30–39	571 (18)
40–49	517 (16)
50–59	710 (22)
60–69	432 (14)
≥70	132 (4)
Unknown	298 (10)
Race	
White/Caucasian	2534 (80)
Black/African	97 (3)
Hispanic/Latino	82 (3)
East Asian	142 (4)
South Asian	95 (3)
Native Hawaiian/Pacific Islander	20 (1)
American Indian/Alaskan Native	34 (1)
Unknown	176 (5)
Annual household income	
Less than $10,000	138 (4)
$10,000–$49,999	618 (19)
$50,000–$99,999	915 (29)
$100,000–$149,999	590 (19)
$150,000–$199,999	318 (10)
$200,000 or more	392 (12)
Unknown	209 (7)
Highest level of education completed	
Some college or below	855 (27)
College degree	919 (29)
Graduate degree	1194 (37)
Unknown	212 (7)
Healthcare provider	
Yes	623 (20)
No	2337 (73)
Unknown	220 (7)
Cancer diagnosis	
Yes	493 (16)
No	2260 (71)
Unknown	427 (13)
Caregiver	
Yes	1332 (42)
No	1462 (46)
Unknown	386 (12)

1.3 Statistical Analysis

The binomial test was performed to verify if the percentage of participants showing negative explicit/implicit attitudes against lung cancer was significantly higher than those showing bias against breast cancer. The same method was applied to test if the percentage of participants more likely to link smoking behavior with lung cancer compared with breast cancer was higher than the percentage of participants who responded in the reverse.

Multivariate regression models were used to analyze the associations between each measure of stigma (explicit and implicit attitudes) against lung cancer and the demographic factors, while adjusting for other covariates. Variables for multivariate regression were determined by backward stepwise variable selection with AIC (Akaike information criterion) as selection criteria.

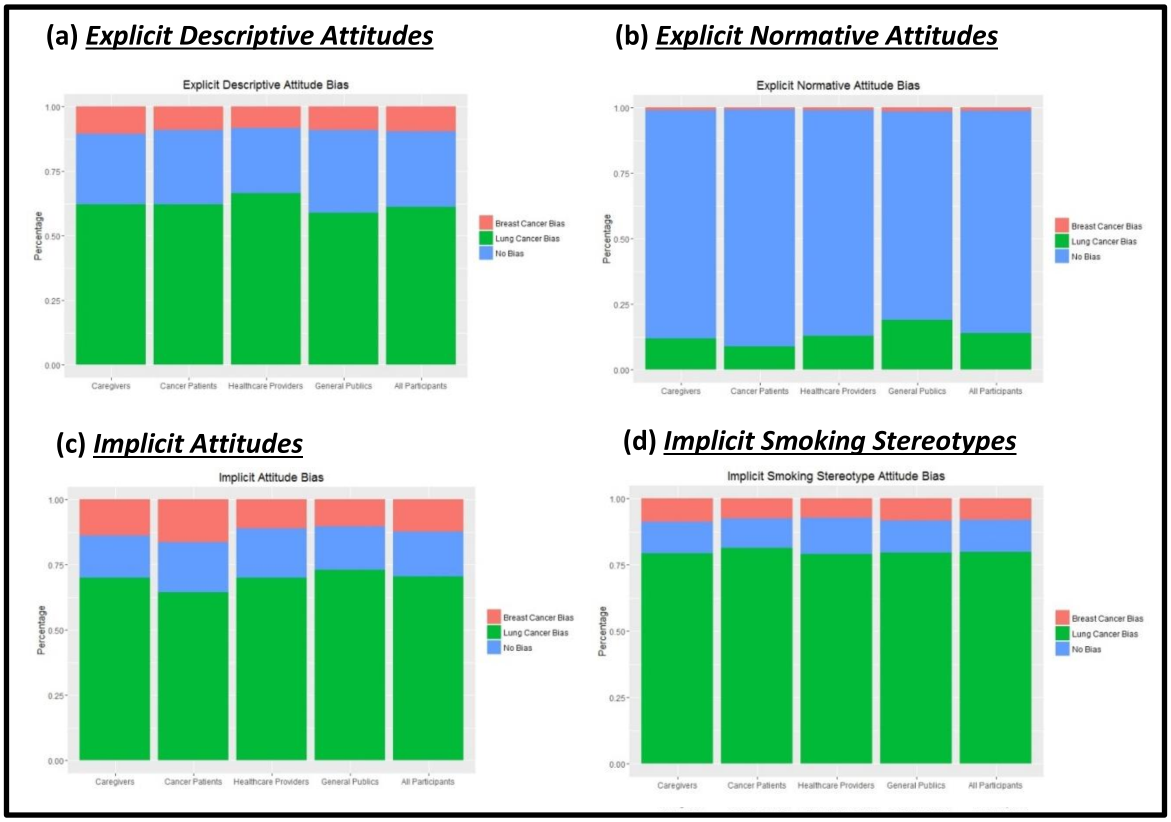
RESULTS

1.4 Results

1.4.1 Negative Explicit Attitudes Toward Lung Cancer

On the Likert scale exam of explicit attitudes, 61% of participants showed negative explicit descriptive attitudes against lung cancer (Figure 2a and Table 2), while 10% showed them against breast cancer. 14% of participants expressed negative explicit normative attitudes against lung cancer (Figure 2b and Table 2), while only 1% expressed them against breast cancer. Concordant results are found among all four participant groups. With a binomial test, it can be shown that the proportion of participants with lung cancer bias is significantly higher than those who showed breast cancer bias ($P < 0.01$). These results are concordant with the results reported by Sriram[6].

Figure 2. Explicit and implicit attitudes toward lung cancer compared with breast cancer



The percentage of participants with (a) Explicit Descriptive Attitudes, (b) Explicit Normative Attitudes, (c) Implicit Attitudes, and (d) Implicit Smoking Stereotypes biases against lung cancer (green) or breast cancer (pink) are shown. The proportion of participants with lung cancer bias is significantly greater than those with breast cancer bias in all attitudes (P<0.01). Detailed percentage numbers can be found in Table 2.

Table 2. Percentage of participants with negative explicit attitudes, implicit attitudes, and implicit stereotypes toward lung cancer, breast cancer, or neither

	All Participants N (%)			Caregivers N (%)			Cancer Patients N (%)			Healthcare Providers N (%)			General Public N (%)		
	LC Bias	**No Bias**	**BC Bias**	**LC Bias**	**No Bias**	**BC Bias**	**LC Bias**	**No Bias**	**BC Bias**	**LC Bias**	**No Bias**	**BC Bias**	**LC Bias**	**No Bias**	**BC Bias**
Negative Explicit Attitudes															
Descriptive attitudes	1343 (61)	642 (29)	207 (10)	632 (62)	279 (28)	106 (10)	233 (62)	107 (29)	34 (9)	306 (66)	117 (26)	38 (8)	482 (59)	262 (32)	73 (9)
Normative attitudes	298 (14)	1803 (85)	24 (1)	118 (12)	863 (87)	9 (1)	33 (9)	333 (90)	2 (1)	59 (13)	392 (86)	4 (1)	148 (19)	623 (80)	11 (1)
Negative Implicit Attitudes															
Bad/Good	433 (71)	107 (18)	65 (11)	194 (71)	33 (12)	45 (17)	62 (64)	21 (22)	14 (14)	85 (70)	22 (18)	15 (12)	180 (74)	43 (18)	20 (8)
Mean IAT D score		0.39			0.38			0.32			0.37			0.41	
Despair/Hope	441 (71)	111 (18)	66 (11)	194 (71)	47 (17)	32 (12)	65 (64)	24 (23)	13 (13)	88 (71)	23 (19)	12 (10)	180 (76)	36 (15)	20 (9)
Mean IAT D score		0.4			0.39			0.33			0.42			0.45	
Shameful/Suitable	377 (68)	89 (16)	86 (16)	172 (68)	39 (15)	44 (17)	56 (67)	9 (11)	19 (22)	94 (69)	28 (21)	14 (10)	136 (67)	37 (18)	29 (15)
Mean IAT D score		0.35			0.34			0.29			0.38			0.35	
Implicit Attitudes Summary	1253 (71)	301 (17)	220 (12)	561 (70)	129 (16)	110 (14)	182 (65)	54 (19)	46 (16)	266 (70)	72 (19)	42 (11)	498 (73)	113 (17)	70 (10)
Mean IAT D score		0.38			0.37			0.31			0.39			0.41	
Implicit Smoking Stereotypes															
Smoking vs Eating	480 (89)	39 (7)	21 (4)	214 (90)	14 (6)	9 (4)	82 (94)	2 (2)	3 (4)	104 (89)	11 (9)	2 (2)	186 (87)	17 (8)	10 (5)
Mean IAT D score		0.63			0.66			0.68			0.72			0.58	
Smoking vs Drinking	430 (71)	105 (18)	68 (11)	187 (70)	47 (17)	35 (13)	58 (68)	17 (20)	10 (12)	90 (70)	22 (17)	16 (13)	171 (72)	41 (17)	26 (11)
Mean IAT D score		0.39			0.38			0.37			0.44			0.38	
Implicit Smoking Stereotype Summary	912 (80)	141 (12)	90 (8)	401 (79)	61 (12)	44 (9)	140 (81)	19 (11)	13 (8)	194 (79)	33 (14)	18 (7)	359 (80)	55 (12)	37 (8)
Mean IAT D score		0.51			0.51			0.53			0.57			0.48	

LC: Lung cancer; BC: Breast cancer

1.4.2 Negative Implicit Attitudes Toward Lung Cancer

About 71% of participants showed negative implicit attitudes against lung cancer when compared with breast cancer (Figure 2c and Table 2). 71% of participants who completed the bad vs. good IAT showed automatic linkage of lung cancer and negative perception. And 71% and 68% of those who completed the despair vs. hope and shameful vs. suitable IATs, respectively, associated lung cancer with negative perception. All four groups showed a strong association between lung cancer and negative perception in the IAT attitudes exams (Figure 2a-2c and Table 2).

In the stereotypes IAT, participants expressed high associations between lung cancer and smoking behavior when compared with eating or drinking (Figure 2d and Table 2). 80% of participants tended to link lung cancer with smoking behaviors, compared with linking breast cancer with smoking or linking lung cancer with eating or drinking.

1.4.3 Demographic Factors Associated with Explicit Attitudes

Among all participants (N=3180), white people compared with non-whites ($p<0.001$), females compared with males ($p<0.001$), participants with high incomes (annual household income equal to or higher than USD$100,000;) compared with low incomes ($p=0.024$), and those who valued themselves as somewhat or very knowledgeable about cancer compared with those who rated themselves as less knowledgeable about cancer ($p<0.001$), had stronger negative explicit descriptive attitudes against lung cancer (Table 3). Compared with healthcare providers, those who were not healthcare providers had stronger negative explicit descriptive attitudes against lung cancer ($p=0.013$).

Among all four participant groups, females showed stronger negative explicit descriptive attitudes against lung cancer than males (Table 4; p=0.006 in healthcare providers, p=0.006 in cancer patients, p=0.002 in caregivers and p=0.008 in the general public). There were also some demographic factors showing differential associations with attitudes against lung cancer among the four participants groups. Healthcare providers (N=623) who were more than 45 years old showed stronger negative explicit descriptive attitudes compared with those equal to or younger than 45 (p=0.030). In the cancer patient (N=493) and caregiver (N=1332) groups, white people tended to have stronger negative descriptive explicit attitudes (p=0.004 and p=0.029, respectively). And the general public participants (N=1356) who rated themselves as very knowledgeable about cancer had stronger negative descriptive explicit attitudes (p=0.003).

The associations between gender and explicit normative attitudes only existed in the caregiver and general public groups, in which males tended to have stronger negative explicit normative attitudes against lung cancer than females (p=0.007 for caregivers and p=0.019 for the general public). Non-white healthcare providers and caregivers tended to have stronger negative explicit normative attitudes compared with white ones (p=0.013 for healthcare providers and p=0.004 for caregivers). Cancer patients older than 45 years old (compared with those ≤ 45 years old; p=0.002) or those self-rated as somewhat or very knowledgeable about cancer compared with those self-rated as less knowledgeable about cancer (p=0.016), had less negative normative attitudes against lung cancer. And general public participants with high incomes (annual household income ≥ 100,000 USD; p=0.002) had stronger negative explicit normative attitudes against lung cancer compared with those participants who had annual household income less than 100,000 USD.

Table 3. The association between demographic factors and explicit attitudes toward lung cancer from multivariate analysis

Explicit Attitudes	Predictors		Sample Size	Explicit Attitudes Scores Mean	Regression Coefficient	P-value
Explicit Descriptive Attitudes	Gender					
		Female	1422	1.261	-	-
		Male	389	0.772	-0.499	0.000*
	Income[1]					
		Low	962	1.074	-	-
		High	849	1.250	0.160	0.024*
	Healthcare provider					
		No	1423	1.205	-	-
		Yes	388	1.143	-0.222	0.013*
	Caregiver					
		No	943	1.058	-	-
		Yes	868	1.263	0.102	0.149
	White					
		No	243	0.642	-	-
		Yes	1568	1.236	0.555	0.000*
	Self-rated knowledge level about cancer					
		Not knowledgeable	133	0.673	-	-
		Somewhat knowledgeable	1137	1.024	0.274	0.045*
		Very knowledgeable	541	1.554	0.822	0.000*
Explicit Normative Attitudes	Gender					
		Female	1392	0.141	-	-
		Male	373	0.202	0.051	0.096
	Income[1]					
		Low	939	0.133	-	-
		High	826	0.179	0.045	0.073
	Healthcare provider					
		No	1381	0.167	-	-
		Yes	384	0.108	-0.057	0.061
	Cancer Patient					
		No	1456	0.165	-	-
		Yes	309	0.104	-0.055	0.097
	Knowledge level about cancer[2]		1765	0.154	-0.008	0.027*

1. Income cut point: Annual household 100,000 USD
2. Knowledge level about cancer is a continuous variable measured with five Likert-scale questions about cancer. The participants were asked to rate five statements, including (1) Cancer is always fatal; (2) Cancer is contagious; (3) Lung cancer is always caused by smoking; (4) There are cancer medicines that can help people live longer than they might have without medicine; and (5) Early diagnosis of lung cancer can help people live longer with the disease. When they rated the true statements (the fourth and fifth statements) higher, they gained a higher score, and vice versa. Scores ranged from 5 to 30.

Table 4. The association between demographic factors and explicit attitudes toward lung cancer in four participant groups from multivariate analysis

Participant Group	Predictors	Regression Coefficient	P-value
Explicit Descriptive Attitudes			
Healthcare Providers	Gender - male vs. female	-0.903	0.006*
	Age - older (>45) vs. younger (<=45)	0.485	0.030*
	Self-rated knowledge level about cancer		
	Somewhat knowledgeable	-0.234	0.789
	Very knowledgeable	0.366	0.674
Cancer Patients	Gender - male vs. female	-1.114	0.006*
	Self-rated knowledge level about cancer		
	Somewhat knowledgeable	0.333	0.698
	Very knowledgeable	0.960	0.270
	White vs. non-white	1.810	0.004*
Caregivers	Gender - male vs. female	-0.700	0.002*
	Income - high vs. low[1]	0.308	0.069
	Self-rated knowledge level about cancer		
	Somewhat knowledgeable	0.134	0.810
	Very knowledgeable	0.785	0.164
	White vs. non-white	0.605	0.029*
General Public	Gender - male vs. female	-0.445	0.008*
	Self-rated knowledge level about cancer		
	Somewhat knowledgeable	0.180	0.438
	Very knowledgeable	0.837	0.003*
	Knowledge level about cancer	0.031	0.129
Explicit Normative Attitudes			
Participant Group	**Predictors**	**Regression Coefficient**	**P-value**
Healthcare Providers	White vs. non-white	-0.282	0.013*
Cancer Patients	Age - older (>45) vs. younger (<=45)	-0.248	0.002*
	Self-rated knowledge level about cancer		
	Somewhat knowledgeable	-0.385	0.029*
	Very knowledgeable	-0.428	0.016*
Caregivers	Gender - male vs. female	0.172	0.007*
	Education Level		
	Bachelor degree	-0.022	0.727
	Graduate degree	0.108	0.064
	White vs. non-white	-0.228	0.004*
General Public	Gender - male vs. female	0.153	0.019*
	Income - high vs. low[1]	0.177	0.002*

1. Income cut point: Annual household 100,000 USD

1.4.4 Demographic Factors Associated with Implicit Attitudes

Participants who were white compared with non-whites ($p=0.031$) or who had never been diagnosed with cancer ($p=0.019$) had stronger negative implicit attitudes against lung cancer. Gender is a strong predictor of implicit attitudes against lung cancer. Among all participants (Table 5) or individual groups (Table 6), females, when compared with males, had stronger negative implicit attitudes against lung cancer ($p<0.001$ in all participants, $p=0.001$ in healthcare providers, $p=0.006$ in cancer patients, $p<0.001$ in caregivers and $p=0.001$ in the general public). Among all participants (combining all four groups) and in the cancer patient participant group, higher education was significantly associated with stronger negative implicit attitudes against lung cancer ($p=0.003$ and $p=0.044$). Moreover, in the cancer patient group those participants who had higher incomes tended to have stronger negative implicit attitudes against lung cancer ($p=0.001$).

Among all participants (Table 5) and in the caregiver group (Table 6), those with high annual household incomes (≥ 100,000 USD) had a stronger tendency to link lung cancer with smoking behavior ($p=0.014$ and $p=0.002$). Among all participants, the caregiver group, and the general public group (Table 6), those participants self-rated as more knowledgeable about cancer were more likely to link lung cancer with smoking behavior ($p=0.007$, $p=0.040$ and $p=0.006$).

Table 5. The association between demographic factors and implicit attitudes toward lung cancer from multivariate analysis

Implicit Attitudes	Predictors		Sample Size	IAT D Scores Mean	Regression Coefficient	P-value
Attitude IATs[1] (Implicit Attitudes)	Gender					
		Female	1127	0.413	-	-
		Male	293	0.247	-0.171	0.000*
	Education Level					
		Some college or below	340	0.321	-	-
		Bachelor degree	469	0.382	0.050	0.107
		Graduate degree	611	0.409	0.088	0.003*
	Caregiver					
		No	751	0.391	-	-
		Yes	669	0.365	-0.034	0.147
	Cancer Patient					
		No	1190	0.391	-	-
		Yes	230	0.316	-0.074	0.019*
	White					
		No	182	0.321	-	-
		Yes	1238	0.387	0.075	0.031*
Stereotype IATs (Implicit Smoking Stereotypes)	Age					
		Young (<= 45)	463	0.485	-	-
		Old (>45)	448	0.541	0.051	0.075
	Income[1]					
		Low	464	0.472	-	-
		High	447	0.554	0.071	0.014*
	Self-rated knowledge level about cancer					
		Not knowledgeable	54	0.344	-	-
		Somewhat knowledgeable	576	0.516	0.159	0.010*
		Very knowledgeable	281	0.538	0.173	0.007*

1. Income cut point: Annual household 100,000 USD

Table 6. The association between demographic factors and implicit attitudes toward lung cancer in four participant groups from multivariate analysis

Participants Group	Predictors	Regression Coefficient	P-value
Implicit Attitudes			
Healthcare Providers	Gender - male vs. female	-0.302	0.001*
Cancer Patients	Gender - male vs. female	-0.281	0.006*
	Age -older (>45) vs. younger (<=45)	-0.188	0.060
	Income - high vs. low[1]	0.261	0.001*
	Education Level		
	Bachelor degree	-0.012	0.901
	Graduate degree	0.187	0.044*
Caregivers	Gender - male vs. female	-0.215	0.000*
	Education Level		
	Bachelor degree	0.097	0.105
	Graduate degree	0.108	0.051
	Self-rated knowledge level about cancer		
	Somewhat knowledgeable about cancer	0.199	0.175
	Very knowledgeable about cancer	0.103	0.491
General Public	Gender - male vs. female	-0.164	0.001*
Implicit Smoking Stereotypes			
Participants Group	**Predictors**	**Regression Coefficient**	**P-value**
Healthcare Providers	Income - high vs. low[1]	0.124	0.054
Cancer Patients	NA	NA	NA
Caregivers	Income - high vs. low[1]	0.138	0.002*
	Self-rated knowledge level about cancer		
	Somewhat knowledgeable about cancer	0.295	0.047*
	Very knowledgeable about cancer	0.309	0.040*
General Public	Self-rated knowledge level about cancer		
	Somewhat knowledgeable about cancer	0.200	0.006*
	Very knowledgeable about cancer	0.121	0.164

1. Income cut point: Annual household 100,000 USD

1.5 DISCUSSION

N. Sriram *et al*. confirmed the negative perceptions of lung cancer[6]. Because of the causal relationship between smoking behavior and lung cancer, there is a negative societal perception toward lung cancer, which may not only create an extra burden for lung cancer patients but also impede medical care[2,11]. However, not every case of lung cancer results from smoking; other factors affecting the occurrence of lung cancer include genetic and environmental factors[12-15]. Yet lung cancer stigma affects both smoking and non-smoking lung cancer patients. Understanding attitudes toward lung cancer could aid in reducing this stigma.

I found that lung cancer bias occurred in all populations in our study. Even healthcare providers, who should be cognizant that not every lung cancer case results from smoking[2], still demonstrated this biased perception. Participants who rated themselves as more knowledgeable about cancer also tended to have stronger lung cancer stigma. This paradox may have a negative effect on lung cancer patients. Further education regarding lung cancer stigma should be focused and especially applied to healthcare providers and those people who were self-rated as knowledgeable about cancer.

Participants with advanced degrees tended to have strong negative implicit attitudes toward lung cancer. Implicit attitudes are produced based on people's memories or past experiences[16], whereas explicit attitudes are products of rational thinking. Although people in our study who had higher levels of education may presumably be predisposed to rational thinking, they still expressed unconscious negative attitudes toward lung cancer. This suggests the importance of removing people's bias toward lung cancer, especially the bias held by well-educated people.

Gender was significantly associated with explicit and implicit attitudes toward lung cancer. Female participants showed stronger negative perception toward lung cancer, as illustrated by both explicit descriptive and implicit attitudes measures. Although males showed stronger negative explicit normative attitudes than females, this phenomenon was found only in the caregiver and general public groups.

There are some limitations to the attitudes data. First, the gender ratio is unbalanced - the number of female participants was about three times that of males. The race ratio is also unbalanced - 80% of the participants are white. However, I performed resampling and found that significant associations between these demographic factors and attitudes remained, indicating the significant differences in explicit descriptive attitudes and implicit attitudes between different genders and races (whites and non-whites) still existed. I also found a regional imbalance – around 18% of the participants came from California, where the social perception of smoking as an unhealthy behavior is well advocated. This may have skewed results for overall negative attitudes at the national level.

The ultimate goals of our study are to reduce lung cancer stigma and improve treatment quality. To develop a strategy and method for reducing discrimination, I must identify which factors are associated with negative attitudes toward lung cancer and how this negative perception is generated. Based on our results, I can state that gender, self-rated knowledge level about cancer, race (white vs. non-white) and income level are significantly associated with people's explicit attitudes toward lung cancer. Gender, education level, income level and self-rated knowledge level about cancer were significantly associated with people's implicit attitudes toward lung cancer. More effort should be given to general education campaigns explaining that smoking is just one of several causes of lung cancer and removing other sources of bias as an obstacle to treatment.

CHAPTER TWO. The Effects of Explicit and Implicit Attitudes against Lung Cancer - Negative Explicit and Implicit Attitudes toward Lung Cancer Are Correlated with Lower Lung Cancer Treatment Rates

INTRODUCTION

2.1 Introduction

Lung cancer is a leading cause of death, and it is known that around 85% of lung cancer cases result from a history of smoking[1]. The strong association between smoking and lung cancer carries the implication that lung cancer is self-inflicted. However, not all lung cancer cases result from smoking behavior [11-14,17]. Such negative social attitudes toward lung cancer[18] affect not only lung cancer patients with a history of smoking but also those who have never smoked[2,3]. In the first chapter, the association between gender, race (white vs. non-white), education level, income level, knowledge level about cancer and self-rated knowledge level about lung cancer with people's attitudes toward lung cancer[19] was discussed. In this chapter, the association between lung cancer stigma and state-level lung cancer treatment rates will be addressed.

MATERIALS AND METHODS

2.2 The Lung Cancer Project Data

The attitude data gathered from *The Lung Cancer Project* were used. The information of *The Lung Cancer Project* was described in chapter 1.2.

2.2.1 State-Level Attitudes

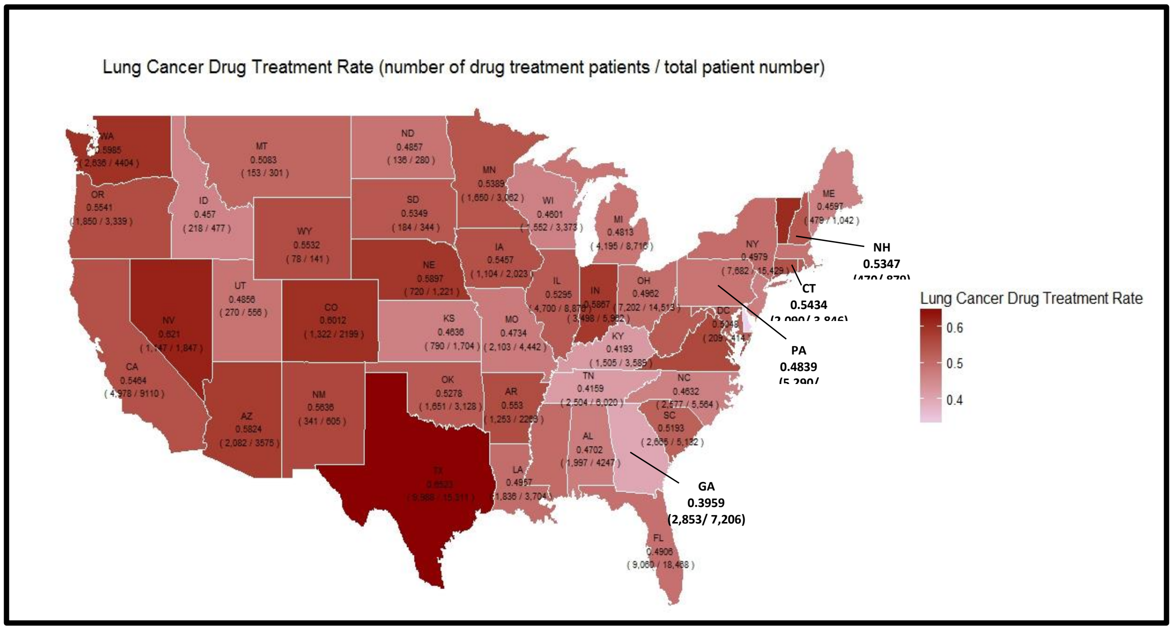
In this chapter, analysis focuses on state-level explicit (descriptive and normative assessments of patients' shame, embarrassment, behavioral attribution, fatalism, and hope) and implicit (good vs. bad; hope vs. despair; suitable vs. shameful) attitudes toward lung and breast cancer patients. The data were gathered from *The Lung Cancer Project.* These state-level attitudes were calculated by averaging the lung/breast difference scores of individual participants within each state. States with fewer than 10 participants were excluded from the analysis to ensure the data's representativeness. After data summarization, cancer patient participants' state-level attitudes were available for the following 16 states - Arizona, California, Colorado, Florida, Georgia, Illinois, Massachusetts, Maryland, North Carolina, New Jersey, New York, Ohio, Pennsylvania, Texas, Virginia, and Washington.

2.2.2 Lung Cancer Drug Treatment Rate Data

For this analysis, state-level lung cancer treatment data were retrieved from the Source Healthcare Analytics (SHA) Medical Claims Data, which is based on ICD9 codes used by doctors for reimbursement of services to insurance companies. The data considered all lung cancer patients who were first diagnosed with lung cancer between 2010 and 2012 and had at least four claims in 12 months after lung cancer diagnosis. The lung cancer patients' coverage rate in the SHA claims data is about 50%. Data included 219,201 lung cancer patients from 50 states.

In this data set, lung cancer patients' treatment categories (drug treatment, surgical/radiation therapy, non-treatment) are displayed. Lung cancer treatment was defined as a) any kind of systemic anti-cancer medicine, e.g., chemotherapy, targeted therapies (anti-VEGF, anti-EGFR or anti-ALK for example) or cancer immunotherapies; b) surgical therapy; or c) radiation therapy. The treatment rates of each state (Figure 3) were calculated as the number of treated lung cancer patients divided by the total number of lung cancer patients.

Figure 3. Map of lung cancer drug treatment rate in each state



The state-level lung cancer drug treatment (abbreviated as DT) rates are shown in the US state map. The color of each state in the map represents the level of DT rates - the deeper the color, the higher the lung cancer DT rate in that state.

2.2.3 State-level Demographic Data Source

The state-level demographic information used in analyzing the association between demographic factors and lung cancer total or drug treatment rates was retrieved from several databases. Median household income (2011-2013) data were from the US Census Bureau[20]. Lung cancer incidence rate data (2012) were from the Surveillance, Epidemiology, and End Results (SEER)[21-23] study. Smoking rate data (2012-2014) were from the Centers for Disease Control and Prevention, Office on Smoking and Health[24-26].

2.3 Statistical Analysis

Univariate analysis was used to explore the state-level demographic variables significantly associated with state-level lung cancer patients' drug or total treatment rates. Multivariate regression analysis was used to study the associations between explicit/implicit attitudes and lung cancer patients' drug or total treatment rates.

RESULTS

2.4.1 Cancer Patients' Implicit Attitudes toward Lung Cancer are Associated with State-level Lung Cancer Drug Treatment Rates

To determine if the negative perceptions of lung cancer were associated with treatment rates, I analyzed the associations of explicit and implicit attitudes/stereotypes and state-level lung cancer patients' drug treatment (abbreviated as DT) rates (Table 7), which were extracted from Source Healthcare Analytics (SHA) Claims Data.

Table 7. The association between state-level cancer patients' attitudes and state-level lung cancer drug treatment rates from multivariate analysis

Predictors	Regression Coefficient	P-value
Explicit Descriptive Attitude	-0.042	0.066
Explicit Normative Attitude	0.148	0.279
Implicit Attitude - Bad vs. good	0.542	0.005*
Implicit Attitude - Despair vs. Hope	-0.389	0.013*
Implicit Attitude - Shameful vs. suitable	-0.169	0.010*
Implicit Stereotype - Smoking vs. drinking	-0.199	0.006*
Implicit Stereotype - Smoking vs. eating	-0.172	0.003*

Data of attitudes toward lung cancer were collected from the *Project Implicit* and summarized to state-level data. Only the 16 states (AZ, CA, CO, FL, GA, IL, MA, MD, NC, NJ, NY, OH, PA, TX, VA, WA) with equal to or more than 10 participants in *The Lung Cancer Project* were included in this analysis.

I found cancer patients' state-level implicit attitudes and stereotypes showed a strong correlation with DT rates. Stronger negative implicit attitudes toward lung cancer (p=0.013 for relating the concept "despair" vs. "hope" to lung cancer and p=0.010 for relating the concept "shameful" vs. "suitable" to lung cancer), and stronger stereotypes regarding the role of smoking in the etiology of lung cancer (p=0.006 for linking "smoking" vs. "drinking" to lung cancer and p=0.003 for linking "smoking" vs. "eating" to lung cancer), were associated with lower lung cancer DT rates.

Because of the data imbalance issue, I assessed the possibility of confounders behind the association between negative implicit attitudes toward lung cancer possessed by cancer patients and lower state-level lung cancer DT rates. I found that state-level lung cancer incidence rate (p=0.003), smoking rate (p=0.030) and age (percentage of participants older than 75 years old;

p=0.012) were significantly associated with lung cancer DT rates (Table 8), which indicates the possibility of confounders. Higher cancer incidence and smoking rate corresponded to a lower treatment rate. And in the states with a higher percentage of patients older than 75, the lung cancer DT rates were higher.

Table 8. The association between potential confounders and state-level lung cancer drug treatment rates from univariate analysis

Demographic Factor	Regression Coefficient	P-value
Gender Ratio (Male/Female)[1]	-0.050	0.523
Percentage of participants older than 75 years old[1]	0.698	0.012*
Medium Income (2011-2013) [2]	0.000	0.087
Lung Cancer Incidence Rate (2012) [3]	-0.002	0.003*
Smoking Rate[4]	-0.006	0.030*

1. State-level gender and age data were from Source Healthcare Analytics (SHA) Claims Data.
2. State-level medium household income (2011-2013) data were from the US. Census Bureau.
3. State-level Lung Cancer Incidence Rate (2012) data were from the Surveillance, Epidemiology, and End Results (SEER) survey.
4. State-level Smoking Rate (2012-2014) were from the Centers for Disease Control and Prevention, Office on Smoking and Health.

Further analysis was performed to explore whether the associations between attitudes and lung cancer DT rates were confounded by demographic factors. After adjusting for all three demographic factors significantly associated with lung cancer DT rates, cancer patients' stronger negative implicit attitudes toward lung cancer and implicit stereotypes were still significantly associated with lower lung cancer DT rates in these states (Table 9), which proves the robustness of the association.

Table 9. The association between cancer patients' explicit/implicit attitudes and state-level lung cancer drug treatment rates adjusted by possible confounders

Confounder	Predictor	Regression Coefficient	P-value
Percentage of participants older than 75 years old	**Explicit Descriptive Attitude**	-0.037	0.122
	Explicit Normative Attitude	0.134	0.346
	Implicit Attitude - Bad vs. good	0.542	0.012*
	Implicit Attitude - Despair vs. hope	-0.393	0.024*
	Implicit Attitude - Shameful vs. suitable	-0.171	0.020*
	Implicit Stereotype - Smoking vs. drinking	-0.189	0.018*
	Implicit Stereotype - Smoking vs. eating	-0.158	0.014*
Lung Cancer Incidence Rate	**Explicit Descriptive Attitude**	-0.034	0.105
	Explicit Normative Attitude	0.139	0.261
	Implicit Attitude - Bad vs. good	0.499	0.011*
	Implicit Attitude - Despair vs. hope	-0.330	0.031*
	Implicit Attitude - Shameful vs. suitable	-0.160	0.016*
	Implicit Stereotype - Smoking vs. drinking	-0.176	0.016*
	Implicit Stereotype - Smoking vs. eating	-0.175	0.005*
Smoking Rate	**Explicit Descriptive Attitude**	-0.043	0.069
	Explicit Normative Attitude	0.191	0.200
	Implicit Attitude - Bad vs. good	0.518	0.012*
	Implicit Attitude - Despair vs. hope	-0.356	0.029*
	Implicit Attitude - Shameful vs. suitable	-0.171	0.016*
	Implicit Stereotype - Smoking vs. drinking	-0.179	0.020*
	Implicit Stereotype - Smoking vs. eating	-0.182	0.006*

Data of attitudes toward lung cancer were collected from *Project Implicit* and summarized to state-level data. Only the 16 states (AZ, CA, CO, FL, GA, IL, MA, MD, NC, NJ, NY, OH, PA, TX, VA, WA) with equal to or more than 10 participants in *The Lung Cancer Project* were included in this analysis.

2.4.2 Other Participants' Implicit Attitudes toward Lung Cancer are Not Associated with State-level Lung Cancer Drug Treatment Rates

I also analyzed the association between other participant groups' implicit and explicit attitudes toward lung cancer and state-level lung cancer patients' drug treatment rates (Table 10). There was no significant association between other participant groups' (healthcare providers, caregivers and general public) state-level attitudes toward lung cancer and state-level lung cancer DT rates found in the analysis. Although the association was not statistically significant, it has been observed that healthcare professional's negative implicit attitudes toward lung cancer show a correlation with lower state-level lung cancer drug treatment rates (Table 10).

Table 10. The association between explicit/implicit attitudes of other participant groups and state-level lung cancer drug treatment rates from multivariate analysis

Participant Group	Predictor	Regression Coefficient	P-value
Healthcare Professional	Explicit Descriptive Attitude	-0.054	0.785
	Explicit Normative Attitude	0.014	0.932
	Implicit Attitude - Bad vs. good	0.023	0.825
	Implicit Attitude - Despair vs. hope	-0.002	0.995
	Implicit Attitude - Shameful vs. suitable	-0.113	0.354
	Implicit Stereotype - Smoking vs. drinking	-0.020	0.846
	Implicit Stereotype - Smoking vs. eating	-0.058	0.565
Caregiver	Explicit Descriptive Attitude	-0.016	0.540
	Explicit Normative Attitude	-0.004	0.961
	Implicit Attitude - Bad vs. good	-0.035	0.332
	Implicit Attitude - Despair vs. hope	-0.074	0.253
	Implicit Attitude - Shameful vs. suitable	0.029	0.584
	Implicit Stereotype - Smoking vs. drinking	0.043	0.530
	Implicit Stereotype - Smoking vs. eating	0.082	0.174
General Public	Explicit Descriptive Attitude	-0.097	0.097
	Explicit Normative Attitude	-0.050	0.660
	Implicit Attitude - Bad vs. good	-0.013	0.917
	Implicit Attitude - Despair vs. hope	-0.045	0.457
	Implicit Attitude - Shameful vs. suitable	0.022	0.783
	Implicit Stereotype - Smoking vs. drinking	0.133	0.242
	Implicit Stereotype - Smoking vs. eating	0.037	0.652

2.4.3 Cancer Patients' Implicit Attitudes toward Lung Cancer are Associated with State-level Lung Cancer Total Treatment Rates

The association between participants' implicit and explicit attitudes toward lung cancer and state-level lung cancer patients' total treatment rates was analyzed. Significant associations were found between the state-level lung cancer total treatment rate and stereotypes regarding the role of smoking in the etiology of lung cancer (Table 11). Cancer patients' stronger implicit stereotypes were associated with lower lung cancer total treatment rates (p=0.029 when comparing "smoking" vs. "drinking" and p=0.028 when comparing "smoking" vs. "eating" as stereotypical behavior in lung cancer; see Table 11).

Table 11. The association between state-level cancer patients' attitudes and state-level lung cancer total treatment rates from multivariate analysis

Predictors	Regression Coefficient	P-value
Explicit Descriptive Attitude	-0.019	0.493
Explicit Normative Attitude	0.235	0.273
Implicit Attitude - Bad vs. good	0.320	0.105
Implicit Attitude - Despair vs. hope	-0.306	0.099
Implicit Attitude - Shameful vs. suitable	-0.122	0.104
Implicit Stereotype - Smoking vs. drinking	-0.197	0.029*
Implicit Stereotype - Smoking vs. eating	-0.142	0.028*

Data of attitudes toward lung cancer were collected from *Project Implicit* and summarized to state-level data. Only the 16 states (AZ, CA, CO, FL, GA, IL, MA, MD, NC, NJ, NY, OH, PA, TX, VA, WA) with equal to or more than 10 participants in *The Lung Cancer Project* were included in this analysis.

The possibility of confounders in the association of lung cancer treatment rates and cancer patients' implicit stereotypes in lung cancer (Table 12) was tested. I found that the state-level higher median income (p=0.045), lower lung cancer incidence rate (p=0.002) and higher population of elderly (percentage of participants older than 75 years old, p=0.006) were significantly associated with lung cancer treatment rate. After adjusting for the lung cancer incidence rate, the significant association between lung cancer patient's treatment rate and implicit stereotypes in lung cancer still existed (p=0.05; see Table 13). Although the significant association between lung cancer treatment rate and cancer patients' stereotypes in lung cancer didn't remain after adjusting for age (percentage of participants older than 75 years old) and median income, the trend that cancer patients' stronger implicit stereotypes in lung cancer indicated lower state-level lung cancer treatment rates was still shown.

Table 12. The association between cancer patients' explicit/implicit attitudes and state-level lung cancer total treatment rates

Demographic Factor	Regression Coefficient	P-value
Gender Ratio (Male/Female)[1]	-0.046	0.476
Percentage of participants older than 75 years old[1]	0.628	0.006*
Medium Income (2011-2013)[2]	0.000 (0.000002)	0.045*
Lung Cancer Incidence Rate (2012)[3]	-0.002	0.002*
Smoking Rate[4]	-0.004	0.079

1. State-level gender and age data were from Source Healthcare Analytics (SHA) Claims Data.
2. State-level medium household income (2011-2013) data were from the US. Census Bureau.
3. State-level Lung Cancer Incidence Rate (2012) data were from the Surveillance, Epidemiology, and End Results (SEER) survey.
4. State-level Smoking Rate (2012-2014) was from the Centers for Disease Control and Prevention, Office on Smoking and Health.

Table 13. The association between cancer patients' explicit/implicit attitudes and state-level lung cancer total treatment rates, adjusted by possible confounders

Confounder	Predictor	Regression Coefficient	P-value
Percentage of participants older than 75 yrs old	Explicit Descriptive Attitude	-0.015	0.644
	Explicit Normative Attitude	0.221	0.358
	Implicit Attitude - Bad vs. good	0.320	0.154
	Implicit Attitude -Despair vs. Hope	-0.309	0.144
	Implicit Attitude -Shameful vs. suitable	-0.124	0.148
	Implicit Stereotype - Smoking vs. drinking	-0.188	0.069
	Implicit Stereotype - Smoking vs. eating	-0.128	0.091
Medium Income	Explicit Descriptive Attitude	-0.006	0.906
	Explicit Normative Attitude	0.193	0.475
	Implicit Attitude - Bad vs. good	0.354	0.169
	Implicit Attitude -Despair vs. hope	-0.374	0.223
	Implicit Attitude -Shameful vs. suitable	-0.142	0.194
	Implicit Stereotype - Smoking vs. drinking	-0.194	0.064
	Implicit Stereotype - Smoking vs. eating	-0.162	0.109
Lung Cancer Incidence Rate	Explicit Descriptive Attitude	-0.013	0.679
	Explicit Normative Attitude	0.228	0.337
	Implicit Attitude - Bad vs. good	0.285	0.201
	Implicit Attitude -Despair vs. hope	-0.258	0.230
	Implicit Attitude -Shameful vs. suitable	-0.114	0.172
	Implicit Stereotype - Smoking vs. drinking	-0.178	0.085
	Implicit Stereotype - Smoking vs. eating	-0.145	0.050*

2.4.4 Other Participants' Implicit Attitudes toward Lung Cancer are Not Associated with State-level Lung Cancer Overall Treatment Rates

The association between other participant groups' (healthcare providers, caregivers and general public) state-level implicit and explicit attitudes toward lung cancer and state-level lung cancer patients' overall treatment rates was analyzed. There was no statistically significant association found among these three participant groups (Table 14).

Table 14. The association between explicit/implicit attitudes of other participant groups and state-level lung cancer total treatment rates from multivariate analysis

Participant Group	Predictor	Regression Coefficient	P-value
Healthcare Professional	Explicit Descriptive Attitude	-0.133	0.394
	Explicit Normative Attitude	0.180	0.182
	Implicit Attitude - Bad vs. good	0.026	0.750
	Implicit Attitude - Despair vs. hope	-0.133	0.487
	Implicit Attitude - Shameful vs. suitable	-0.095	0.316
	Implicit Stereotype - Smoking vs. drinking	0.017	0.829
	Implicit Stereotype - Smoking vs. eating	-0.040	0.607
Caregiver	Explicit Descriptive Attitude	-0.007	0.749
	Explicit Normative Attitude	0.098	0.125
	Implicit Attitude - Bad vs. good	-0.031	0.313
	Implicit Attitude - Despair vs. hope	-0.065	0.246
	Implicit Attitude - Shameful vs. suitable	0.024	0.600
	Implicit Stereotype - Smoking vs. drinking	0.068	0.260
	Implicit Stereotype - Smoking vs. eating	0.040	0.432
General Public	Explicit Descriptive Attitude	-0.048	0.417
	Explicit Normative Attitude	-0.118	0.345
	Implicit Attitude - Bad vs. good	0.124	0.363
	Implicit Attitude - Despair vs. hope	-0.031	0.634
	Implicit Attitude - Shameful vs. suitable	0.038	0.663
	Implicit Stereotype - Smoking vs. drinking	0.224	0.077
	Implicit Stereotype - Smoking vs. eating	0.060	0.499

2.5 DISCUSSION

A burgeoning literature demonstrates widespread negative attitudes (e.g., enacted stigma) toward lung cancer patients. This stigma is associated with negative psychosocial outcomes among patients, and may also have a pervasive impact on patient care, including referrals for evidence-based treatments [2,27]. The current study expands our knowledge of this potential connection by demonstrating that higher state-level rates of negative attitudes are associated with lower treatment rates for lung cancer patients in each state.

This study is the first to quantitatively assess these relationships and provides further understanding of the potential societal impact of lung cancer stigma. I found that cancer patients' implicit attitudes against lung cancer and implicit stereotypes were significantly associated with state-level lung cancer drug and total treatment rates. In states where cancer patients tended to implicitly link lung cancer with the term "despair" and "shameful", the lung cancer DT rates were lower. However, I also found that the stronger the implicit links between lung cancer and "bad", the higher the state-level lung cancer DT rates. These results seem inconsistent at first glance. However, "despair" and "shameful" are terms describing a feeling toward people, while "bad" may indicate a feeling toward the disease itself. When cancer patients feel shameful about having lung cancer, it may result in lung cancer patients being less willing to undergo treatment. Conversely, when cancer patients feel that the disease itself is bad, it may provide lung cancer patients with a motivation to overcome the disease, which would increase the state-level lung cancer DT rates. Concordant with our hypothesis, in the states where cancer patients showed a stronger linkage between lung cancer and lung cancer's stereotypical behavior of "smoking", the DT rates are lower. Interestingly, associations between lung cancer DT rates and explicit attitudes were not found. This indicates the importance of studies focusing on implicit attitudes. Although a significant association was only observed between cancer patients' attitudes and lung cancer DT rate, this association remained significant after adjusting for the demographic factors. The lack of association in other participant groups may result from information loss in the procedure of summarizing individual attitudes data into state-level data since only the states with no fewer than 10 participants were included in the state-level data. I also assessed the association between the negative attitudes toward lung cancer and lung cancer patients' overall treatment rates. The consistent results were observed.

There are certain limitations to the current analysis. First, attitudes of study respondents may not be generalized to overall societal attitudes. Individuals who chose to participate in the study may have specific biases not seen among non-responders. Second, demographic characteristics (e.g., gender, race) are likely not reflective of the state population overall. Also, the participants' smoking status, which may be a great indicator of their attitudes toward lung cancer, was not available in the data.

I also found a regional imbalance – around 18% of participants came from California, where the social perception of smoking as an unhealthy behavior is well advocated. This may have skewed results for overall negative attitudes at the national level. The regional imbalance also resulted in data lost when I summarized the individual attitudes to the state level, since only the states with 10 or more participants were included. To study the effects of general attitudes toward lung cancer and lung cancer patients' treatment rates, state-level analysis was performed. Only 16 states were included in the analysis to ensure enough participants in each state. Larger studies are needed to further investigate how the attitudes toward lung cancer affect treatment choices.

In conclusion, stronger negative implicit attitudes and implicit stereotypical attitudes toward lung cancer are negatively associated with treatment rates of lung cancer patients. These findings underscore the need for large-scale, anti-stigma interventions focused on perceptions of lung cancer.

Topic II.

CHAPTER THREE. Using *Research Domain Criteria Project (RDoC)* to Predict Remission Rates of Major Depressive Disorder Patients

3.1 Introduction

According to the World Health Organization (WHO), depressive disorders alone are the third leading cause of disability-adjusted life years, worldwide, and by 2020 are estimated to be second only to ischemic heart disease[28,29]. This debilitating illness will affect up to 16.2% of Americans in their lifetime[30].

The goal of treatment for those suffering from mental illnesses such as major depressive disorder (MDD) is remission (i.e., the absence of symptoms). However, two-thirds of patients treated with a first step antidepressant do not achieve remission of symptoms[31], and successive treatment steps lead to diminishing remission rates[32]. Furthermore, large numbers of patients either discontinue treatment prematurely due to side effects, or become discouraged and drop out of treatment altogether. In fact, disease heterogeneity is likely to complicate pharmacological approaches going forward, and a likely cause for such varying treatment response of patients in mental disease[33,34]. As a result, establishing methods for identifying which patients are likely to respond (and have fewer side effects) to current treatment options is an essential priority for our field[35].

Studies of cardiovascular disease[36], asthma[37], breast cancer[38], lung cancer[39], multiple sclerosis[40] and other medical illnesses have been successful in identifying important moderators of treatment response, leading to the development of personalized treatment approaches. Given the ineffectiveness of first-step treatments for mental illnesses such as depression, there is a clear and urgent need to identify factors that can be used to individualize treatment (i.e., markers that maximize effectiveness and minimize risk for toxicity)[35]. Personalizing treatments for medical illnesses requires selecting the right treatment for the right patient at the right time[41].

The clinical assessments that are often collected as part of clinical treatment trials can provide a collection of a broad spectrum of behavioral and emotional measures. These are used in a variety of ways, and most often by looking at summary scores that reduce multiple behaviors into a single score, such as a DSM (Diagnostic and Statistical Manual of Mental Disorders) diagnosis. An alternative is to take these self-reporting and clinical evaluations and map them to the positive and negative valance constructs specified in the *Research Domain Criteria project (RDoC)*[42-44]. However, there are so many variables that using them individually to predict patients' response to the treatment would be impossible. Thus, it is critical to develop methods to identify the most important measures related to treatment outcomes.

The *RDoC* paradigm provides a framework for developing new ways of classifying psychopathology based on dimensions of observable behavioral and neurobiological measures[43]. It begins with current understandings of behavior-brain relationships and links them to clinical phenomena[43]. It contains five domains, including Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, and Arousal and Regulatory Systems. However, how to quantify each construct in an efficient and concrete way and to identify the clinical validity and utilities of these constructs become two important questions.

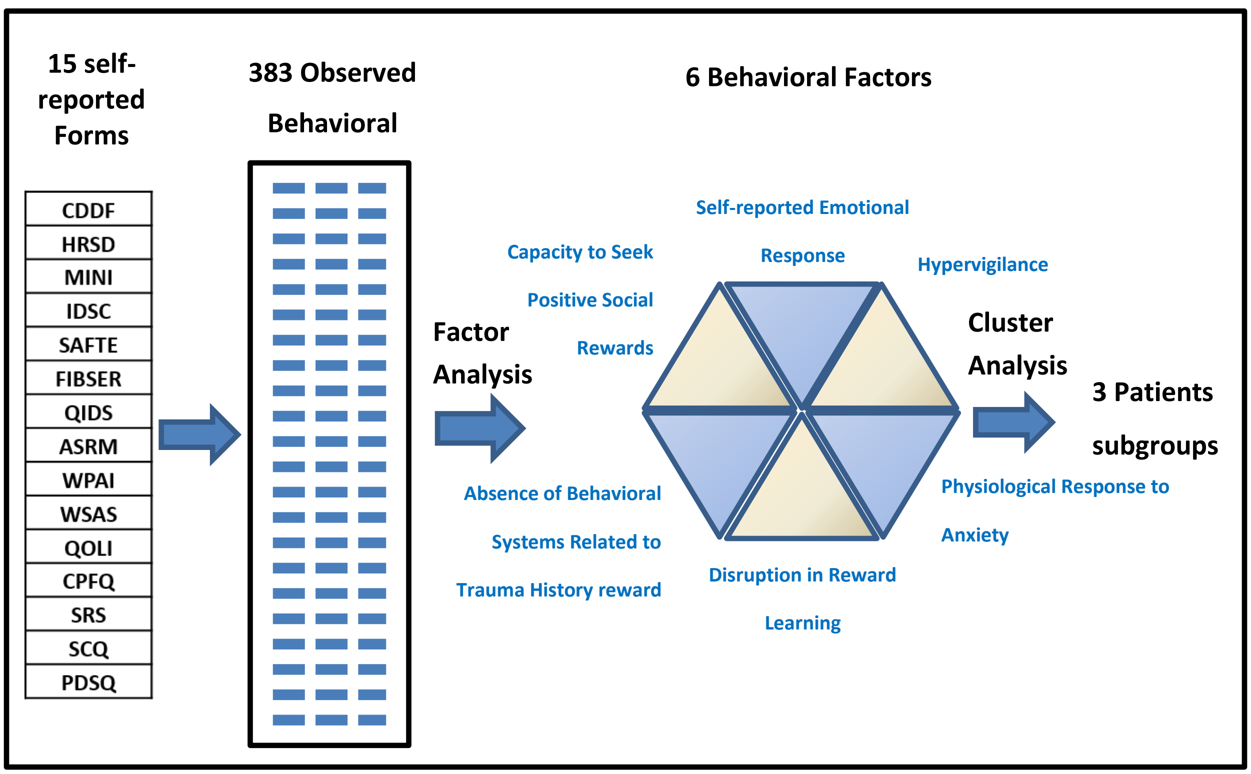
In this study, the existing data from the *Combining Medications to Enhance Depression Outcomes (CO-MED)*[45] trial were utilized. *CO-MED* was a randomized, placebo-controlled clinical trial with 665 participants aiming to determine whether combinations of two antidepressant medications could produce a higher remission rate than antidepressant monotherapy. Using existing data, I developed a data-driven method for mapping the behavioral factors to the constructs defined in *RDoC*, and used the defined behavioral factors to discover patient subgroups. In further analysis, I found that the discovered patient subgroups had significantly different remission rates to the antidepressant treatment. The results from this study provide a new way to further understand disease pathology, enhance the selection of existing treatments, and further the development of novel treatments.

Method

3.2.1 Analysis Overview

In this study, I developed a methodology for integrating the self-reported measures onto the *RDoC* constructs, and then tested the clinical associations between these newly constructed structures with treatment response. Figure 4 demonstrates the overall flowchart of the study.

Figure 4. The flow chart of *CO-MED* trial data analysis



The 383 observed behavioral measures from the 15 self-reported questionnaires for the major depressive disorder patients were analyzed with exploratory factor analysis (EFA) and summarized to the six behavioral factors. Each of these factors can be mapped to one of the Research Domain Criteria constructs. Then I defined patient subgroups from the mapped behavioral factors via clustering analysis methods.

After data selection, exploratory factor analysis (EFA) was employed to summarize the 383 observed behavioral measures from the 15 self-reported questionnaires for the major depressive disorder patients into six behavioral factors, and each of them was mapped to one of *Research Domain Criteria* constructs. Then I defined patient subgroups from the mapped behavioral factors via clustering analysis methods.

3.2.2 Participants and Baseline Characteristics of *Combining Medications to Enhance Depression Outcomes (CO-MED)* trial

I used data from a large clinical trial, *Combining Medications to Enhance Depression Outcomes (CO-MED)*[45], to map clinical symptoms to the *RDoC* constructs. *CO-MED* was a randomized, placebo-controlled clinical trial conducted to determine whether combinations of two antidepressant medications could produce a higher remission rate than monotherapy. *CO-MED* enrolled 665 patients with major depressive disorder (MDD) who were randomized into three arms (Escitalopram plus placebo, Bupropion plus Escitalopram, and Venlafaxine plus Mirtazapine) with 1:1:1 ratio. The primary clinical outcome in *CO-MED* was symptom remission, which was based on the score on the 16-item self-reported Quick Inventory of Depressive Symptomatology at 12 weeks. Secondary clinical outcomes included attrition, anxiety measured by the Work and Social Adjustment Scale, Quality of Life, and side effect burden. The baseline characteristics (Table 15) and the clinical outcomes were collected for all patients in the *CO-MED* trial.

Table 15. Patient baseline characteristics of *CO-MED* trial

Characteristic	Escitalopram +Placebo (N=224)	Bupropion-SR +Escitalopram (N=221)	Venlafaxine-XR +Mirtazapine (N=220)
	N (%)	**N (%)**	**N (%)**
Sex			
Male	81 (36.2)	72 (32.6)	60 (27.3)
Female	143 (63.8)	149 (67.4)	160 (72.7)
Race			
White	147 (67.7)	142 (67.0)	142 (66.4)
Black	56 (25.8)	58 (27.4)	60 (28.0)
Other	14 (6.5)	12 (5.7)	12 (5.6)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
Age			
	43.6 (13.1)	42.4 (13.5)	42.1 (12.4)
Education (years)			
	13.8 (3.2)	13.8 (2.6)	13.7 (3.1)
Score on clinical rating			
HAM-D	23.4 (4.9)	23.8 (4.6)	24.3 (5.0)
IDS-C	37.0 (8.8)	37.8 (9.2)	39.3 (9.3)
QIDS-C	15.6 (3.4)	15.7 (3.5)	16.1 (3.5)
QIDS-SR	15.2 (4.0)	15.3 (4.6)	15.9 (4.2)
Altman self-rated mania	1.6 (2.4)	1.6 (2.2)	1.3 (2.2)
Cognitive and physical functioning questionnaire	27.4 (5.7)	27.7 (6.1)	27.8 (5.8)
Quality of life inventory	-1.2 (1.9)	-1.1 (1.9)	-1.3 (1.9)
Work and social adjustment	26.2 (8.8)	26.7 (9.2)	27.9 (8.4)

In this study, the 665 patients in the *CO-MED* study[45] were under analysis. The outpatient enrollees were 18-75 years old and met the DSM-IV-TR criteria for either recurrent or chronic major depression, confirmed with a DSM-IV-based symptom checklist. Eligible participants had to have an index episode lasting for at least 2 months and had to score at least 16 on the 17-Item Hamilton Depression Rating Scale (HAM-D). Patients with any psychotic illness, bipolar disorder or hospitalization need were ineligible.

Table 15 is the patient demographics. Of these 646 patients, 213 were male (32%) and the remaining 452 (68%) were female. Among them, 224 patients were assigned to the Escitalopram plus Placebo treatment arm, 221 were assigned to the Bupropion-SR plus Escitalopram treatment arm, and 220 were assigned to the Venlafaxine-XR plus Mirtazapine treatment arm.

Table 16. The 15 self-report questionnaires in *CO-MED* trial

Clinical, Demographic, and Prior Treatment History
1. Clinical/Demographic Data Form (CDDF)
Clinical Measures of Psychiatric Comorbidity
2. MINI International Neuropsychiatric Interview (M.I.N.I.)
3. Psychiatric Diagnostic Screening Questionnaire (PDSQ)
4. Suicidality Rating Scale (SRS)
5. Altman Self-Rating Mania Scale (ASRM)
6. Cognitive and Physical Functioning Questionnaire (CPFQ)
Measures of Depressive Severity
7. Hamilton Rating Scale for Depression (HRSD17)
8. Inventory of Depressive Symptomatology - Clinician rated (IDS-C30)
9. Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR16)
Measures of Quality of Life
10. The Quality of Life Inventory (QOLI)
11. The Work Productivity and Activity Impairment scale (WPAI)
12. The Work and Social Adjustment Scale (WSAS)
Measures of Medication Side Effects
13. Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)
14. Systematic Assessment for Treatment Emergent Events-Specific Inquiry (SAFTEE-SI)
Measures of Medical Comorbidities
15. Self-administered Comorbidity Questionnaire (SCQ)

The assessments used in the *CO-MED* study assessed a wide range of psychiatric symptoms and therefore provided an ideal opportunity to assess how well current symptomatic assessment of state and trait functions of psychiatric symptoms, quality of life, medication side effects, and medical comorbidities mapped onto the *RDoC* constructs. The 15 self-reported questionnaires were summarized in Table 16.

3.2.3 Data selection and Measure Rescaling

First, the outliers were removed from the data. The variables with a maximum value larger than 10 or smaller than 0 were removed. And the variables with a minimum value larger than 2 or smaller than -1 were excluded from the data as well. Then the remaining data were rescaled based on formula 1.

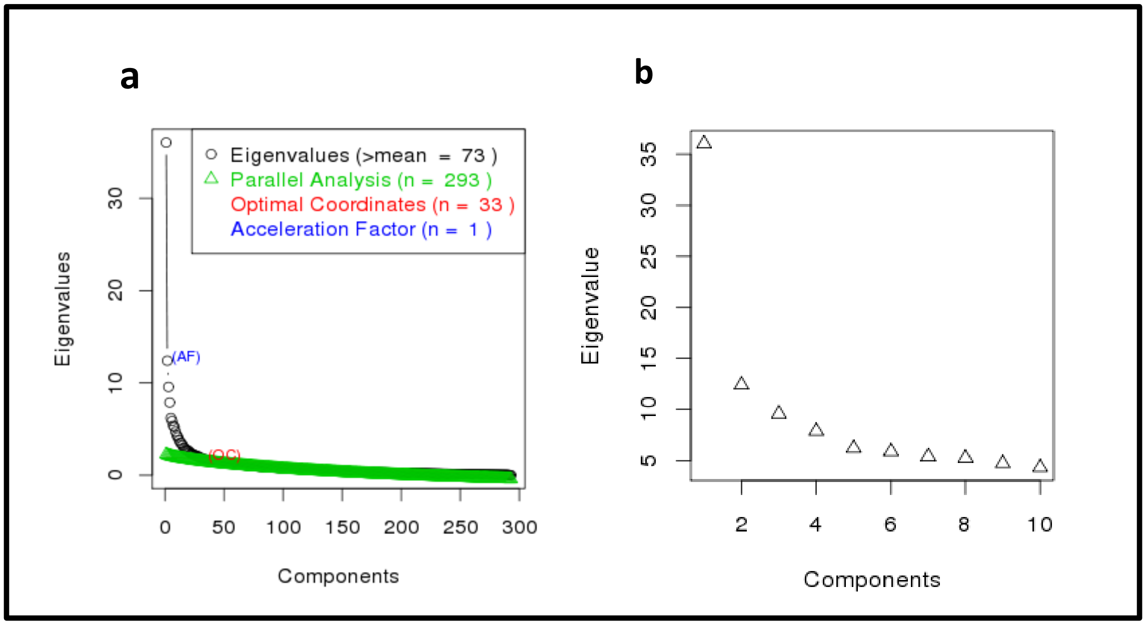
$$\mathbf{r_i}^* = \frac{\mathbf{r_i} - \mathbf{r_{min}}}{\mathbf{r_{max}} - \mathbf{r_{min}}} \quad \text{(formula 1)}$$

In formula 1, $\mathbf{r_i}$ indicates value of a certain clinical measure. $\mathbf{r_{min}}$ means the minimum value of this certain measure and $\mathbf{r_{max}}$ is the maximum. And $\mathbf{r_i}^*$ is the rescaled measurement ranging from 0 to 1. Then the measures with standard deviations > 0.2 were retained for further factor analysis. After this step, the filtered data are composed of 646 patients and 293 measures and subjected to the following analysis.

3.2.4 Exploratory Factor Analysis and Domain Mapping

Before factor analysis, the scree test was employed to decide the number of factors in the factor analysis. In the scree plot (Figure 5), it was shown that 6 factors retained great enough information in factor analysis. Thus, 6 was chosen as the number of factors in the following factor analysis.

Figure 5. Parallel analysis performed to determine the factor number in factor analysis



The factor analysis was applied on the 293 measures with varimax rotation method and these measures were summarized to six factors.

$X = LF + \varepsilon$ (formula 2)

In formula 2, X is a 293 * 646 matrix in which each column denoted the rescaled self-reported measures of one patient and each row denoted the data of a certain measure of the *CO-MED* patients in the analysis. L was the loading matrix (293*6) and F was the factors (6*646).

Then these six factors were mapped to the *RDoC* constructs according to the measures with high loading scores within each factor. For example, in the first factor, the measures with high loading factors are EMSIT, EMSOC, STRANGE, FRSIT, ANSYM, EMAVD, BOTHER and EMANX. Since most of these measures (EMSIT, EMSOC, FRSIT, ANSYM, EMAVD) are related to patients' anxiety, this factor shall be mapped to the 'ANXIETY' domain of *RDoC* constructs. With the same method, each factor was mapped to one of the *RDoC* constructs (Table 17).

Table 17. The summary of the 6 mapped factors

Factor	Information	RDoC Construct
1	Self-reported Emotional Response	Negative Valance System : Potential Threat (Anxiety) Construct
2	Hypervigilance	Negative Valance System: Sustained Behavioral Response to Potential Threat Construct
3	Physiological Response to Anxiety	Negative Valance System: Potential Threat (Anxiety) Construct
4	Disruption in Reward Learning	Positive Valance System: Reward Learning Construct
5	Absence of Behavioral Systems Related to Trauma History	Negative Valance System: Acute Threat (Fear) Construct
6	Capacity to Seek Positive Social Rewards	Positive Valence System: Approach Motivation Construct

3.2.4 Clustering Analysis

Based on the factor analysis, the observed behavioral measures were summarized to six factors, and each factor was related to one of the constructs defined in *RDoC*. In this step, a new matrix N (6 * 646), the product of the transverse matrix of Factors F in formula 2, F^T (6 * 293) and the rescaled patient measures matrix X (293 * 646) in formula 2, was generated.

$N = F^T X$ (formula 3)

In the formula 3, N denoted the six scores corresponding to these six factors of the *CO-MED* patients. With these six scores for each patient, the Euclidian distance matrix was calculated to characterize the pair-wise dissimilarity between patients. Based on the distance matrix, the hierarchical clustering method with average linkage was employed to assign the 646 *CO-MED* patients into three remission groups.

Result

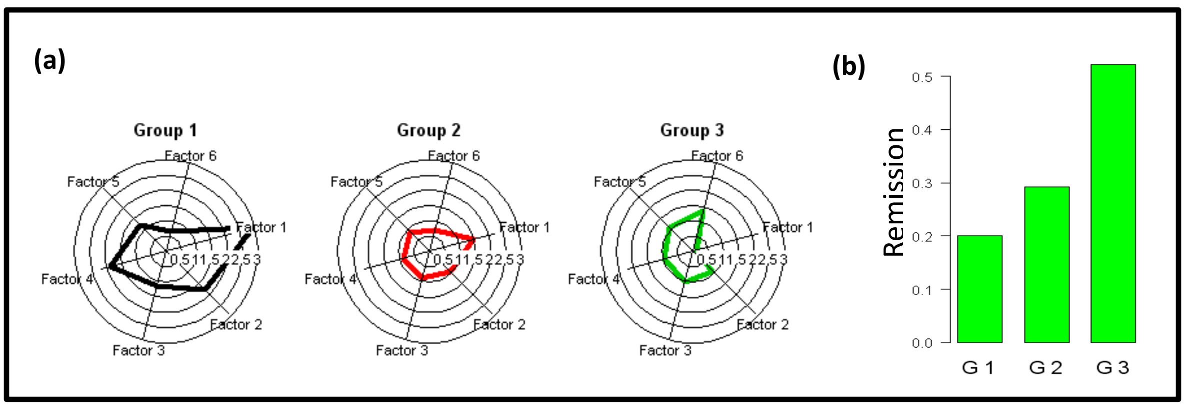
3.3.1 Mapping the behavioral factors to *RDoC* constructs

The original assessments of the patients who participated in the *CO-MED* trial from HAM-D, IDS-C, QIDS-C, QIDS-SR, Altman self-rated mania, Cognitive and physical functioning questionnaire, Quality of life inventory, Work and social adjustment were selected and rescaled as described in the Methods. All 15 questionnaires (Table 16) were self-reported forms, which contain 383 questions. After data cleaning, the remaining 293 rescaled measures were analyzed using maximum likelihood factor analysis with varimax rotation method and summarized to six behavioral factors. According to the loading score of each variable in the factors, and hence the psychological meanings of the variables, I determined the key variables and their psychological meanings (Table 17). These six factors correspond to (1) Self-reported Emotional Response, which was mapped to the Potential Threat (Anxiety) Construct of Negative Valance System in *RDoC*; (2) Hypervigilance, which was mapped to the Sustained Behavioral Response Construct of potential threat of Negative Valance System; (3) Physiological Response to Anxiety, which was mapped to the Potential Threat (Anxiety) Construct of Negative Valance System; (4) Disruption in Reward Learning, which was mapped to negative value of the Reward Learning construct of Positive Valance System; (5) Absence of Behavioral Systems Related To Trauma History, which was mapped to the Acute Threat (Fear) Construct of Negative Valance System; and (6) Capacity to Seek Positive Social Rewards, which was mapped to the Approach Motivation Construct of Positive Valence System.

3.3.2 Using the defined behavioral factors to discover patient subgroups

All the patients were then grouped into three sub-groups based on their behavioral factors using hierarchical clustering analysis (Figure 5 and Figure 6). The average score for each factor across the patients in each subgroup was summarized in the polar plots (Figure 6b). Patients in different subgroups had different value distributions in these six behavioral factors (Figure 7). For example, patients in the first subgroup had the highest score in the first behavioral factor (Anxiety) among all these subgroups, which demonstrated the Anxiety construct in the *RDoC*. In the second subgroup, patients had lower scores in the first behavioral factor compared to patients in the first subgroup. In the third subgroup, patients had the lowest score in the first behavioral factor among these three subgroups of patients.

Figure 6. Characteristics of patient subgroups defined with the 6 behavioral factors



(a) The polar plot represented the average score for each factor across the patients in each subgroup. In the first subgroup, patients had high scores in every factor. In the second subgroups, patients had lower scores in the six factors than patients in the first subgroup. And in the third subgroup, patients had the lowest scores for all the factors.

(b) The bar plot described the patient remission rate in different subgroups.

G1: Group 1

G2: Group 2

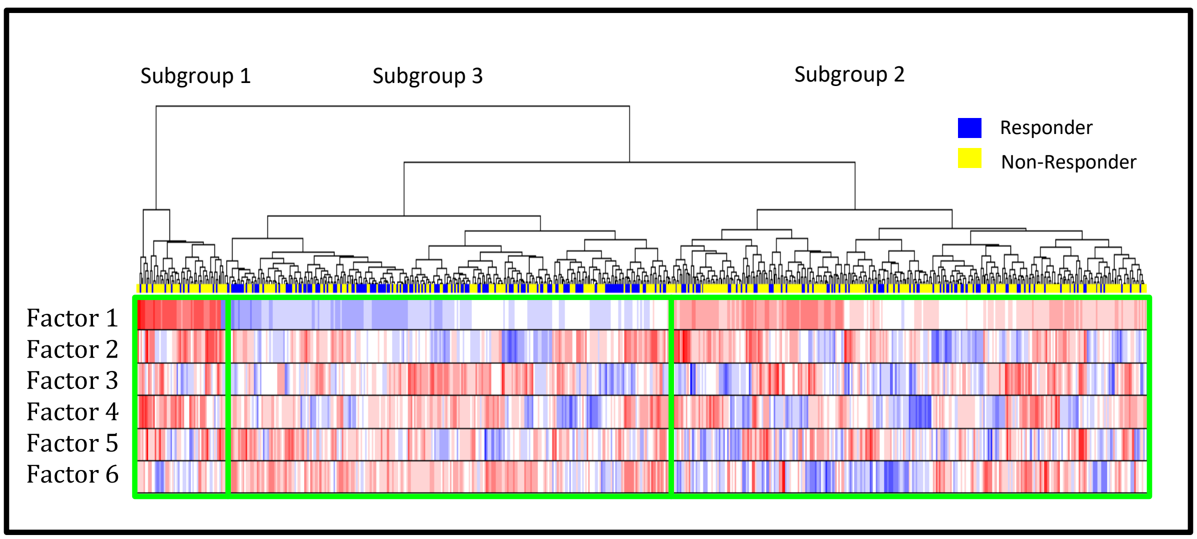
G3: Group 3

Table 18. The main behavioral factors in the hierarchical factor analysis

Factor	Information
1	Self-reported Emotional Response (Anxiety)
2	Hypervigilance
3	Physiological Response to Anxiety
4	Disruption in Reward Learning
5	Absence of Behavioral systems related to trauma history
6	Capacity to seek positive social rewards

The summary of the six mapped factors summarized from the 293 self-reported measures from Major Depressive Disorder patients in *CO-MED* trial.

Figure 7. The heatmap



The Heatmap represents the clustering result of the *CO-MED* patients based on the six factors scores. In the heatmap, it is shown that in the first subgroup, the score of factor one which represented anxiety is extremely high. And the patients in subgroup 3 had the lowest score of factor one and highest score of factor six, which represented the highest level of capacity to seek positive social rewards.

3.3.3 Patients with different major behavioral factor scores had different remission rates to the treatments

The average treatment remission rate of patients in each subgroup is summarized in Figure 6b and Table 19. It is shown that patients in different subgroups had different remission rates to the antidepressant treatments ($p < 0.01$, Fisher's exact test). The patients in the 3rd subgroup had the highest remission rate, which was around 52.3%, and the patients in the 2nd subgroup had the medium remission rate (29.3%). The patients in the 1st subgroup had the lowest remission rate, which was 20%. The results indicate that the three clusters defined by the six behavioral factors might correspond to three unknown endo-phenotypes in the depression patients[46], and these three endo-phenotypes may result in different patients' remission rates. The first endo-phenotype shown by the first patient subgroup may indicate a high level of anxiety and hypervigilance combined with poor ability of reward learning. The second endo-phenotype can be described as a medium level of anxiety combined with a poor level of reward learning ability. The third endo-phenotype shows a low level of anxiety, a normal level of reward learning and a greater capacity to seek positive social rewards.

Table 19. Remission rates of patients in the three subgroups

Subgroup	Non-remission	Remission
Group 1	44 (80%)	11 (20%)
Group 2	215 (70.7%)	89 (29.3%)
Group 3	137 (47.7%)	150 (52.3%)

The exact numbers of the patients remitted after treatments in the three different subgroups.

Only 20% of the patients in the first subgroup remitted after treatment. The remission rate of the patients in the second subgroup was 29.3%. The remission rate of the patients in the third subgroup was the highest one among these three groups, which is 52.3%. The Fisher's exact test was conducted and P-value was 7.3E-10.

3.4 Discussion

Using the data-driven analysis method, I found three endo-phenotypes in the major depressive disorder based on the six factors summarized from the 293 self-reported measures of the *CO-MED* trail. And patients with different endo-phenotypes had different remission rates to the antidepressants.

In the current *RDoC* frame work, the constructs were defined based on the consensus of current knowledge in the field. In this study, data-driven methods were used to map the behavioral factors to the *RDoC* constructs, which might provide new insights into the current definition of *RDoC* constructs. With the clustering analysis based on the factors summarized from the self-reported measures of the *CO-MED* major depressive disorder patients, the patients were clustered into three subgroups. Each subgroup may denote one undefined endo-phenotype, which may be useful to diagnose or decide the appropriate treatments for patients in major depressive disorders. Here I discovered new endo-phenotypes from the self-reported measures in major depressive disorder and found that patients in different endo-phenotypes had different remission rates. In our model, the patients in the first endo-phenotype (the first subgroup), who had the highest level of anxiety among all three subgroups, showed the lowest remission rate. The reported truth that anxiety impairs depression remission[47] suggests the validity of our model.

Timely selection of the best treatment for patients with mental disorders is critical to the goal of improving remission rates. Due to the biological heterogeneity and variable symptom presentation of mental disorders, it is unlikely that a single clinical or biological marker can guide treatment selection. Rather, a prediction model developed from a systematic exploration of a group of clinical and biological markers is more likely to be successful. In this study, I developed a methodology to integrate different self-reported measures into a comprehensive prediction model for treatment response and to beneficially assist in the clinical decision. This approach has great potential to personalize treatment and maximize the benefit of patients, not only in major depressive disorder but in other mental diseases as well.

A key component to finding novel classification systems is to look across diagnostic spectrums. Although the primary diagnosis of the *CO-MED* population is depression, it provides unique data for testing the clinical validity and utility of *RDoC* for the following reasons: It approximates real-world practice settings, which include patients with a host of psychiatric and medical comorbidities. Moreover, the clinical response for treatments from this cohort is highly heterogeneous. Therefore, classifying this population into subgroups using new dimensional criteria will be clinically informative and important. Furthermore, as a clinical trial designed to evaluate treatment efficacy, the *CO-MED* trial has collected detailed treatment and clinical outcome information for all patients and provides ideal data for evaluating predictive models for individual antidepressant treatment response. It provides a well-characterized population for developing a methodology and testing our central hypothesis in a cost-effective way. With this information, the methodology and results generated from this study can be applied in other real-world settings with samples across diagnostic spectrums.

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