

**Determinants Associated with Improvement in Depression Scores in a Cohort of Adult
Patients Followed over 1 Year**

A Thesis submitted to the
College of Graduate and Postdoctoral Studies
In Partial Fulfillment of the Requirements
For the Degree of Master of Science
In the Department of Community Health and Epidemiology
College of Medicine
University of Saskatchewan
Saskatoon

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ABSTRACT

Background

The prevalence of depression in Canada as reported in 2015 was 4.7%. Major Depressive Disorders are the second leading cause of global disability. The mainstay of therapy for depression continues to be psychopharmacology. The purpose of my study was to ascertain determinants associated with change in depression scores over one year in a cohort of adults.

Methods

The study was based on the data collected by The Neural Health Project (NHP) and was based on improvement in Beck Depression Inventory-II scores over a 12-month period (completed scores were available for 90 participants, n=90). There were two arms, standard medical care arm and integrative medical care (intervention) arm. Percentage change between baseline scores and those at one year were calculated based on Beck scores. A $\geq 30\%$ percentage change in Beck scores was viewed as an improvement in depression. Binomial logistic regression was performed to determine the effects of sex, treatment group, age as a category, and happiness, on the likelihood of predicting improvement in Beck scores over a 12-month period.

Results

Beck scores were available for 93 participants at visit 1, and for 90 at the final visit. Mean difference (\pm SE) in Beck scores over 12 months for standard medical care was 3.63(\pm 1.105) and for integrative medical care 8.13(\pm 1.094) ($p=0.005$). Improvement in depression symptoms based on the percentage change in Beck scores was 16.89 (\pm 5.421) for standard medical care and 34.07(\pm 8.622) for integrative medical care ($p=0.005$). The logistic regression model was statistically significant with $p=0.018$. The model correctly classified 65.2 % of the cases. Sensitivity was 76.1%, specificity was 53.5%, positive predictive value was 63.6% and negative predictive value was 67.67%. Of the 4 predictor variables, only study group was statistically significant at $p=0.006$. Those in the integrative medical care group were 3.64 times more likely to show $\geq 30\%$ improvement in Beck scores than those in the standard medical care group.

Conclusion

Integrative medical care was superior to standard medical care in the treatment of adult depression. This was the first study of its kind in Canada. More studies are suggested to explore these findings with a larger sample, and in multi-center trials.

ACKNOWLEDGEMENTS

Firstly, I would like to thank my thesis supervisor Dr Anne Leis, for all the valuable help, guidance, and encouragement I received. Dr Leis your mentoring meant a lot to me.

My thesis committee- Dr Punam Pahwa (Chairperson, and my statistics guru), Dr Donna Goodridge and Dr Shirley (Dee Dee) Maltman. Thank you so much for your valuable feedback and constructive criticism. I would not have got this far without your help.

Dr Punam Pahwa, thank you for the numerous meetings on Zoom, and for patiently explaining to me the complexities of statistics!

Dr Donna Goodridge, thank you for encouraging me to join the masters program, and for helping me along the way. Despite many hiccups you helped me stay on course.

Dr Dee Dee Maltman, thank you for opening my eyes to the wonderful world of integrative medical care, and reminding me of old school medicine- thorough history taking, listening and partnering with patients on their journey.

Dr Scotty Butcher, thank you for being my external examiner and drawing the best out of me at my oral defense. I really did appreciate that.

I would be failing if I did not thank profusely, Wendy Verity the Project Manager of The Neural Health Project. You did a tremendous job and were such a valuable resource for all things relating to The Neural Health Project.

A big shout out to Laerd statistics on the internet (for helping me bridge my knowledge of statistics, with the intricacies of applying it to SPSS).

Thank you, Marissa Alarcon and Ha Le at the Clinical Research Support Unit of College of Medicine at University of Saskatchewan. Ha Le thank you for your help and guidance with SPSS.

I would also like to thank all the administrative and support staff of department of Community Health & Epidemiology for the countless ways you helped and encouraged me. A special word of thanks to Stephanie Kehrig, for her positivity and enthusiastic support.

Finally, a big thank you to my wife, Vinita for having faith in me and being a pillar of support.

DEDICATION

Dedicated to Anushka, who is embarking on her journey in Health Sciences.

TABLE OF CONTENTS

DETERMINANTS ASSOCIATED WITH IMPROVEMENT IN DEPRESSION SCORES IN A COHORT OF ADULT PATIENTS FOLLOWED OVER 1 YEAR.....	
PERMISSION TO USE	I
ABSTRACT	II
ACKNOWLEDGEMENTS.....	IV
DEDICATION.....	V
TABLE OF CONTENTS.....	VI
LIST OF TABLES.....	X
LIST OF FIGURES.....	XII
LIST OF ABBREVIATIONS	XIII
CHAPTER 1	1
INTRODUCTION	1
1.1 INTRODUCTION.....	1
1.2 RATIONALE	2
1.3 OBJECTIVES OF THE STUDY	3
1.3.1 HYPOTHESIS OF THE STUDY	3
1.3.2 RESEARCH QUESTIONS	4
CHAPTER 2	5
LITERATURE REVIEW.....	5
2.1 CHARACTERISTICS OF DEPRESSION	5
2.2 THEORIES ABOUT DEPRESSION	6
2.2.1 MONOAMINE HYPOTHESIS OF DEPRESSION.....	6
2.2.1.1 PATIENT BUY IN OF MODERN ANTIDEPRESSANTS	6
2.2.1.2 DEFICIENCIES IN MONOAMINE HYPOTHESIS OF DEPRESSION	7
2.2.1.3 RECENT METANALYSIS ON ASSOCIATION BETWEEN SEROTONIN AND DEPRESSION	7
2.2.2 NEUROPLASTICITY HYPOTHESIS OF MAJOR DEPRESSIVE DISORDER (MDD)	7
2.2.2.1 STRESS AS A DRIVER OF DEPRESSION.....	7
2.2.2.2 NEUROPLASTICITY	8
2.3 MICROBIOME, DIET, AND DEPRESSION.....	9
2.4 PHARMACOLOGICAL TREATMENT OF DEPRESSION	10
2.4.1 KETAMINE A NEWER ANTIDEPRESSANT	11
2.4.2 TREATMENT RESISTANT DEPRESSION	11
2.5 NONPHARMACOLOGICAL INTERVENTIONS FOR DEPRESSION	12
2.5.1 PSYCHOLOGICAL APPROACHES	12
2.5.1.1 COGNITIVE BEHAVIORAL THERAPY.....	12

2.5.1.2 MINDFULNESS BASED INTERVENTIONS.....	12
2.5.2 PHYSICAL ACTIVITY AND EXERCISE.....	13
2.5.3 NUTRITION- VITAMINS, MINERALS, SUPPLEMENTS.....	13
2.5.3.1 S-ADENOSYL-METHIONINE (SAM-E).....	13
2.5.3.2 FOLIC ACID	13
2.5.3.3 OMEGA-3 FATTY ACIDS	14
2.5.3.4 ST JOHN’S WORT	14
2.6 INTEGRATIVE MEDICINE	15
CHAPTER 3	17
METHODS	17
3.1 ORIGINAL STUDY (THE NEURAL HEALTH PROJECT)	17
3.1.1 DESIGN OF STUDY AND INTERVENTION.....	17
3.1.2 STUDY POPULATION	18
3.1.2.1 INCLUSION CRITERIA	18
3.1.2.2 EXCLUSION CRITERIA.....	18
3.1.3 HYPOTHESIS OF ORIGINAL STUDY.....	18
3.1.4 DESCRIPTION OF THE INTEGRATIVE MEDICAL CARE INTERVENTION	18
3.1.5 DATA COLLECTION INSTRUMENTS.....	21
3.1.5.1 DEMOGRAPHIC QUESTIONNAIRE	22
3.1.5.2 BECK DEPRESSION INVENTORY (BDI)-II	22
3.1.6 DATA ENTRY	22
3.2 MY STUDY, BASED ON THE NEURAL HEALTH PROJECT	23
3.2.1 MY STUDY POPULATION	23
3.2.2 OUTCOME VARIABLES	23
3.2.2.1 MEAN BECK SCORES.....	23
3.2.2.2 MEAN DIFFERENCE IN BECK SCORES AND PERCENTAGE CHANGE IN BECK SCORE	23
3.2.3 MINIMAL CLINICALLY IMPORTANT DIFFERENCE (MCID).....	24
METHODS OF CALCULATING MCID	24
WHAT CONSTITUTES A SATISFACTORY MCID FOR BDI-II SCORES IN DEPRESSION?	25
3.2.3.1 PROBLEMS ASSOCIATED WITH ATTEMPTING TO USE MCID IN MY STUDY	25
3.2.4 INDEPENDENT VARIABLES.....	26
3.2.4.1 MODE OF DELIVERY AT BIRTH (VAGCES)	26
3.2.4.2 ADVERSE CHILDHOOD EXPERIENCE	26
3.2.4.3 LEVEL OF HIGHER EDUCATION	27
3.2.4.4 SELF-RATED HAPPINESS.....	27

3.2.4.5 CO-MORBIDITIES.....	27
3.2.4.6 BIRTHPLACE.....	28
3.2.5 DATA CHECKING AND CLEANING.....	31
3.2.6 STATISTICAL ANALYSIS.....	31
3.2.6.1 DATA MANIPULATION.....	31
3.2.6.2 RECODING OF VARIABLES.....	31
3.2.6.3 DESCRIPTIVE STATISTICS.....	33
3.2.6.4 CHECKING DISTRIBUTION OF DATA.....	33
3.2.6.4.1 RESULTS OF TESTS ON DISTRIBUTION OF DATA.....	33
3.2.6.4.2 NONPARAMETRIC TESTS.....	33
3.2.6.4.3 PARAMETRIC TESTS.....	35
3.2.6.5 INFERENCE STATISTICS.....	35
3.2.6.5.1 UNIVARIABLE ANALYSIS.....	35
3.2.7 MULTIVARIABLE BINARY LOGISTIC REGRESSION.....	36
3.2.7.1 INDEPENDENT VARIABLES.....	36
3.2.7.2 DEPENDENT VARIABLE/OUTCOME VARIABLE.....	36
3.2.7.3 MULTIVARIABLE BINARY LOGISTIC REGRESSION MAIN EFFECTS.....	36
3.2.7.4 MULTIVARIABLE BINARY LOGISTIC REGRESSION POSSIBLE CONFOUNDER.....	37
CHAPTER 4.....	38
RESULTS.....	38
4.1 DESCRIPTIVE STATISTICS.....	38
4.1.1 CONTINUOUS VARIABLES.....	39
4.1.2 CATEGORICAL VARIABLES.....	41
4.2 LOGISTIC REGRESSION.....	53
4.2.1 SIMPLE LOGISTIC REGRESSION.....	53
4.3 RECEIVER OPERATING CHARACTERISTICS FOR MODEL A.....	57
4.3.1 AREA UNDER CURVE (AUC) FOR MODEL A.....	58
4.4 OTHER MODELS CONSIDERED BEFORE SETTLING FOR FINAL PARSIMONIOUS MODEL.....	58
4.4.1 MODEL B.....	59
4.4.2. ROC FOR MODEL B.....	60
4.4.2.1 AUC FOR MODEL B.....	61
4.4.3 MODEL C.....	62
4.4.3.1 ROC FOR MODEL C.....	63
4.4.3.2 AUC FOR MODEL C.....	64
CHAPTER 5.....	65

DISCUSSION	65
5.1 STRENGTHS AND LIMITATIONS	70
5.1.1 STRENGTHS.....	70
5.1.1.1 SOLE INTEGRATIVE MEDICAL CARE PHYSICIAN IN STUDY	70
5.2.1 LIMITATIONS.....	70
5.2.1.1 HIERARCHY OF EVIDENCE	70
5.2.1.2 NUMBER OF PARTICIPANTS	71
5.2.1.3 IMPROVEMENT BASED ON CHANGE IN DEPRESSION SCORES ALONE	71
5.3 IMPLICATIONS FOR CLINICAL PRACTICE.....	72
5.3.1 SHARING KNOWLEDGE WITH FAMILY PHYSICIANS AND PATIENTS	72
5.3.2 TEAM BASED APPROACH FOR DELIVERING INTEGRATIVE MEDICAL CARE FOR DEPRESSION	72
5.3.3 COST IMPLICATIONS OF WIDESPREAD ADOPTION OF INTEGRATIVE MEDICAL CARE IN THE TREATMENT OF ADULT DEPRESSION	72
5.3.4 LIMITATIONS TO STANDARD MEDICAL CARE FOR THE MANAGEMENT OF DEPRESSION.....	73
5.4 IMPLICATIONS FOR FUTURE RESEARCH	73
5.4.1 SUGGESTION THAT INTEGRATIVE MEDICAL CARE IS BETTER THAN STANDARD MEDICAL CARE ALONE.....	73
5.4.2 POSSIBLE EXPLANATION AS TO WHY INTEGRATIVE MEDICAL CARE SHOWED BETTER RESULTS THAN STANDARD MEDICAL CARE IN THIS STUDY.....	73
5.4.3 EXPLORING DIFFERENT OPTIONS AVAILABLE FOR THE MANAGEMENT OF ADULT UNIPOLAR DEPRESSION USING THE INTEGRATIVE MEDICAL CARE APPROACH.....	74
5.4.4 SETTING UP TRIALS WITH MCID IN MIND.....	74
5.4.5 CAN IMPROVEMENTS IN DEPRESSION AS DETERMINED BY BDI-II SCORES BE SUSTAINED BEYOND 12 MONTHS?	74
5.4.6 LESSONS LEARNED.....	74
5.5 CONCLUSION	75
REFERENCES	76
APPENDICES.....	84
APPENDIX A: ETHICS APPROVAL	84
APPENDIX B: CENTRE FOR EPIDEMIOLOGICAL STUDIES DEPRESSION SCALE.....	86
APPENDIX C: DEMOGRAPHIC QUESTIONNAIRE.....	87
APPENDIX D: BECK DEPRESSION INVENTORY-II.....	92
APPENDIX E: HOSPITAL ANXIETY AND DEPRESSION SCALE.....	95
APPENDIX F: CHILD EXPERIENCE QUESTIONNAIRE	96

LIST OF TABLES

TABLE 3.1.....	21
COMPARISON OF VISITS TO DOCTOR AND PROJECT MANAGER FOR BOTH TREATMENT ARMS	21
TABLE 3.2 VARIABLES USED IN UNIVARIABLE ANALYSIS	30
TABLE 3.3 RECODED VARIABLES	32
TABLE 3.4 TESTS OF NORMALITY.....	33
TABLE 3.5 CHECKING NULL HYPOTHESIS (BETWEEN TREATMENT ARMS) BASED ON BECK SCORE AT VISIT 1.....	34
TABLE 3.6 CHECKING NULL HYPOTHESIS (BETWEEN TREATMENT ARMS) BASED ON BECK SCORE AT VISIT 5.....	34
TABLE 3.7 HOMOGENEITY OF VARIANCE BECKDIFF	35
TABLE 3.8 ONE WAY ANOVA ON BECKDIFF (BECK SCORE VISIT 1-VISIT5)	35
COMPARING GROUPS OF STANDARD MEDICAL CARE, WITH INTEGRATIVE MEDICAL CARE	35
TABLE 4.1 DESCRIPTIVE STATISTICS FOR BECK SCORES AT VISIT 1	38
TABLE 4.2 DESCRIPTIVE STATISTICS FOR BECK SCORES AT VISIT 1 AND VISIT 5.....	39
TABLE 4.3 DESCRIPTIVE STATISTICS FOR BECK SCORE VARIABLES STRATIFIED BY SEX.....	40
TABLE 4.4 BASELINE CHARACTERISTICS OF COHORT BASED ON BDI-II, N=93	41
TABLE 4.5 BASELINE CHARACTERISTICS OF COHORT BASED ON STUDY GROUP	42
TABLE 4.6 RESULT OF THE UNIVARIABLE BINARY LOGISTIC REGRESSION OF PERCENTAGE IMPROVEMENT IN BECK SCORES AT 30 % CUT OFF	54
TABLE 4.7 RESULT OF THE MULTIVARIABLE BINARY LOGISTIC REGRESSION OF PERCENTAGE IMPROVEMENT IN BECK SCORES AT 30 % CUT OFF	55
TABLE 4.8 CLASSIFICATION TABLE FROM SPSS OUTPUT FOR BINOMIAL LOGISTIC REGRESSION, 4 MAIN EFFECTS (SEX, STUDY GROUP, AGE AS CATEGORY, SELF RATED HAPPINESS)	56
TABLE 4.9 AUC FOR MODEL A	58
TABLE 4.10.....	59
MULTIVARIABLE LOGISTIC REGRESSION WITH SEX, AGE AS A CATEGORY, STUDY GROUP AND SELF RATED HEALTH	59
TABLE 4.11.....	61
AUC FOR MODEL B WITH 4 MAIN EFFECTS (SEX, AGE AS A CATEGORY, GROUP AND SELF RATED HEALTH)	61
TABLE 4.12.....	62
MULTIVARIABLE LOGISTIC REGRESSION WITH SEX, STUDY GROUP, AGE AS A CATEGORY, SELF RATED HAPPINESS, SELF RATED HEALTH.....	62
TABLE 4.13.....	64
AUC FOR MODEL C WITH 5 MAIN EFFECTS (SEX, AGE AS CAT, GROUP, SELF RATED HAPPINESS, SELF RATED HEALTH)	64

LIST OF FIGURES

FIGURE 4.1 DEPRESSION STATUS BASED ON PERCENTAGE CHANGE IN BECK SCORE (30 % OR GREATER) STRATIFIED BY TREATMENT GROUP AND SEX.....	44
FIGURE 4.2 DEPRESSION STATUS BASED ON PERCENT CHANGE IN BECK SCORE (30 % OR GREATER) STRATIFIED BY BIRTHPLACE AND SEX	45
FIGURE 4.3 DEPRESSION STATUS BASED ON PERCENTAGE CHANGE IN BECK SCORE (30 % OR GREATER) STRATIFIED BY SELF RATED HAPPINESS AND SEX	46
FIGURE 4.4 DEPRESSION STATUS BASED ON PERCENTAGE CHANGE IN BECK SCORE (30 % OR GREATER) STRATIFIED BY SELF RATED HEALTH AND SEX.....	47
FIGURE 4.5 DEPRESSION STATUS BASED ON PERCENTAGE CHANGE IN BECK SCORE (30 % OR GREATER) STRATIFIED BY HOUSEHOLD COMPOSITION AND SEX.....	48
FIGURE 4.6 DEPRESSION STATUS BASED ON PERCENTAGE CHANGE IN BECK SCORE (30 % OR GREATER) STRATIFIED BY TREATMENT GROUP AND BIRTHPLACE	49
FIGURE 4.7 DEPRESSION STATUS BASED ON PERCENTAGE CHANGE IN BECK SCORE (30 % OR GREATER) STRATIFIED BY TREATMENT GROUP AND SELF RATED HEALTH	50
FIGURE 4.8 DEPRESSION STATUS BASED ON PERCENT CHANGE IN BECK SCORE (30 % OR GREATER) STRATIFIED BY TREATMENT GROUP AND SELF RATED HAPPINESS	51
FIGURE 4.9 DEPRESSION STATUS BASED ON PERCENTAGE CHANGE IN BECK SCORE (30 % OR GREATER) STRATIFIED BY TREATMENT GROUP AND HIGHER EDUCATION	52
FIGURE 4.10 RECEIVER OPERATING CHARACTERISTICS FOR MODEL A WITH 4 MAIN EFFECTS (SEX, AGE CAT, GROUP AND SELF RATED HAPPINESS)	57
FIGURE 4.11	60
RECEIVER OPERATING CHARACTERISTICS FOR MODEL B WITH 4 MAIN EFFECTS (SEX, AGE CAT, GROUP AND SELF RATED HEALTH).....	60
FIGURE 4.12	63
RECEIVER OPERATING CHARACTERISTICS FOR MODEL C WITH 5 MAIN EFFECTS (SEX, AGE CAT, GROUP, SELF RATED HAPPINESS, AND SELF RATED HEALTH)	63

LIST OF ABBREVIATIONS

ACES Adverse Childhood Experience Score

BDI Beck Depression Inventory

BDNF Brain Derived Neurotrophic Factor

CAMH The Centre for Addiction & Mental Health

CBT Cognitive Behavioral Therapy

CRP C Reactive Protein

DII Dietary Inflammatory Index

DSM Diagnostic and Statistical Manual of Mental Disorders

ECT Electroconvulsive treatment

EPA Eicosapentaenoic Acid

FDA Food and Drug Administration

GBA Gut Brain Axis

HADS Hospital Anxiety and Depression Scale

HPA Hypothalamic-pituitary-adrenocortical axis

IntM Integrative Medicine

MBCT Mindfulness Based Cognitive Therapy

MDD Major Depressive Disorder

MDE Major Depressive Episode

NHP Neural Health Project

NMDA N-methyl-D-aspartate

OCD Obsessive Compulsive Disorder

PAF Population Attributable Fractions

PFC Prefrontal Cortex

PTSD Post Traumatic Stress Disorder

RCT Randomized Controlled Trial

SAM-e S-adenosyl-methionine

SJW St John's Wort

SSRI Selective Serotonin Reuptake Inhibitor

CHAPTER 1

INTRODUCTION

1.1 Introduction

The global health burden of depression is thought to have exceeded 300 million people as per a WHO document on depression and other common mental disorders(1). This document further states that depression is one of the largest contributors to global disability. What is more worrisome, is that depression contributes to about 800,000 suicides per year. This same report identifies the global prevalence of depression at 4.4 %, with depression being more common among females at 5.1%, as opposed to a rate of 3.6 % among males. This prevalence rate is not uniform across the globe, with a low of 2.6 % among males in the West Pacific, and a high of 5.9 % among females in Africa.

The prevalence of depression in Canada according to this report for 2015, was 4.7 %. In 2016, the Canadian Network for Mood and Anxiety Treatments published its guidelines(2).The authors had the same annual prevalence of 4.7 % in Canada for depression; and a lifetime prevalence of 11.3 %. When bipolar disorders were excluded, unipolar depression had an annual prevalence of 3.9 % in Canada, with a lifetime prevalence of 9.9 %. The authors further went on to say that Major Depressive Disorders (MDD) were the second leading cause of global disability. This translates into substantial numbers globally.

1.2 Rationale

Apart from blighting the lives of those affected, depression also robs them of earnings, and prevents them from realizing their full potential. Western countries can recognise the rise in mental health disorders largely because of increased awareness, and the resources made available to treat these conditions. This means that poorer, less developed countries are under reporting the incidence and prevalence of mental disorders. This is probably due to the stigma attached to mental disease, and the lack of availability of trained healthcare professionals who are able to recognize the magnitude of the problem. This is further compounded with the difficulty of accurately collecting data.

According to the data reported by Statistics Canada for Mental Health Indicators in Saskatchewan(3), among those 15 years and above, those who had a major depressive disorder within the last 12 months were 4.1 % (30,650, both sexes) in 2002. In 2012 the percentage slightly reduced by 0.4 % to 3.7 % (30,107). However, even in developed countries like Canada, there still remains a stigma about mental disease and a general reluctance to be diagnosed as depressed. Consequently, the reported incidence and prevalence of depression are probably below the real rates out in the community. More recently, the impact that the Covid pandemic has had on the mental health of individuals has yet to be quantified accurately and analyzed. Anecdotally, it appears that Covid has affected mental health across all ages. This may have well been because there has not been a pandemic of these proportions in recent times. Accessing mental health professionals during times of Covid has been both difficult and challenging. This is thought to have had a negative impact on the mental health of individuals. Furthermore, the social isolation of individuals during the early days of Covid had a profound effect on the mental health of the general population. How online learning impacted the mental health of young students pivoting suddenly to online learning will only be understood in the future, when this cohort is followed. Traditional therapy for depression has largely relied on pharmacotherapy, often for lengthy periods of time. In view of a large subset of depressed individuals not responding to conventional therapy, it is imperative to establish better and improved ways of treating mental health in general, and depression in particular.

Closer to home in Saskatoon, the tragic deaths of Ian Buckwold and Jordan Chartier due to mental illness in 2013, catalyzed a community of friends and health care professionals to raise the

alarm about the lack of appropriate and timely treatments. This momentum created a very powerful fund-raising initiative, which became *The Neural Health Project*. The goal of the project was to highlight an integrative medical approach to address mental health issues and evaluate them. One of the projects on which this study is based, sought to assess the effectiveness of an integrative medical care intervention and compare it to standard medical care for adults diagnosed with depression.

Standard medical care for the treatment of depression is largely psychopharmacological and is considered to be the conventional form of therapy for depression. The researchers in *The Neural Health Project* hypothesized that the integrative medical care approach for treating depression, was as effective as standard medical care. The researchers also strove to study specific blood biomarkers of depression that might aid in identifying a subpopulation of depressed persons who would be most likely to benefit from an integrative medical care approach in the management of their depression. This study uses the data already collected for the project and aims to examine what determined the change in depression scores after 1 year.

1.3 Objectives of the study

1. To describe the baseline characteristics of study participants in each arm.
2. To compare the mean depression scores of the integrative medical care arm to the standard treatment arm at baseline and at 12 months.
3. To determine what are the factors associated with improved depression scores at 12 months.

1.3.1 Hypothesis of the study

The null hypothesis for my study was that the mean change in BDI-II scores in standard medical care arm would be the same as the mean change in BDI-II scores in the integrative medical care arm, over a 12 month period.

1.3.2 Research questions

- What is the difference in mean depression score from baseline to 12 months between the integrative medical care arm and the standard medical care arm?
- Is the change in mean depression score from baseline to 12 months significantly different between integrative and standard medical care arms?
- What are the determinants associated with improvement in depression scores in a cohort of adult depressed patients followed over 1 year?

CHAPTER 2

LITERATURE REVIEW

2.1 Characteristics of depression

The Centre for Addiction and Mental Health website provides extensive information about depression(4). According to this site, depression is much more than simple unhappiness. It is recognized to be a complex mood disorder with multifactorial causation. This website states that the causes of depression include genetic predisposition, personality, stress and brain chemistry. Spontaneous remission is known to occur, but generally it is not the norm, and some sort of intervention is often required. The CAMH website further goes on to state that for purposes of classification, there are different types including Seasonal Affective Disorder (worse during winter months), post partum depression (in mothers after delivering a baby), dysthymia (chronically low mood with moderate symptoms of depression). There is also a more worrisome form of depression associated with psychosis. Depression is more common in females than males.

As described in this website, the signs and symptoms of depression are extensive and varied. Those suffering with depression are depressed most days, symptoms last for most of the day and the depression has been present for more than 2 weeks. It directly impacts personal performance at work, school, or in social relationships. Oftentimes it is associated with changes in weight, sleep problems, and a general loss of interest in work, hobbies, people, or sex. Classic early morning wakefulness is not always present. Depressed individuals can suffer with poor appetite, or at the other extreme have enormous appetites. The same website continues on to describe how depressed individuals withdraw from friends and family, feel useless, and have low self-esteem. They often slow down, feel irritable, feel tired, lack energy and can be tearful. Hobbies or interests that previously gave them joy, now suddenly leave them unimpressed. Some can become suicidal, and this is a risk that mental health professionals are constantly assessing and looking for(4).

Thus, it is evident that depression has far-reaching consequences at an individual level, and to the larger group that person belongs to (be it family, workplace, or the community at large).

2.2 Theories about depression

2.2.1 Monoamine hypothesis of depression

Much of recent psychiatry, and the treatment of depression has been based on this hypothesis(5). Unfortunately this somewhat simplistic hypothesis has been criticized for the delayed onset and inadequate efficacy of commonly used SSRIs (selective serotonin reuptake inhibitors)(5).

According to this hypothesis, depression is a consequence of depletion of monoamines like serotonin, norepinephrine or dopamine. The current crop of antidepressants largely works on monoamine transmitters or receptors. The earlier generation of antidepressants that belonged to the tricyclic family such as amitriptyline, were very good at treating severe melancholic depression but they came with a price of poor tolerability and were dangerous in overdose. They were found accidentally, to work on depression more than 60 years ago, by increasing synaptic concentration of serotonin and norepinephrine(6). This action was thought to be the underlying mechanism of its antidepressant action, and contributed to the advancement of the monoamine hypothesis. The risk of suicide by overdosing on tricyclic antidepressants was very real. This gave rise to the need for a safer alternative, that was more selective in inhibition of the reuptake of serotonin and norepinephrine(7). These newer antidepressants rapidly gained ground and soon became the mainstay of current antidepressant therapy. Consequently, these drugs were largely embraced by academics, researchers, clinicians and even patients.

2.2.1.1 Patient buy in of modern antidepressants

To both clinician and patient, the monoamine hypothesis offered a very elegant solution to the pathogenesis of depression, the concept of a chemical imbalance. Many patients with depression bought into the idea that antidepressants were going to correct the deficient levels of some neurotransmitters in their brain, and once that deficiency was corrected, they would feel better very much like prescribing thyroxine to a hypothyroid patient.

2.2.1.2 Deficiencies in monoamine hypothesis of depression

The main drawback of this hypothesis was that there was a lag in clinical improvement of depression, from time of initiation of antidepressants. This lag could vary from 2-4 weeks(8). Despite antidepressants such as SSRIs rapidly increasing levels of serotonin at synaptic cleft in hours, the alleviation of symptoms took weeks. So much so, that the remission rate for first line antidepressant treatment(drugs and cognitive behavioral therapy) is only about 60-70 %(9). These discrepancies led to a search for an alternative theory for the pathogenesis of depression.

2.2.1.3 Recent metanalysis on association between serotonin and depression

Joanna Moncrieff and others published a paper dated 20 July 2022 in Molecular Psychiatry(10). They sought to evaluate evidence as to whether depression is associated with reduced serotonin concentration or activity. They conducted a systematic umbrella review with 17 studies reviewed. 12 were systematic reviews and meta-analyses, 1 collaborative meta-analysis, 1 meta-analysis of a large cohort study, 1 systematic review and narrative synthesis, 1 genetic association study and 1 umbrella study. The authors concluded that there was no consistent evidence of an association between serotonin and depression and no support for the hypothesis that depression is caused by lowered serotonin activity or concentration. The authors went on to state that it was time to acknowledge that serotonin theory of depression is not empirically substantiated. There is no doubt that this paper will attract a lot of attention. It remains to be seen if this view gains wide acceptance or not, particularly among mental health professionals. Hopefully, this will lead to changes in the management of depression.

2.2.2 Neuroplasticity hypothesis of major depressive disorder (MDD)

This alternative hypothesis may provide a better framework for clarifying the pathogenesis of MDD and antidepressant efficacy(5).

2.2.2.1 Stress as a driver of depression

Stress as an environmental factor that contributes to depression is fairly well established. In fact major depressive episodes (MDEs) are associated 2.5 times more frequently among those exposed to stress prior to the event, as compared to controls within a similar period (11). Furthermore, it has been found that a single stressful event increases the risk of MDE by

1.41(12). Clearly not everyone who is exposed to stress goes onto develop a major depressive event though.

Different theories have been proposed as to how stress and depression are linked. One of these theories put forward is based on dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis and the morphological and functional deficits in the hippocampal formation, linking stress with depression(5). According to the neuroplasticity hypothesis, stress is important to the pathogenesis of major depressive disorders (MDD).

It is thought that stress in some predisposed individuals can precipitate depression. It is multifactorial and there is no single gene for depression(13).

Elevated circulating cortisol levels as seen in response to chronic stress, exert a deleterious effect on hippocampal neurons and are neurotoxic acting via glucocorticoid receptors(13). This morphological loss leads onto functional deficits, eventually leading onto structural atrophy and functional deficit of the hippocampal formation(5).

2.2.2.2 Neuroplasticity

Unfortunately, there is no single validated definition of neuroplasticity that is universally accepted. Neuroplasticity generally refers to the ability of neural systems to adapt to internal and external stimuli, and to respond adaptively to future stimuli(14). Neuroplasticity is a key element in how the brain adapts to stress. Conversely, maladaptive neuroplasticity may well be the underlying basis of depression and post-traumatic stress disorder(5). The neuroplasticity hypothesis of depression was put forward to explain some of the inadequacies of the monoamine hypothesis.

According to Serafini, the neuroplasticity hypothesis is supported by evidence from 3 domains(15):-

1. Decreased neuroplasticity in hippocampus and prefrontal cortex (PFC) in depressed adults.
2. Decreased concentration of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) in depressed individuals.
3. Antidepressants elevating concentrations of neurotrophic factors and improving neuroplasticity in hippocampus and PFC.

2.3 Microbiome, diet, and depression

“An ecosystem of microbiota is collectively known as microbiome. In the human gastrointestinal tract, there is a well developed bidirectional relationship between central nervous system and gastrointestinal tract including microbiota colonising gastrointestinal tract, with each area seemingly capable of influencing the condition and functionality of each other. This relationship is termed gut-brain axis GBA” (16–19). Microbiome is being researched extensively now, and its importance is being recognised even in the lay press. While disruption to the GBA and its association with a wide range of disorders is common, GBA still remains poorly understood(20), with much of the work on animals, and few human studies. According to Pandey et al, food containing bacteria that positively influence gastro-intestinal microbiome are termed probiotics, and compounds that promote flourishing of these bacteria are termed prebiotics. These food supplements are called functional foods(21). According to Noonan et al who performed a systematic review of the role of probiotics and prebiotics in the treatment of anxiety and depression, there is currently no established consensus on their use in the treatment of depression and or anxiety(20).

In many conditions where probiotics have been found to be useful, they appear to be related to their ability to reduce endogenous pro-inflammatory substances like cytokines, such as seen in ulcerative colitis(22). Given that there is growing evidence that inflammation is related to the pathogenesis of depression and other mental disorders(17,23), it would seem logical that probiotics would have a role to play in their treatment. However, there has been no conclusive evidence to support this, although it has been shown that depressed patients show increased gastro-intestinal tract permeability, which in turn enables gut microbiota to enter the systemic circulation and set off pro-inflammatory states(23–25). Many factors have been noted to influence gut microbiota including mode of delivery at birth, genetics and epigenetics, and most significantly, diet(19). In fact, these factors influenced the design of the demographic questionnaire for The Neural Health Project. Jian Wang and others performed a systematic review looking at the association between inflammatory potential of diet, determined by dietary inflammatory index (DII) score and depression. The authors looked at 4 prospective studies and 2 cross-sectional studies, with a total of 49,584 subjects. Their overall conclusion was that when the highest DII score was compared with the lowest DII score, the former showed a 23 % higher risk of depression (RR =1.23, 95 % CI 1.12-1.35)(26). Further, they concluded that a pro-

inflammatory diet estimated by higher DII scores was independently associated with increased risk of depression, particularly women. Conversely, healthy, and Mediterranean diets were associated with a reduced risk of depression. A healthy diet comprises increased intake of fruits, vegetables, fish, seafood and wholegrain products. The dietary inflammatory index (DII) is a validated measure of the inflammatory potential of diet(27,28).

2.4 Pharmacological treatment of depression

The conventional treatment of depression has largely relied on the use of pharmacotherapy, more specifically antidepressants from about the 1950s (29). The authors assert that in the 1950s, tricyclic antidepressants and monoamine oxidase inhibitors were discovered. At this point, pharmaceutical companies spent a lot of money on research and development, looking for drugs that specifically targeted neurochemical imbalances. This, combined with the need for safer drugs in the treatment of depression, saw the arrival and expansion of selective serotonin reuptake inhibitors (SSRIs) in the 1980s. They rapidly gained wide acceptance and use, to the point where they became the standard of care for major depressive disorders (MDD) of any severity by 2008. Astoundingly, antidepressants in USA, became the third most prescribed medication.

According to a review article that compared the guidelines for treatment of unipolar depression with regard to major depressive disorders (MDD) there was a general consensus with regard to the use of antidepressants in severe depression(30). The benefits of the use of antidepressants for mild to moderate depression was less clear. There was some agreement about the choice of first line treatment, but much greater variability with regard to choice of second and third line management. Electroconvulsive (ECT) treatment found wide consideration in almost all of the guidelines. There was very low agreement in the management of dysthymia, persistent depressive disorder, and the treatment of resistant depression.

It is evident that the mainstay of therapy for depression of any severity is largely pharmacological, with a huge cost that comes with it. Furthermore, with such a very large number of antidepressants being dispensed, it is inevitable that side effects and allergic reactions to antidepressants become more commonplace.

2.4.1 Ketamine a newer antidepressant

Ketamine has been hailed as a major breakthrough in the management of treatment resistant depression(31). Ketamine is classified as a non-competitive N-methyl-D-aspartate(NMDA) antagonist, and is a glutamatergic modulator(32).

In the 1990s animal models were beginning to show the importance of glutamate as an excitatory neurotransmitter. The role of NMDA receptors in the etiology and treatment of mood disorders was also beginning to be explored during that period(32).

Berman and colleagues showed that ketamine exerted rapid, robust and relatively sustained anti depressant effect. They showed that ketamine exerted antidepressant effect within 4 hours of infusion, peaked at 72 hours and persisted for 1-2 weeks post infusion(33).This has potential use in situations where depressed patients have strong and persistent suicidal ideation.

On 5 March 2019, FDA approved esketamine for treating treatment resistant depression. Bearing in mind that almost 33 % of depressed individuals do not respond to the currently available antidepressants(9), the approval of esketamine appears promising. However, it must be tempered with caution. Ketamine has a long history of abuse and use as a party drug. It has been known on the street as Special K, Kit Kat and Cat Valium! Apart from the abuse potential there is also the danger of ketamine dependence. In North America, we are in the throes of a huge opioid crisis. We must be careful that we do not repeat our mistakes and unleash a ketamine crisis unless it is carefully monitored and regulated. The prescription of ketamine should be confined to suitably trained specialists like psychiatrists. Thus, it is evident that in a country like Canada, it is unlikely that ketamine will have the widespread availability and use, that SSRIs currently enjoy. Ketamine is also being investigated for use in other conditions like post traumatic stress disorder (PTSD) and obsessive-compulsive disorders (OCD).

2.4.2 Treatment resistant depression

It has become increasingly evident that the current antidepressants do not always induce remission. There remains a relatively large subset of such treated depressed patients, who do not respond to therapy. To expand treatment options, many nonpharmacological approaches have been studied and in the next few pages I will summarize the main ones.

2.5 Nonpharmacological interventions for depression

2.5.1 Psychological approaches

The effects of psychological intervention for treatment of adult depression has been shown to be comparable to those achieved with pharmacological intervention and are probably longer lasting(34). This has some merit, as the fear of side effects of pharmacological interventions is not present with psychological interventions and nonadherence to treatment is minimized or absent.

2.5.1.1 Cognitive Behavioral Therapy

Cognitive Behavioral Therapy(CBT) is a common and effective form of psychological intervention for the treatment of depression(35–38). This has led to its popularity as a treatment modality. CBT is a broad umbrella with many tools, therapies and intervention protocols in the toolkit(36,39). They can be used alone or in combination, and include diverse components like psychoeducation, homework, behavioral activation and problem solving(40). Generally, CBT interventions are face to face, either individually or in a group. Over the last decade or so, multimedia CBT has become increasingly popular.

The recent Covid pandemic brought digital CBT into sharp focus, during this time, many health insurances companies in Canada popularized telehealth and made it available to a wide group of clients.

2.5.1.2 Mindfulness based interventions

Mindfulness is a meditative form with its roots in ancient Buddhist meditative practises. It has gained wide acceptance now and there is a substantial body of research based on Mindfulness-Based Cognitive Therapy(MBCT)(41). MBCT is an 8-week program designed to prevent depressive relapse by loosening the association between negative thoughts and negative mood and increasing conscious awareness of moment to moment changes in body sensations, emotional states, and thought patterns using mindfulness meditation based techniques (e.g., mindful breathing, body scan). This process allows patients to notice the oncoming signs of depression and pro-actively engage in activities to prevent downward mood spirals(42).

2.5.2 Physical activity and Exercise

Some researchers have studied the role of physical activity in the treatment of depression. It must be pointed out that exercise is a subcategory of physical activity. For example, walking, attending to household chores, walking a pet and gardening are some examples of physical activity and are not necessarily seen as extra activities outside the scope of day to day living. Even these activities have been found to improve depression. Nagata et al in their conceptual paper made the following conclusions with regard to physical activity and depression(43) :-

1. There is convincing evidence that both primary and co-morbid depression maybe reduced by exercise.
2. Antidepressant effects of physical activity are mediated by improved brain functions. Furthermore, physical activity improves sleep quality, which restores cognitive and emotional brain functions.
3. All types of physical activities are effective in the treatment of depression.

2.5.3 Nutrition- Vitamins, minerals, supplements

2.5.3.1 S-adenosyl-methionine (SAM-e)

SAM-e is a naturally occurring physiological substance that plays a role in biochemical pathways of the central nervous system(44). The same paper states that SAM-e when compared with placebo, showed significant effect as monotherapy treatment for depression-both moderate and severe. However, the author asserts that these effects have not been replicated in double-blind studies of SAM-e in the treatment of depression.

2.5.3.2 Folic Acid

There is some evidence that folic acid can be an adjunct to antidepressant therapy particularly in those with low folate levels(45). Further, it has been observed that there is an association between low folate levels and depression. However, many of these studies have not been double blind, placebo-controlled trials thus making conclusions somewhat inconclusive. What is known though, is that folic acid is inactive and does not cross the blood brain barrier in that form. Consequently, L-methyl folate(which is the active form that crosses the blood brain barrier) has been approved by FDA for use in depressed patients as a prescription drug, with a view towards

augmenting their antidepressant response by elevating folic acid levels in conjunction with antidepressants(46).

2.5.3.3 Omega-3 Fatty Acids

A meta-analysis of 13 randomized, placebo controlled studies was performed and showed that the greatest effect was observed among those with severe depression(47), however the effect was small and not very significant. However, a subsequent sub analysis of this data looking at those patients who had a diagnosis of depression that met with DSM criteria showed that omega-3 was associated with significant antidepressant activity(48), furthermore it was noted that the dose and composition of omega-3 fatty acids was important. The greatest symptom reduction was seen when omega-3 fatty acids had > 60 % eicosapentaenoic acid(EPA) composition(48).

Omega-3s had similar effect if used as monotherapy, or as an adjunct to standard medical care for depression(47,48).

A large double blind RCT (N=432) study found that omega-3 was associated with greater symptom reduction when compared to placebo, only among those who did not have co-morbidities of anxiety symptoms(49).

2.5.3.4 St John's wort

Known as SJW with the botanical name of *Hypericum perforatum*. St John's wort has an extensive history of medicinal use. Research suggests that it is more effective than placebo, comparable to antidepressants, with fewer side effects than antidepressants(42).

A systematic review of 17 double blind randomized controlled trials found that SJW as monotherapy, was superior to placebo and comparable to antidepressants in reducing short term (4-12 weeks) of depressive symptoms for patients with mild to moderate depression, but not severe depression(44). However, it was not associated with long term improvement, but appeared to be relatively free of side effects. Unfortunately a major drawback is that it has significant drug interactions with a multitude of prescription drugs acting via cytochrome P450 to reduce plasma concentrations of many prescription drugs(50). In this author's view, this

precludes the possibility of its widespread use without the physician taking an extensive drug history and checking for potential drug interactions before prescribing SJW.

2.6 Integrative Medicine

Luberto and coworkers(42) - critically reviewed scientific evidence for the treatment of adult, unipolar depression using Integrative Medicine(IntM). IntM combines conventional therapy for depression along with evidence based complementary medicine. They discovered that mindfulness-based interventions, along with the use of St John's wort worked best as monotherapy.

The evidence for the effectiveness of omega-3 supplements and exercise was less robust, hence was best reserved as forms of adjunct therapy. Also quoted in this paper were the results of a national sample of healthy adults (n=22,000) and adults with depression (n=2,000) in the United States, and their use of some form of IntM in the past year. What was found was that 40 % of healthy adults, and 54 % of depressed individuals used IntM, most commonly natural products and mind body medicine (36,37) Thus it is evident, that there are many patients who are comfortable using IntM for the management of their depression.

According to the University of Arizona, Andrew Weil Center for Integrative Medicine, Integrative Medicine(51) is best described as below:-

1. Patient and practitioner are partners in the healing process.
2. All factors that influence health, wellness, and disease are taken into consideration, including mind, spirit, and community, as well as the body.
3. Appropriate use of both conventional and alternative methods facilitates the body's innate healing response.
4. Effective interventions that are natural and less invasive should be used whenever possible.
5. Integrative medicine neither rejects conventional medicine nor accepts alternative therapies uncritically.
6. Good medicine is based in good science. It is inquiry driven and open to new paradigms.
7. Alongside the concept of treatment, the broader concepts of health promotion and the prevention of illness are paramount.
8. Practitioners of integrative medicine should exemplify its principles and commit themselves to self-exploration and self-development.

A hallmark of integrative medical care is the therapeutic relationship and the individualised treatment plan that is made in conjunction with the patient. Many treatment options are available and the following treatment wheel (52) which is attributed to Dr Noshene Ranjbar, was obtained from the Paediatric Integrative Medicine website at Stanford Children’s Health. This treatment wheel illustrates some of them.



The Neural Health project, on which this study is based, assessed this Integrative Medical intervention using a quasi-experimental design. (See the methods chapter for details).

CHAPTER 3

METHODS

3.1 Original Study (The Neural Health Project)

The data that I used for my research came from the prospective *The Neural Health Project* conducted in Saskatoon, Saskatchewan, Canada. It was a 3-year project, beginning in 2017, ending in late 2020 with follow up of a cohort of depressed adults who were allocated in two arms: an integrative medical care arm and a standard medical care arm. Those that completed 12-months of follow up were considered to have completed the study. A total of 130 persons entered the study, and 103 completed it at 12 months.

At baseline and subsequent 3-month visits (total of 4), patients filled out questionnaires socio-demographic questions, Beck Depression Inventory (BDI), Hospital Anxiety and Depression scale (HADS).

At each visit a finger prick blood sample was obtained and a saliva sample was collected, in order to investigate salivary cortisol and peripheral blood smear for 5 biomarkers (looking for patterns of membrane clustering in peripheral lymphocytes and different proteins such as serotonin transporter; serotonin 2 A; beta adrenergic glu R1; PRPC). Note that biomedical sampling was stopped when in person visits ceased due to Covid-19 pandemic. Information about the biomedical portion of the study is for background only and is not part of this particular study.

3.1.1 Design of study and intervention

The original study used a pre and post-test quasi-experimental design, which compared the effectiveness of integrative medical care with standard medical care for treatment of depressed patients over a one-year period. In this study, integrative medical care was the intervention. The study had regular follow-up in 3-months intervals, beginning at baseline and continuing for 12 months (total of five visits). **Please see appendix A for ethics approval.**

3.1.2 Study population

All patients included in the study came from primary care clinics or from University of Saskatchewan PAWS website alerting students to this study. Patients with depressive symptoms were recruited as potential participants by either a family physician/ integrative care family physician or self-referred. Those recruited into the integrative medical arm were referred by psychiatrists, family doctors or self-referred when interested in exploring integrative medical care. It must be emphasised that some individuals in this arm, had multiple chronic diseases. Some of them had exhausted other treatment options and tried integrative medicine as the final option. Regardless of the recruitment strategy, they were considered for the study if they met the inclusion criteria.

3.1.2.1 Inclusion criteria

Participants were asked to complete a self-reported screening questionnaire. If they scored 16 or more(53,54) in the CES-D questionnaire (55), consented to participate in the study, and were between the ages of 18 and 65 years, they were included in the study. This was a study of depression and anxiety, among adult patients only.

3.1.2.2 Exclusion criteria

They were excluded from the study if they were pregnant, had a known neurological disorder (example, stroke, Parkinson's disease etc.) or had a history of substance abuse.

3.1.3 Hypothesis of original study

The null hypothesis of this study was that the integrative medical arm would be as effective as the conventional standard medical arm in treating depression over the period of study.

3.1.4 Description of the integrative medical care intervention

The first visit between the integrative care physician and participant (which was 1 hour long) was more in line with getting to know each other. At this visit enquiry was made about various aspects of their lifestyle including, but not limited to, diet, sleep and bowel movements. Participants were also provided with a paper to record a timeline of their life, highlighting specific major health related events and traumas. Significant life events such as their mode of birth, marriage, divorce, disease, loss, death etc., were to be recorded. The purpose of this information gathering was to visualise the buildup of trauma over a person's lifetime. Participants

were also asked to record details of the food consumed. These papers were to be brought for subsequent visits. These initial visits (within the first 3 months) were as often as deemed necessary and at least once a month. At this first visit, participants were taught 4-7-8 breathing (72) and encouraged to practise 4 times a day, until the next visit at the very least. At later visits, participants were encouraged to continue with 4-7-8 breathing in the long term.

This technique (4 seconds inhalation through nose, 7 seconds of holding breath, breathing out through mouth forcefully and rapidly over 8 seconds. Cycle repeated four times) was developed by Dr Weil and is sometimes referred to as relaxing breath. The technique is simple and as a practise can be a powerful relaxation tool(56). If performed regularly and is sustained , it can be calming and energising(57). The technique itself is not complicated and does not require any special equipment as demonstrated in a YouTube clip by Dr Weil(56). Furthermore, in can be performed at any time or in any position. The practise of 4-7-8 breathing on a sustained basis is said to aid in rewiring the brain much like other meditative practises.

On subsequent visits, blood work including but not limited to, such things as CRP (looking for inflammation) serum Vit D levels and tests for gut function including celiac disease were sought. The details of diet and significant life events were also reviewed together.

Participants were made aware of concepts regarding inflammation, and types of anti inflammatory diets. Participants were encouraged to exclude inflammatory foods from their diet such as processed foods and in some cases dairy and gluten was eliminated from their diets, to see if it was effective. At all times, they were provided information, links to research and resources to explore these diet issues further at their leisure.

The integrative care wheel attributed to Dr Noshene Ranjbar(52), mentioned earlier, was used as a template to customize the treatment plan with exercise, social connections, mind body connections, dietary supplements (such as magnesium, multivitamins, omega 3) and spirituality to name a few. It must be emphasised that in the case of spirituality, it was very much led by the participant. The views of the participant were always taken into account before suggestions were made about meditative practises. A subset of these participants were referred for Neural therapy (brain mapping and neural feedback) and other modalities such as acupuncture, if it were felt that these participants in particular, would benefit from them.

As part of the therapeutic relationship, participants were also made aware of the other team members and specialists whose expertise they could draw upon, such as trauma counsellors and nutritionists to name a few. *All participants were referred for trauma counselling.*

Table 3.1

Comparison of visits to doctor and project manager for both treatment arms

Type of visit	Integrative medical care arm	Standard medical care arm
Visit to doctor	During initial 3 months, as frequently as needed. Subsequently regular follow up	No fixed schedule. Appointments if needed
Visit to project manager of The Neural Health Project	Baseline, and then every 3 months. Total of 5 visits in 1 year. Apart from filling out questionnaires at each visit, biological samples collected too, except during Covid period.	Baseline, and then every 3 months. Total of 5 visits in 1 year. Apart from filling out questionnaires at each visit, biological samples collected too, except during Covid period.

3.1.5 Data collection Instruments

On visit 1(baseline) – participants answered questions about co-morbidities (clinical history) as well as questions pertaining to demographics and childhood trauma (ACES)-please see appendix F. The demographic questions were derived from those used by Statistics Canada. Participants also self reported on 2 different scales Hospital Anxiety and Depression scale (HADS)(58) and Beck Depression Inventory-II (BDI-II).

At subsequent visits (2-5) only the questionnaires of HADS and BDI-II(59) were completed. My research is based on responses to BDI-II at baseline, and after a 12-month period, which is at visits 1 and 5.

3.1.5.1 Demographic questionnaire

The demographic questionnaire which was administered to participants at baseline (visit 1), had 24 questions, with many of them derived from questions used by StatsCan. Questions included some socio-demographic information, income, job history, unemployment, disability, whether a student, and the presence or absence of co-morbidities/medical conditions. Please see Appendix C.

3.1.5.2 Beck depression inventory (BDI)-II

This scale was created by Beck, and published in 1961(60) . It was later revised in 1978, and the current version BDI-II was published in 1996. According to a review paper on psychometric properties of BDI-II (61) , the internal consistency (Average Alpha coefficient{Cronbach's}) was 0.9 (0.83-0.96) and Test-Retest reliability, Pearson coefficient ranged between 0.73 and 0.96. BDI-II is a self-administered 21 item questionnaire that is scored from 0-63, with 63 most depressed, and 0 least. Each item scored from 0-3. Please see appendix D

The total Beck score(62) can be used to classify the severity of depression as follows:-

0-9 no or minimal depression

10-18 mild to moderate depression

19-29 moderate to severe depression

30-63 severe depression

It must be noted that, the number of divisions for each category of depression is not the same. For example, no or minimal depression has 10 divisions, but this is not the same for the number of divisions under severe depression. This poses a challenge. How do you determine, improvement in depression over a period of time, based on Beck scores?

3.1.6 Data entry

The original dataset was in Excel format. The dataset was created by inputting data obtained from questionnaires administered to participants at 5 visits. The questionnaires were self-administered. The data was imported into SPSS Premium Grad Pack version 27.

3.2 My study, based on The Neural Health Project

My study was based on a 1-year period (visit 1 at onset of study and visit 5 at end of study).

3.2.1 My study population

The Neural Health Project, Saskatoon began in 2017, with 130 participants entering the study. The study ended towards the latter part of 2020, with 103 participants completing the study. Of these 103 participants, *93 participants completed BDI-II in full at baseline* and only 90 completed Beck scores in full at visit 1 and visit 5 one year later. Thus, my *study population encompassed 90 participants who completed the Beck Depression Inventory-II at both visit 1 and visit 5.*

3.2.2 Outcome variables

My research is based on improvement in depression as measured by the 21 item BDI-II (Beck Depression Inventory). The scores range from 0-63 (with 63 the most depressed). Consequently, an improvement in depression will show a reduction in Beck scores over a period of time.

Study period of interest was 12 months, with improvement in Beck scores measured as the difference in scores, between visit 1 (baseline) and visit 5 (final visit). Completed data for Beck scores at visit 1 (baseline) and at visit 5 (12 months) were available for 90 participants.

3.2.2.1 Mean Beck scores

These were calculated for each treatment group- standard medical care arm and the intervention arm of integrative medical care arm at baseline and end of study.

3.2.2.2 Mean difference in Beck scores and percentage change in Beck score

This was the mean difference in Beck scores between visit 1 and 5. Percentage change in Beck scores, was calculated as a ratio of (Beck difference/Beck score at visit 1) X 100. Based on this definition of percentage change in Beck score, a *dichotomous variable was created.*

Percentage change in Beck score $\geq 30\%$ - Yes= Improvement in depression

Percentage change in Beck score $< 30\%$ - No=No improvement in depression

3.2.3 Minimal clinically important difference (MCID)

This was an idea first propounded by Jaeschke and colleagues in 1989(63). The concept revolved around the fact that statistical significance in a study, may not always translate into clinically important difference, say between 2 arms of an experimental study. According to these authors minimal clinically important difference was defined as the “smallest difference in score in domain of interest which patients’ perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in patient’s management.” It is clear from this definition, that the perspective and inputs of patients is paramount in the definition of MCID.

On the face of it, it would appear that The Neural Health Project in general, and my study in particular would lend itself eminently to the calculation of MCID for Beck scores. I will explain subsequently why this was not so, and how I ended up using another measure.

Methods of calculating MCID

According to Caitlin Finley(64) in her Masters thesis at University of Alberta in 2017, there are 3 methods used to calculate MCID. They are:

- 1.Anchor based methods
- 2.Distribution methods
- 3.Delphi(consensus) method

I will concentrate largely on the anchor-based methods, as it is the only one that meets the original definition of MCID, by having patient participation. Here, the methods employed can use- within patient score changes, between patient score changes, receiver operating characteristic curve analysis and a social comparison approach(65). Anchor based approach links changes of an outcome (say Beck scores) with change in global rating of change(65). In this method, the score of interest like Beck scores are anchored with patient’s rating of change. The global rating of change could be something like “is your depression today, same as 3 months before, better or worse?” A valid criticism of this method mentioned by McGlothlin(66) was the possibility of recall bias in this approach. Patients have to recollect how they feel today, when compared to a specific time before, and how they felt before they started treatment.

In the case of my study, they would have to recollect how they felt at the start of the study, and then later at 12 months (at completion of study).

Distribution methods of calculating MCID are purely based on statistical methods and have no patient input. This I believe, negates the very definition of MCID.

The Delphi method relies on a panel of experts to reach a consensus as to what constitutes MCID(66).

What constitutes a satisfactory MCID for BDI-II scores in depression?

According to a paper published by Button and colleagues in 2015, they analyzed the data from 3 randomized, controlled trials on depression with n=1039. Here, they compared improvement in global rating of change (anchor question) with change in BDI-II scores using general linear modeling. They concluded that MCID was best measured by percentage reduction of score over a period of time. Their estimate of MCID was 17.5 % reduction in score and was based on ROC analysis.

Other researchers such as Wilson(67) have concluded that a percentage reduction in BDI(original Beck Depression Inventory, predating BDI-II) scores of 29.64 % was the MCID. He used a combination of anchor and distribution methods.

3.2.3.1 Problems associated with attempting to use MCID in my study

Unfortunately, the Neural Health Project was never set up with MCID in mind. Hence, I could not use MCID in my study, as the global rate of change (anchor question) was not asked at every visit. I decided to go with the idea that percentage reduction in BDI-II scores over a 12-month period would be a good measure of improvement in depression. I further decided to set the bar high and use a 30 % or more reduction in BDI-II scores to define improvement (Yes) and < 30 % reduction in BDI-II scores to define lack of improvement in depression (No). *This became my dichotomous outcome/dependent variable.* Please see section 3.2.7.2 for more details.

3.2.4 Independent variables

In view of the number of participants who completed the Beck score at both visits 1 and 5 numbering 90, I decided to have a maximum of 9 independent variables in my Univariable analysis.

These variables were: the 2 comparison arms of the study (Group), sex of the participants (Sex), age as a category, based on median age (AgeCategory).

The other variables were- mode of birth (VagCes), place of birth (BirthCodeNew), self rated happiness (HappyNew), self rated health (OverallHealthNew), highest level of education attained (HighEdRevised) and the number of questions answered with a response Yes, in ACES questionnaire.

3.2.4.1 Mode of delivery at birth (VagCes)

This question was added to demographic questionnaire, of The Neural Health Project. In a normal vaginal delivery, the gut microbiome of a newborn baby would be colonised by mother's microbiota while passing through birth canal. For more on microbiome, please see section 2.

3.2.4.2 Adverse Childhood Experience

This 10-item questionnaire was incorporated into the Childhood Experience Questionnaire of The Neural Health Project that was self administered by patients on visit 1(baseline). This questionnaire seeks out unpleasant experiences prior to turning 18 years old. Points are scored for each Yes item(68). A maximum score would be 10, with a score of zero implying a lack of negative childhood experiences. A score of 4 or more is considered significant, and according to the same study has been noted to be associated with a 390 % increase in chronic pulmonary disease as an adult, 240 % increase in Hepatitis, 460 % increase in depression, and a whopping 1220 % increase in suicide. The ACE study(69) was published in 1998 and was considered to be ground breaking. Interestingly, the participants were mostly white, middle, or upper middle class, and from San Diego. In this landmark study, 13,494 adults were mailed a questionnaire about adverse childhood experiences and had a standardized medical evaluation at Kaiser Permanente's San Diego Health Appraisal Clinic. 9,508 patients responded (70.5 %). Seven adverse childhood experiences were studied: -

Psychological

Physical

Sexual

Violence against mother

Living with household members with a) substance abuse b) mental illness or suicidal c) imprisonment.

What they found in the ACES study was quite astonishing at that time. They found that individuals who had 4 or more adverse childhood experiences, had a 4-to-12-fold increased risk for alcoholism, drug abuse, depression, or suicide attempt; when compared to those that did not have any adverse childhood experiences.

Please see appendix F.

3.2.4.3 Level of higher education

Lower educational achievement has been noted to be associated with an increased risk of depression, particularly in western countries. This association was found to be true in a study conducted by Peyrot and others in 2015. In this study 9,662 individuals with major depressive disorder (MDD) were compared with 14,949 controls (no lifetime diagnosis of MDD). Here too what was found was that those with lower educational achievement, had an increased risk of depression(70).

3.2.4.4 Self-rated Happiness

Shutz and others did a study in US based on affective profiles, which is widely used in Sweden. The affective profiles model categorizes individuals as self-fulfilling (high positive affect, low negative affect), high affective (high positive affect, high negative affect), low affective (low positive affect, low negative affect), and self-destructive (low positive affect, high negative affect). Unsurprisingly what they found was that self fulfilling individuals were less depressed, happier, and more satisfied with life. Conversely self destructive individuals were more depressed, unhappy and less satisfied than other profiles(71).

3.2.4.5 Co-morbidities

Dai et al analysed data from the Canadian Community Health survey of 2014. They included individuals who were aged ≥ 18 years and excluded those who had missing information on physical or mental disorders. Chronic diseases referred to both physical and mental disorders.

According to these authors, respondents included in their analysis represented 27,221,856 Canadians aged ≥ 18 years. Of these, 53.9% (95% CI 53.1–54.6) had one or more chronic diseases, 11.5% (95% CI 11.0–12.0) had mental disorder, and 8.4% (95% CI 8.0–8.8) had physical and mental comorbidity. Compared with those without chronic diseases, people with one or more chronic diseases had higher sex- and age-adjusted prevalence of severe impairment of health-related quality of life (HRQoL), suicidal ideation, and healthcare utilization; and the risks increased consistently with the number of chronic diseases, according to these authors. However, among those with the same number of chronic diseases, people with mental disorder or physical and mental comorbidity were more likely to have these adverse consequences than people with only physical disorders(72).

Chireh et al conducted a systematic review and meta-analysis to determine diabetes and depression risk in a longitudinal cohort(73). Longitudinal studies with criteria for depression and self-reported doctors' diagnoses or diagnostic blood test measurement of diabetes were assessed. Systematic review with meta-analysis synthesized the results. Pooled odds ratios were calculated using random effects models. Population attributable fractions (PAFs) were used to estimate potential preventive impact. The authors found twenty high quality articles that met the inclusion criteria and were analyzed by them. They found the pooled odds ratio (OR) between diabetes and depression was 1.33 (95% CI, 1.18–1.51). For the various study types, the ORs were for prospective studies (OR 1.34, 95% CI 1.14–1.57); retrospective studies (OR 1.30, 95% CI 1.05–1.62); self-reported diagnosis of diabetes (OR 1.37, 95% CI 1.17–1.60); and diagnostic diabetes blood test (OR 1.25, 95% CI 1.04–1.52). PAFs suggest that over 9.5 million of global depression cases are potentially attributable to diabetes. The authors assert that a 10–25% reduction in diabetes could potentially prevent 930,000 to 2.34 million depression cases worldwide. In my view this however is an ambitious target for reduction in number of cases of diabetes worldwide, and if achievable would have far reaching consequences beyond mental health alone. Their systematic review provided evidence to support the view that diabetes is an independent risk factor for depression(73).

3.2.4.6 Birthplace

The data on Canadian immigrants' health is less clear, and authors Bukola Salami et al studied it, analyzing 3 cycles of Canadian Health Measures survey. Their outcome variables were self-

perceived mental health and reported diagnosis of mood disorders. What they found was that recent migrants (within 5 years) reported better self-perceived mental health (odds ratio 3.98, 95% confidence interval [CI]: 2.06–7.70) but this effect disappeared with longer time since immigration. Other predictors of positive self perceived mental health according to these authors were older age, higher income, better sense of community belonging, and being employed. The diagnosis of mood disorders was also associated with older age, being a woman, lower income, weak sense of community belonging, and being unemployed (74).

Table 3.2 Variables used in univariable analysis

Variable	Description	Coding in SPSS
Group	Treatment arms	1.Standard 2.Integrative
Sex		1.Female 2.Male
AgeCategory	Age as a category	1.32 years and < 2.33 years and >
VagCes	Mode of delivery	1.Vaginally 2.C section 3.Do not know
BirCodeNew	Place of birth	1.Saskatchewan 2.Canada 3.International
HappyNew	Self rated happiness	1.Happy 2.Unhappy
OverallHealthNew	Self rated health	1.Good 2.Poor
HighEdRevised	Highest level of education	1.University 2.Non university
ACEYesNum	Continuous variable. Number of questions answered yes in ACE	

3.2.5 Data checking and cleaning

The data was checked for inaccuracies, missing data, and corrected as appropriate.

The original data set had BDI-II scored from 1-4 (as opposed to the more familiar 0-3).

Additionally, some of the participants (despite instructions otherwise), had ticked 2 responses for some questions. In the Excel data set, this was scored as 0.5. When I imported it into SPSS, these half marks were rounded up. There were 7 such participants at visit 1 (4 in standard medical care, 3 in integrative medical care). At visit 5, there was only 1 such participant (in integrative medical care). I believe that the rounding up (making the Beck score slightly worse) and the few numbers of participants involved would have had minimal impact on my analysis.

Cronbach's Alpha test was run on BDI-II at visit 1 and it was 0.821. Cronbach's Alpha for BDI-II at visit 5 was 0.906. The minimum acceptable value for Cronbach's alpha is 0.70, with a maximum expected value of around 0.90.

Cronbach's alpha is a measure of internal consistency/reliability. A common use is to determine if a scale is reliable, and if the items on the scale are measuring the underlying dimension(75).

3.2.6 Statistical analysis

3.2.6.1 Data manipulation

With sample size being relatively small, I did encounter problems relating to exceedingly small cell sizes, and consequent unstable statistical values. To get round this problem, I had to recode some of my categorical variables, and have only 2 categories for these variables. I also converted age (continuous variable) into 2 categories (based on median age). This was a categorical variable.

3.2.6.2 Recoding of variables

Table 3.3 gives further details about the recoding of variables.

Table 3.3 Recoded variables

Old categorical variable	Description	Old coding in dataset	New variable name	Recoding
HighED	Highest educational achievement	1 University 2 Some university but no degree 3 College degree 4 Some college but no degree 5 High school diploma or eq 6 Some high school 7 No high school	HighEdRevised	1 University 2 Non University
Happy	Self rated happiness	1.Very happy 2.Somewhat happy 3.Somewhat unhappy 4.Generally unhappy	HappyNew	1.Happy 2.Unhappy
OverallHealth	Self rated overall health	1 Excellent 2 Very good 3 Fair 4 Poor	OverallHealthNew	1 Good 2 Poor
HouseCMP	Household composition	1 Single adult only 2 1 adult + at least 1 kid 3 Partnership adults only 4 Partnership adults + at least 1 kid 5 Multiple adults > 16 + only 6 Multiple adults + at least 1 child	HouseCompRevised	1 Single adult 2 Rest
BirCode	Birthplace	1 Saskatoon 2 Saskatchewan other urban 3 Saskatchewan other rural 4 Canada 5 International	BirCodeNew	1 Saskatchewan 2 Canada 3 International

3.2.6.3 Descriptive statistics

Descriptive statistics including mean, median, standard error were obtained for continuous variables. Frequencies were obtained for categorical variables, and crosstabs where relevant were created.

3.2.6.4 Checking distribution of data

To apply the appropriate tests, continuous variables where relevant were assessed to see if they met the assumptions of normality. Based on these results, parametric tests (for normal distribution) and non-parametric tests (for non-normal distribution) were performed.

3.2.6.4.1 Results of tests on distribution of data

The 3 variables referred to here were BeckTot (refers to Beck score at visit 1), BeckTot5(refers to Beck score at visit 5), and Beckdiff (which refers to difference in Beck score between visit 1 and visit 5)

Table 3.4 Tests of normality

Variable	Shapiro-Wilks test p value	Interpretation
BeckTot	0.003	Not normal (<0.05)
BeckTot5	0.0001	Not normal (<0.05)
Beckdiff	0.097	Normal (>0.05)

3.2.6.4.2 Nonparametric tests

Nonparametric tests were used to obtain descriptive results for BeckTot and BeckTot5. Independent samples Mann-Whitney U test was performed to compare standard medical care with integrative medical care.

BeckTot (Beck score at visit 1)

Table 3.5 Checking null hypothesis (between treatment arms) based on Beck score at visit 1

Null hypothesis	Test	Significance	Decision
Distribution of BeckTot across Standard medical care group and Integrative medical care group is the same	Independent Samples Mann Whitney U test	0.513	Retain null hypothesis

BeckTot5 (Beck score at visit 5)

Table 3.6 Checking null hypothesis (between treatment arms) based on Beck score at visit 5

Null hypothesis	Test	Significance	Decision
Distribution of BeckTot5 across Standard medical care group and Integrative medical care group is the same	Independent Samples Mann Whitney U test	0.037	Reject null hypothesis

Interpretation: The difference in mean ranks of Beck score between standard medical care and integrative medical care groups, at visit 1 is not significant. This however becomes significant by visit 5.

3.2.6.4.3 Parametric tests

Levene's homogeneity of variance test is used to test the null hypothesis that the variance of two or more groups are not significantly different from each other. This would be signified by a p value > 0.05.

Table 3.7 Homogeneity of variance Beckdiff

Variable	Tests of Homogeneity of variance	p value	Interpretation
Beckdiff	Based on Mean	0.783	Assumption met
	Based on Median	0.721	

Table 3.8 One way ANOVA on Beckdiff (Beck score visit 1-visit5)

Comparing groups of standard medical care, with integrative medical care

	Sum of squares	df	Mean square	F	p value
Between groups	453.301	1	453.301	8.338	0.005
Within groups	4794.780	88	54.886		

Interpretation: Beck difference in mean scores over a 12-month period is significantly different between Standard medical care and Integrative medical care groups.

3.2.6.5 Inferential statistics

3.2.6.5.1 Univariable analysis

Since the effective sample size was 90, the number of independent variables that could be tested in the model was a maximum of 9. The variables evaluated individually were, Sex, Age as a

category, Group, VagCes, ACEYesNum, self rated Health, self rated Happiness, Birthplace, and Higher Education. Using $p \leq 0.25$ as a cut-off, the potential independent variables were evaluated individually using simple logistic regression (with binary outcome variable Yes/No based on 30 % cut off in Beck scores). From this analysis those that could be considered for entry into the multivariable regression model were Group ($p=0.012$) and self rated Health ($p=0.04$). The other variables tested for in the model, had biological and or clinical significance, and they were Sex and Age (as a category).

3.2.7 Multivariable binary logistic regression

3.2.7.1 Independent variables

The variables used in the final parsimonious, regression model (model A in section 4.3) was, sex, age as a category, group, and self rated happiness. These variables were arrived at after performing univariable analysis.

3.2.7.2 Dependent variable/outcome variable

The binary outcome variable was a variable derived from change in Beck score (between visit 1 and 5). This variable was named BeckDiff in my dataset. BeckDiff was the difference between BeckTot and BeckTot5. Beckdiff was converted to percentage change.

Percentage change in depression scores was calculated by dividing Beckdiff by the Beck score at visit 1(BeckTot) and converting it into a percentage.

I selected a 30 % or greater improvement in depression scores to be indicative of improvement (Yes), and less than 30 % improvement to be indicative of no improvement (No) This was my binary outcome variable. No, with < 30 % improvement in BDI-II scores implied a reduction in Beck score (over 1 year period) by less than 30 % (based on initial score). Rationale for this is explained in section 3.2.2.2

Yes, was coded as 1, and No as zero (0) in SPSS.

3.2.7.3 Multivariable binary logistic regression main effects

In addition to the 4 main effects (sex, group, age as a category, self rated happiness), interactions terms were tried out one at a time. The interaction terms tried were sex*group, sex*age cat, sex*self rated happiness, group*age cat, group*self rated happiness, self rated happiness*age cat,

self rated health * self rated happiness. None of the interaction terms were statistically significant ($p < 0.05$) and hence only the main effects were retained in the model.

3.2.7.4 Multivariable binary logistic regression possible confounder

The crude Odds Ratio (OR) was calculated with only 3 main effects in the model (sex, age cat, group).

Next, the adjusted Odds Ratio was calculated with the addition of self rated happiness to the other 3 main effects.

Evidence of confounding was looked for using formula $[(OR \text{ (crude)} - OR \text{ (adjusted)}) / OR \text{ (crude)}] * 100$. Any change by 15 % or more, was taken to be evidence of confounding.

CHAPTER 4

RESULTS

4.1 Descriptive statistics

Of the 93 participants who completed the 21 item Beck questionnaire in full at visit 1, 71(76.3%) were female and 22(23.7%) were male. The standard medical care arm had 47(50.5%), and integrative medical care arm 46(49.5%) participants at visit 1 (baseline).

The mean (\pm SE) for age in years was 34.48(\pm 1.35) for the entire cohort, with slightly older participants in integrative medical care arm 38.17(\pm 1.99), compared to 30.87(\pm 1.69) in standard medical care. The difference in mean ages between the 2 arms was statistically significant ($p=0.004$).

Table 4.1 Descriptive Statistics for Beck Scores at visit 1

Entire cohort at visit 1. N = 93						
Male	Female	Mean age entire cohort(\pm SE)	Mean age standard medical care(\pm SE)	Mean age integrative medical care(\pm SE)	Standard medical care arm, count	Integrative medical care arm, count
22(23.7%)	71(76.3 %)	34.48(\pm 1.35)	30.87(\pm 1.69)	38.17(\pm 1.99)	47(50.5%)	46(49.5%)

The Beck score at visit 1 was not statistically significant between the 2 treatment arms ($p=0.513$). The mean (\pm SE) Beck score at final visit (visit 5) for entire cohort was 14.94 (\pm 0.09), with lower Beck score at visit 5 (meaning greater improvement), in the integrative medical care arm 12.92(\pm 1.49), when compared with Beck score 16.00 (\pm 1.23) in standard medical care arm. This difference in scores between the arms was statistically significant with $p=0.037$.

Regarding difference in Beck scores between visit 1 and 5, the mean(\pm SE) was 5.83(\pm 0.81) for entire cohort and again, the integrative medical care arm showed a larger mean difference in

Beck score of 8.13(±1.09) (meaning better improvement in depression score), as compared to 3.63(±1.09) in standard medical care arm (p = 0.005).

Moving onto percentage change in Beck score, the mean percentage (±SE) was 25.29(±5.10) for the entire cohort, with statistically significant percentage change in Beck score of 34.07(±8.62) in integrative medical arm (p value 0.005). The mean percentage change in Beck score in standard medical care arm was 16.89(±5.42).

4.1.1 Continuous variables

Descriptive statistics for variables related to Beck scores (at visit 1, visit 5, difference in scores and percentage change in Beck scores) are presented in table 4.2 and 4.3 below.

Table 4.2 Descriptive Statistics for Beck Scores at visit 1 and visit 5

Variable name	Standard Medical Care Mean (±SE)	Integrative Medical Care Mean (±SE)	p value
Beck score at visit 1	19.70 ¹ (±1.03)	21.08 ¹ (±1.26)	0.513
Beck score at visit 5	16.00 ¹ (±1.23)	12.92 ¹ (±1.49)	0.037
Difference in Beck scores between visit 1 & 5	3.63 (±1.105)	8.13 (±1.09)	0.005
Percentage change in Beck score	16.89 ¹ (±5.42)	34.07 ¹ (±8.62)	0.005

Note. Figures in **bold** represent significant results

Based on independent samples Mann Whitney U test no statistically significant difference in the mean Beck depression score between standard medical care and integrative medical care was observed at baseline.

¹ Mann Whitney U test is often seen as the nonparametric equivalent of independent t test. Consequently, median is commonly compared in the former, and mean in the latter. However, this is actually dependent in Mann Whitney U test, on the distribution of scores in both groups of independent variables. *If the shape of distribution is the same, median is used, if different as in these cases, then mean is used. Hence mean is used in above table for both parametric and nonparametric tests.*

However, at end of 1 year (visit 5), the mean Beck score in the integrative medical care arm was statistically significantly lower when compared to mean Beck score in standard medical care arm. At visit 5, the independent samples Mann Whitney U test demonstrated a statistical difference between integrative and standard medical care arms, $p= 0.037$.

The mean change in Beck score over a one year period, showed that those in integrative medical care arm had statistically significant improvement (greater reduction in mean Beck score) when compared to those in standard medical care arm, $p=0.005$.

Finally, the mean percentage change in Beck score at end of one year follow up, showed that those in the integrative medical care arm had little more than twice the percentage improvement in Beck score compared to those in standard medical care arm. This too was statistically significant, $p=0.005$.

Table 4.3 Descriptive Statistics for Beck Score Variables Stratified by Sex

Variable name	Male Mean (\pm SE)	Female Mean (\pm SE)	p value
Beck score at visit 1 BeckTot	19.48 (\pm 1.27)	20.66 (\pm 0.99)	0.789
Beck score at visit 5 BeckTot5	12.77 (\pm 1.79)	15.05 (\pm 1.18)	0.279
Difference in Beck scores between visit 1 and 5	6.70 (\pm 1.70)	5.54 (\pm 0.93)	0.541
Percentage change in Beck scores	25.71 (\pm 14.95)	25.15 (\pm 4.80)	0.252

As is evident above in table 4.3, no statistically significant difference was observed for any of the continuous variables described above when stratified by sex.

4.1.2 Categorical variables

Table 4.4 Baseline characteristics of Cohort based on BDI-II, n=93

Categorical variable	Count (%)
Sex	
Female	71 (76.3)
Male	22 (23.7)
Study group	
Standard care	47(50.5)
Integrative care	46 (49.5)
Age as a category	
32 years or less	46(49.5)
33 years or more	47 (50.5)
Higher education	
University	41(44.1)
Non university (< high school/high school/< College/< University)	52 (55.9)
Happiness self rated	
Happy (v happy/somewhat happy)	59(63.4)
Unhappy (somewhat unhappy/generally unhappy)	33 (35.5)
Missing	1 (1.1)
Health self rated	
Good (excellent/v good)	40(43.0)
Poor (fair/poor)	53 (57.0)
Household composition	
Single adult	15(16.1)
Rest of households (others with only adults/and or kids)	77 (82.8)
Missing	1 (1.1)
Percentage change in Beck scores with 30 % cut off (Binary variable improvement 30% Yes/No)	
Yes	47(50.5)
No	43(46.2)
Missing	3(3.2)
Birthplace	
Saskatchewan (Saskatoon, SK urban/SK rural)	57 (61.3)
Canada (other than SK)	27 (29.0)
International	9 (9.7)

Table 4.5 Baseline characteristics of Cohort based on study group

Categorical variable	Count (% row across)		p value
	Standard medical care	Integrative Medical care	
Sex			0.954
Female	36(50.7)	35(49.3)	
Male	11(50.0)	11(50.0)	
Age as a category			0.120
32 years or less	27(58.7)	19(41.3)	
33 years or more	20(42.6)	27(57.4)	
Higher education			0.593
University	22(53.7)	19(46.3)	
Non university (< high school/high school/ < College/< University)	25(48.1)	27(51.9)	
Happiness self rated			0.828
Happy (v happy/somewhat happy)	30(50.8)	29(49.2)	
Unhappy (somewhat unhappy/generally unhappy)	16(48.5)	17(51.5)	
Health self rated			0.004
Good (excellent/v good)	27(67.5)	13(32.5)	
Poor (fair/poor)	20(37.7)	33(62.3)	
Household composition			0.187
Single adult	10(66.7)	5(33.3)	
Rest of households (others with only adults/ and or kid)	37(48.1)	40(51.9)	
Percentage change in Beck scores (Binary variable)			0.011
Improvement 30% Yes/No			
Yes	18(38.3)	29(61.7)	
No	28(65.1)	15(34.9)	
Birthplace			0.004
Saskatchewan (Saskatoon, SK urban/SK rural)	21(36.8)	36(63.2)	
Canada (other than SK)	19(70.4)	8(29.6)	
International	7(77.8)	2(22.2)	

Males and females in this cohort were evenly matched between the 2 study groups. Similarly, those who self rated Happiness were also approximately evenly matched between the two study arms.

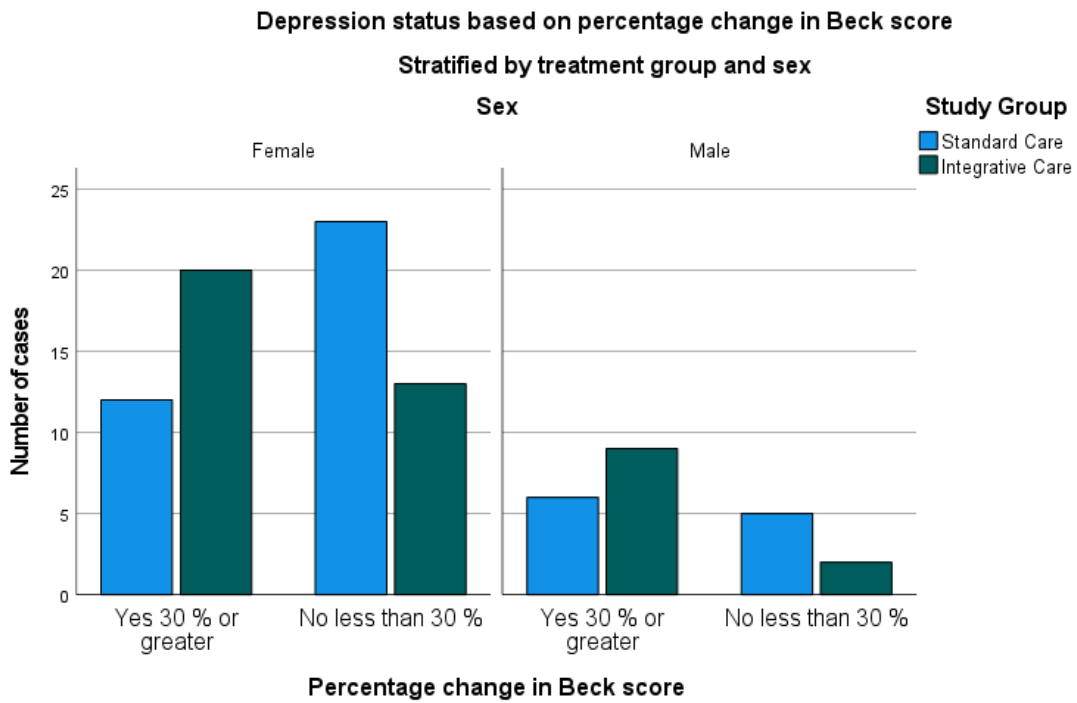


Figure 4.1 Depression Status Based on percentage change in Beck score (30 % or Greater) Stratified by Treatment Group and Sex

Figure 4.1 shows that improvement in depression for both sexes was greater amongst those in integrative medical care group.

Improvement in depression (as measured by reduction in Beck scores) over a 12-month period was converted into a binary outcome variable (improvement $\geq 30\%$ of percent change in Beck score= Yes, No improvement $< 30\%$ percent change in Beck score).

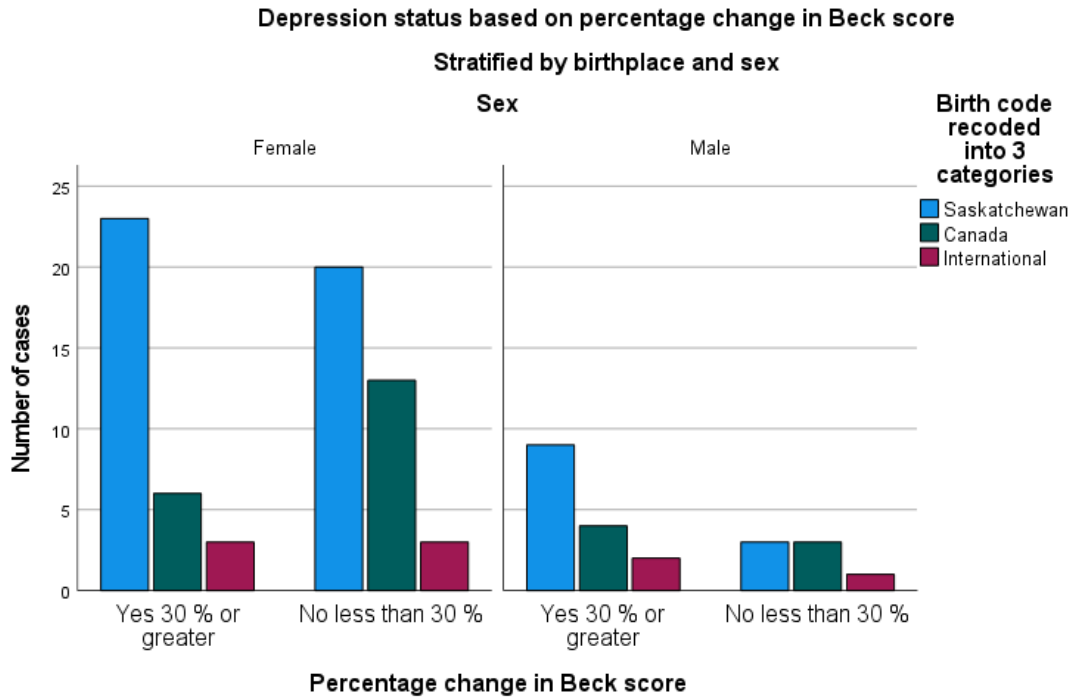


Figure 4.2 Depression Status Based on percent change in Beck score (30 % or Greater) Stratified by Birthplace and Sex

The above figure shows that for females who improved or not, the largest group were Saskatchewan born.

For males that improved, the largest group were Saskatchewan born. For males that did not improve, the Saskatchewan and Canada born were roughly equal in number, followed by International born.

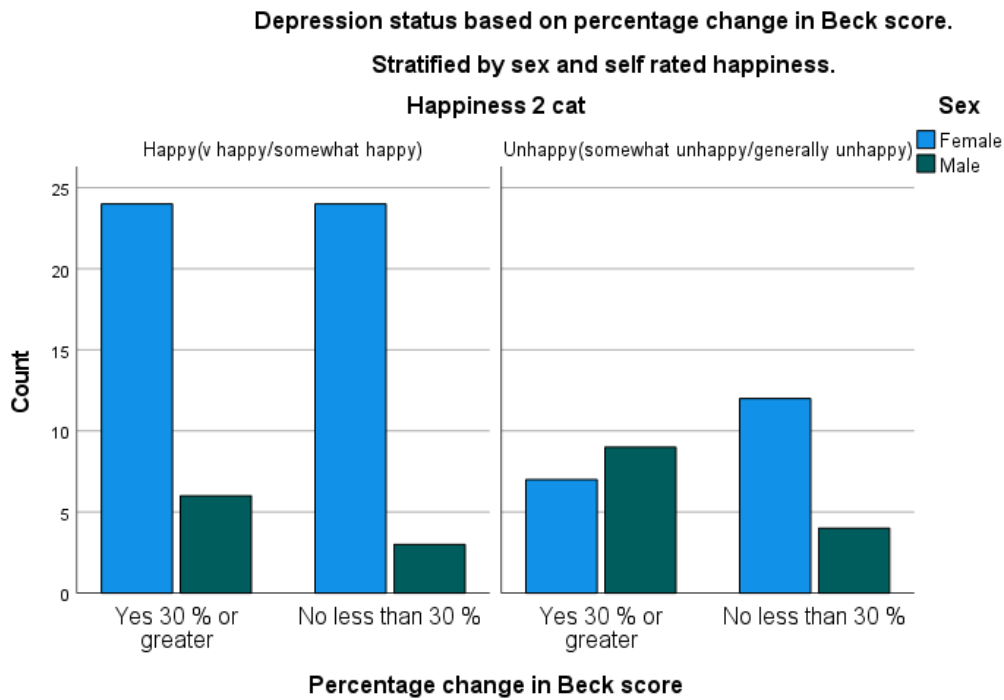


Figure 4.3 Depression Status Based on percentage change in Beck score (30 % or Greater) Stratified by Self Rated Happiness and Sex

Among those who self-rated as very or somewhat happy, most of them were female

Of those unhappy and improved, the majority were males. Among those unhappy and not improved, the majority were females.

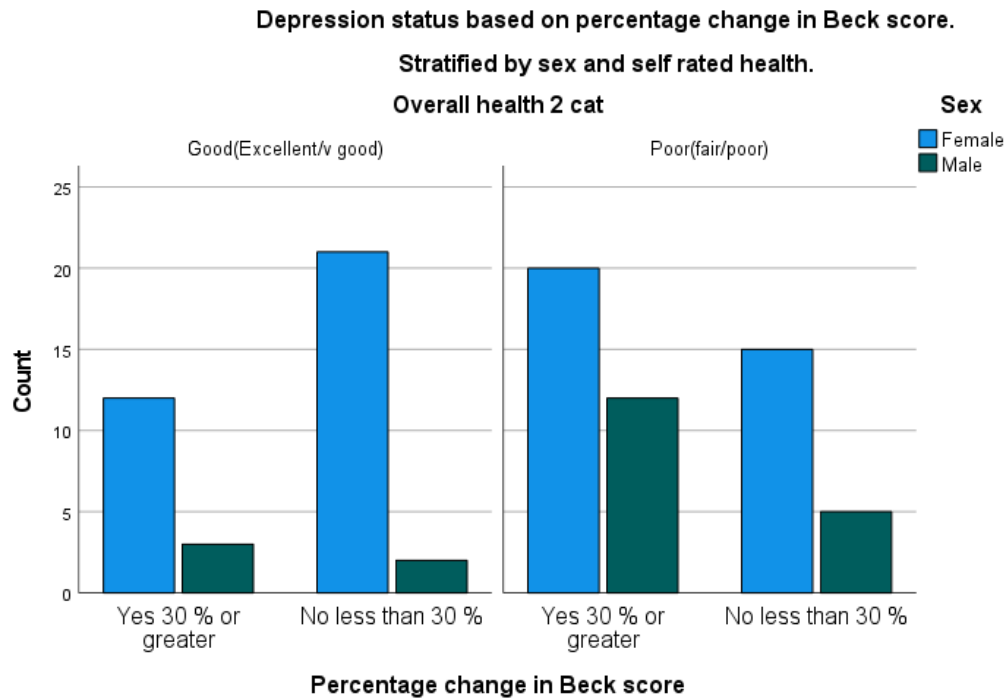


Figure 4.4 Depression Status Based on percentage change in Beck score (30 % or Greater) Stratified by Self Rated Health and Sex

For both sexes that improved, most felt that their health was poor.

Females that did not improve felt that their health was good. Males that did not improve felt that their health was poor.

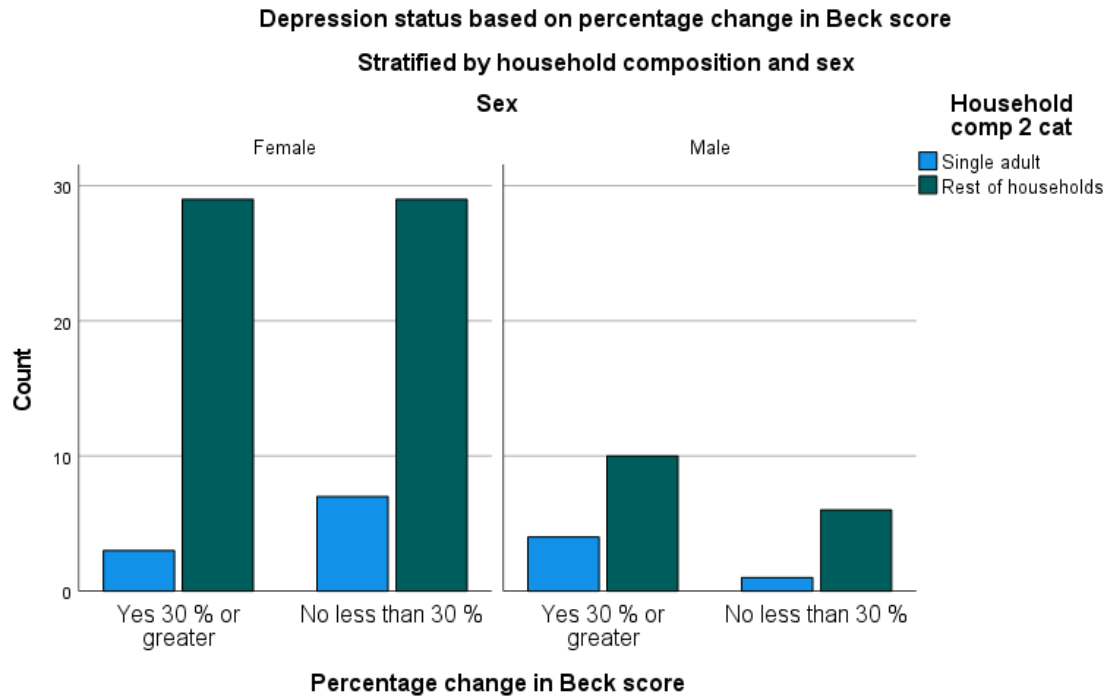


Figure 4.5 Depression Status Based on percentage change in Beck score (30 % or Greater) Stratified by Household Composition and Sex

Most males and females that showed improvements in depression scores came from households with more than 1 adult.

A similar pattern for both sexes was observed among those that did not improve.

Regardless of sex and improvement in depression, only a minority of participants came from single adult households.

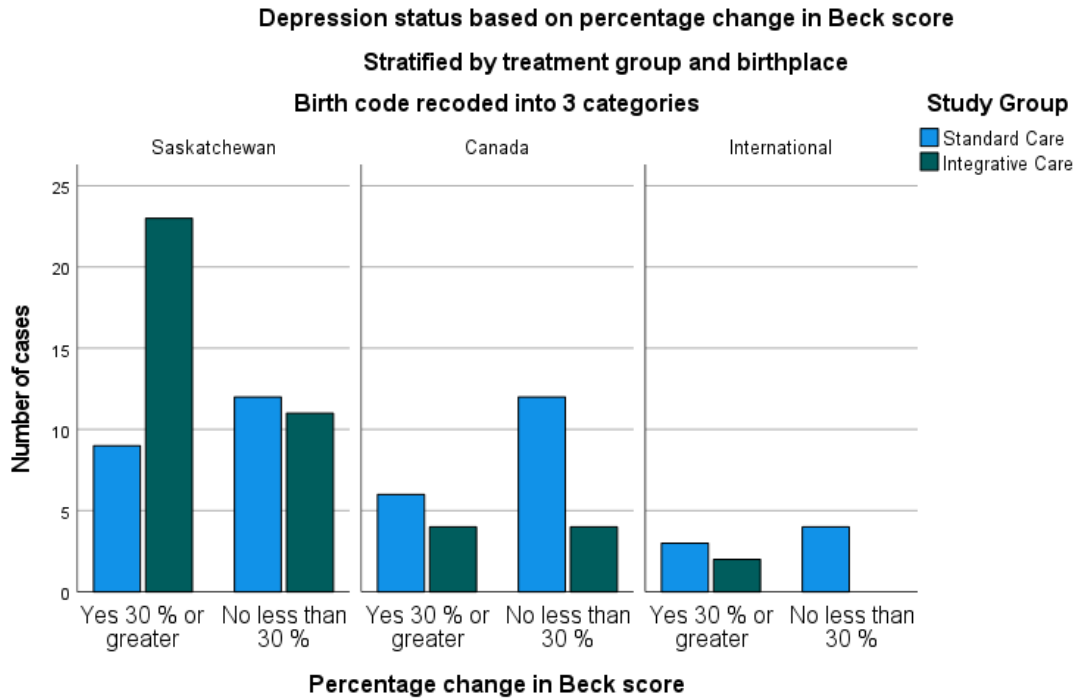


Figure 4.6 Depression Status Based on percentage change in Beck score (30 % or Greater) Stratified by Treatment Group and Birthplace

The majority of those that improved irrespective of study group were born in Saskatchewan.

The largest number that improved were Saskatchewan born and in the integrative care group.

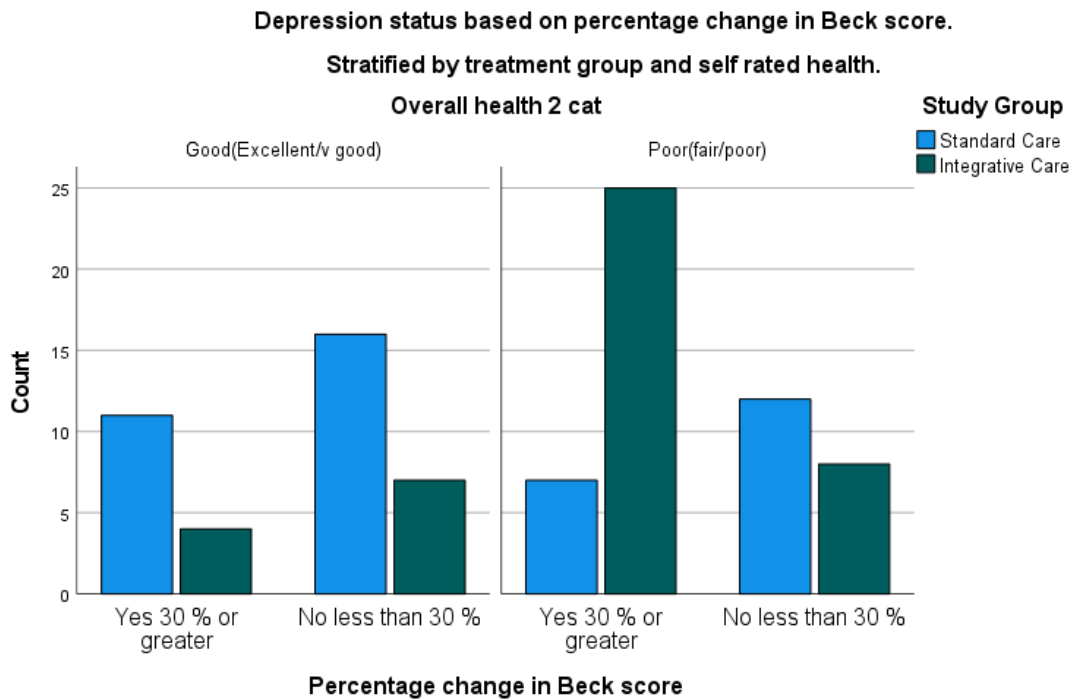


Figure 4.7 Depression Status Based on percentage change in Beck score (30 % or Greater) Stratified by Treatment Group and Self Rated Health

The bulk of the participants with poor health who improved were in the integrative medical care arm. The largest number of those who described their health as good were in the standard medical care arm and did not improve.

For those that did not improve, and were in integrative medical care arm, there was a slight majority that described themselves as having poor health.

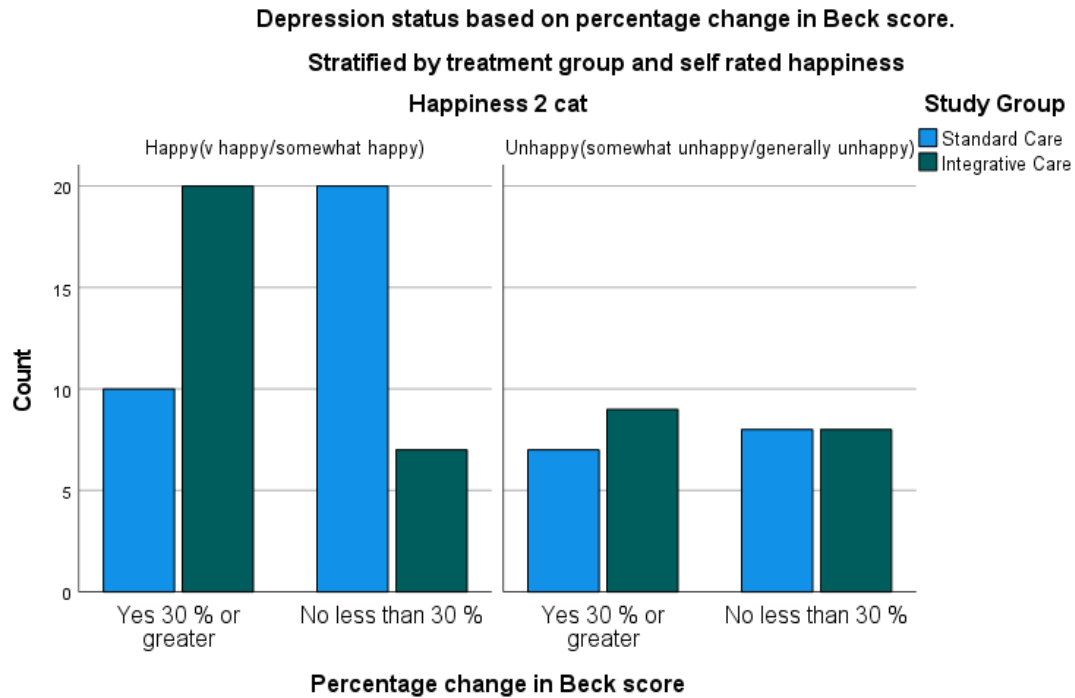


Figure 4.8 Depression Status Based on percent change in Beck score (30 % or Greater) Stratified by Treatment Group and Self Rated Happiness

Of those who improved over 30% and described themselves as happy, the majority were in integrative medical care group. Of those who improved less than 30% and described themselves as happy, the majority were in the standard medical care group.

Of those who did not improve and self-rated as unhappy, there were equal numbers of participants in each treatment arm.

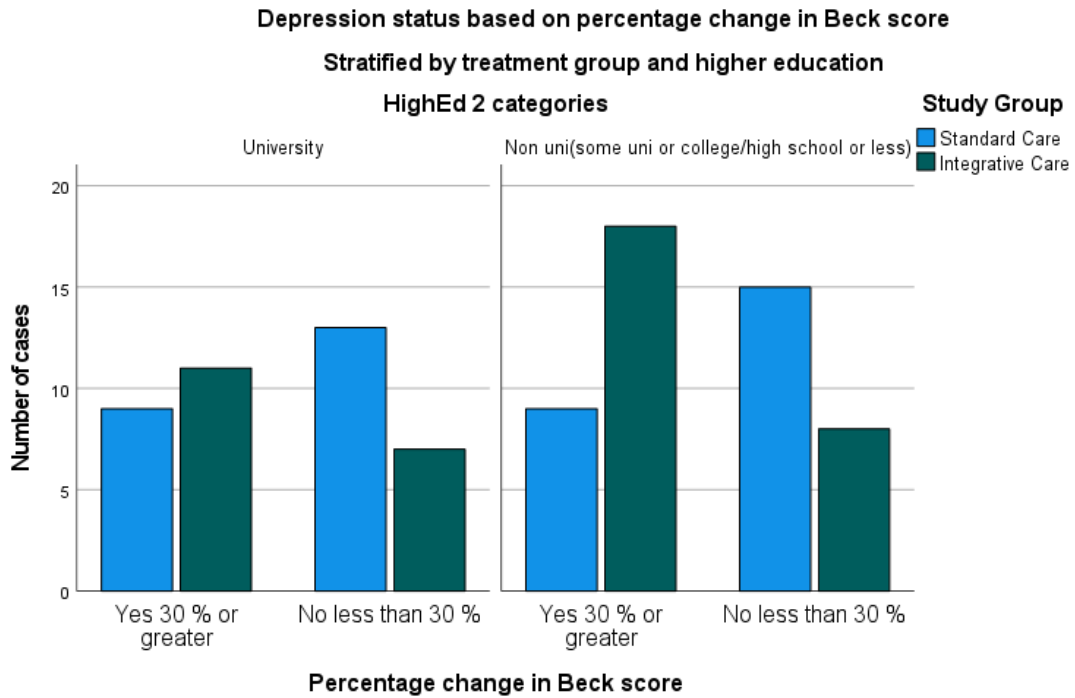


Figure 4.9 Depression Status Based on percentage change in Beck score (30 % or Greater) Stratified by Treatment Group and Higher Education

Among those that were university educated and showed improvement, the majority were in integrative medical care arm. A similar picture was seen among with those that did not have a university education and improved, they were largely in the integrative medical care arm. Of those that did not improve, irrespective of their level of education, the majority were in standard medical care arm.

4.2 Logistic regression

4.2.1 Simple logistic regression

Standard model building techniques as explained by Hosmer and Lemeshow (76) were used to decide on the final selection of variables for the multivariable model that would provide the best predicted model.

Based on simple logistic regression analysis, any independent variable with p value ≤ 0.25 became a potential candidate for the multivariable binary logistic regression model. Here the binary outcome variable was based on improvement in Beck score as a ratio over 12-month period. Each potential independent variable was tried out, one at a time, finally settling on the independent variables if the p value was ≤ 0.25 .

Table 4.6 Result of the Univariable binary logistic regression of percentage improvement in Beck scores at 30 % cut off

Categorical Variable	Percent change in Beck score		n(%) Total across n	Unadjusted OR(95% CI)	p value
	>30% Yes	<30% No			
Sex					
Female(Ref)	32(68.1%)	36(83.7%)	68		
Male	15(31.9%)	7(16.3%)	22	0.42(0.15-1.15)	0.090
Study Groups					
Integrative Care	29(61.7%)	15(34.9%)	44	0.33(0.14-0.79)	0.012
Standard Care(Ref)	18(38.3%)	28(65.1%)	46		
Birthplace					
Saskatchewan(Ref)	32(68.1%)	23(53.5%)	55		
Canada	10(21.3%)	16(37.2%)	26	2.23(0.86-5.78)	0.100
Internationally	5(10.6%)	4(9.3%)	9	1.11(0.27-4.60)	0.882
Highest level of education					
University(Ref)	20(42.6%)	20(46.5%)	40		
Some Uni or college	21(44.7%)	22(51.2%)	43	1.05(0.44-2.48)	0.916
High school or less	6(12.8%)	1(2.3%)	7	0.17(0.02-1.51)	0.111
Self described happiness					
Very happy(Ref)	2(4.3%)	3(7.0%)	5		
Somewhat happy	28(60.9%)	24(55.8%)	52	0.57(0.09-3.71)	0.558
Somewhat unhappy	15(32.6%)	9(20.9%)	25	0.40(0.057-2.87)	0.362
Generally unhappy	1(2.2%)	7(16.3%)	8	4.67(0.30-73.38)	0.273
Birth mode					
Vaginally(Ref)	35(74.5%)	35(81.4%)	70		
c-section	7(14.9%)	8(18.6%)	15	1.14(0.37-3.49)	0.815
don't know	5(10.6%)	0	5	0.000	0.999
Self described Overall Health					
Excellent(Ref)	3(6.4%)	2(4.7%)	5		
Very good	12(25.5%)	21(48.8%)	33	2.63(0.38-17.99)	0.326
Fair	31(66.0%)	15(34.9%)	46	0.736(0.11-4.82)	0.740
Poor	1(2.1%)	5(11.6%)	6	7.50(0.46-122.70)	0.158

Based on the univariable analysis, only the variables of sex, group, birthplace, higher education and self-described overall health could be considered for entry into multivariable logistic regression model.

Table 4.7 Result of the Multivariable binary logistic regression of percentage improvement in Beck scores at 30 % cut off

Variable	OR (95%CI) ¹	OR (95% CI) ²
Sex		
Male	2.46 (0.85-7.09)	2.99 (0.97-9.23)
Female (Reference)	1.00	1.00
Study group		
Standard (Reference)	1.00	1.00
Integrative	3.24 (1.32-7.94)	3.64 (1.45-9.17)
Age categories		
32 years and less	1.26 (0.51-3.09)	1.31 (0.52-3.31)
33 years and more (Reference)	1.00	1.00
Self rated happiness		
Happy (v happy/somewhat happy)		1.56 (0.58-4.19)
Unhappy (v unhappy/generally unhappy) (Reference)		1.00

Those participants in the integrative medical care group were 3.64 times more likely to show an improvement in Beck scores over 12 month period when compared with those in standard medical care arm for the same period. OR (adjusted) was not significant based on 95% CI, for the other variables (Self rated happiness, age as a category and sex). Self rated happiness was a confounder to Sex (21.53%).

¹ OR crude

² OR adjusted

Table 4.8 Classification table from SPSS output for Binomial logistic regression, 4 main effects (sex, study group, age as category, self rated happiness)

Classification Table^a

Observed		Predicted		Percentage Correct
		0 No	1 Yes	
Step 1	0 No	23	20	53.5
	1 Yes	11	35	76.1
Overall Percentage				65.2

a. The cut value is .500

Sensitivity- $(35/46) * 100 = 76.1\%$, meaning, of the 46 observed to have improved, 35 were correctly predicted to show improvement.

Specificity- $(23/43) * 100 = 53.5\%$, meaning, of the 43 observed to have shown no improvement, 23 were correctly predicted as to show no improvement.

Positive Predictive Value- $(35/55) * 100 = 63.6\%$. Here out of the 55 predicted to have improved, only 35 were actually observed to have improved.

Negative Predictive Value- $(23/34) * 100 = 67.6\%$. Out of the 34 predicted to not show improvement, only 23 were actually observed not to have improved.

Percentage accuracy in classification 65.2 %

Sensitivity was 76.1 %, specificity was 53.5 %, positive predictive value was 63.6 % and negative predictive value was 67.6 %

*A binomial logistic regression was performed to ascertain the effects of sex, study group, age as a category, and happiness (model A), on the likelihood of predicting improvement in Beck scores over a 12-month period. The interaction terms tried were sex*group, sex*age cat, sex*self rated happiness, group*age cat, group*self rated happiness, self rated happiness*age cat, self rated health * self rated happiness. None of the interaction terms were statistically significant ($p < 0.05$) and hence only the main effects were retained in the model A.*

The logistic regression model was statistically significant with $p=0.018$. The model correctly classified 65.2 % of the cases. Of the four predictor variables, only study group was statistically significant $p=0.006$. Sex was nearly significant with a p value of 0.057.

Those in the integrative medical care group were 3.64 times more likely to show improvement in Beck scores than those in standard medical care group.

This was my final parsimonious model. Denoted as model A.

4.3 Receiver Operating Characteristics for model A

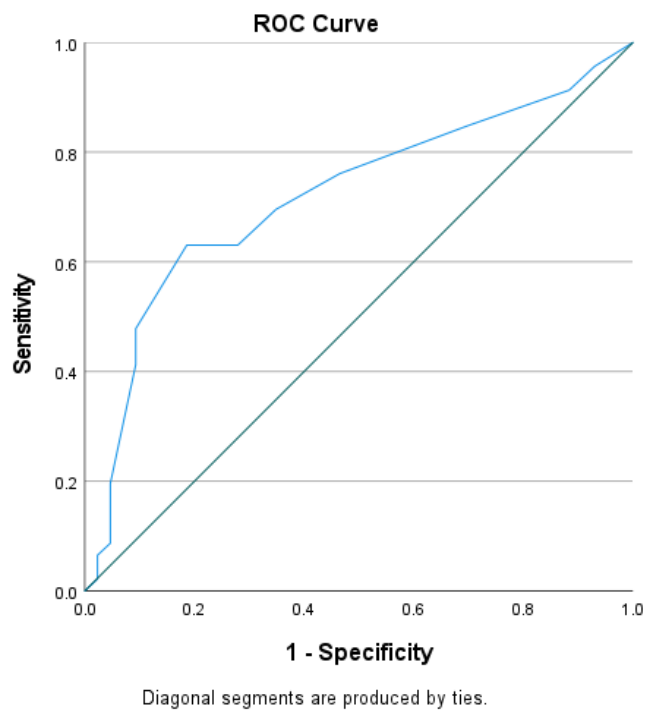


Figure 4.10 Receiver Operating Characteristics for Model A with 4 Main Effects (Sex, Age Cat, Group and self rated Happiness)

4.3.1 Area under curve (AUC) for model A

The area under the ROC curve was 0.720(95% CI 0.61-0.83), which is considered an acceptable level of discrimination according to Hosmer et al (76)

Table 4.9 AUC for Model A

Area Under the Curve				
Test Result Variable(s): Predicted probability				
Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.720	.056	.000	.611	.829

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

4.4 Other models considered before settling for final parsimonious model

4.4.1 Model B

Table 4.10

Multivariable logistic regression with sex, age as a category, study group and self rated health

Variable	OR (95%CI) ³	OR (95% CI) ⁴
Sex		
Male	2.46 (0.85-7.09)	2.195 (0.74-6.49)
Female (Reference)	1.00	1.00
Study group		
Standard (Reference)	1.00	1.00
Integrative	3.24 (1.32-7.94)	2.797 (1.09-7.21)
Age categories		
32 years and less	1.26 (0.51-3.09)	1.24 (0.50-3.057)
33 years and more (Reference)	1.00	1.00
Self rated health		
Good (Excellent/ v good)		0.64 (0.25-1.66)
Poor (Fair/poor) (Reference)		1.00

No evidence of confounding was found

Sensitivity 74.5 %

Specificity 55.8 %

Positive predictive value 64.8 %

Negative predictive value 66.7 %

Percentage accuracy in classification 65.6 %

p value for this model (sex, age as a category, group, and self rated health) was 0.029

³OR Crude ⁴OR Adjusted

4.4.2. ROC for Model B

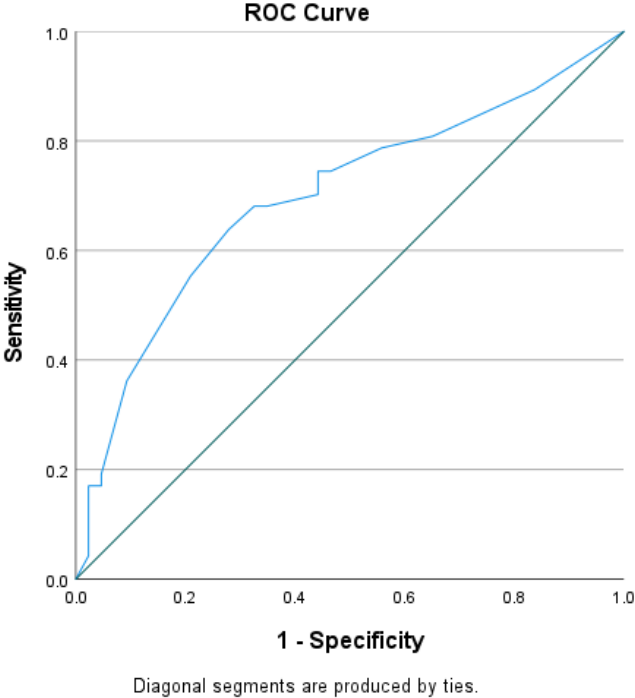


Figure 4.11

Receiver Operating Characteristics for Model B with 4 Main Effects (Sex, Age Cat, Group and self rated Health)

4.4.2.1 AUC for Model B

Table 4.11

AUC for Model B with 4 main effects (sex, age as a category, group and self rated health)

Area Under the Curve

Test Result Variable(s): Predicted probability

Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.698	.056	.001	.588	.808

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

AUC for model B was 0.70 (95 % CI 0.59-0.81)

The other models reviewed were as below: -

- (1) 4 Main effects of sex, study group, age as a category and self rated health. Model B.
- (2) 5 Main effects of sex, study group, age as a category, self rated happiness, and self rated health. Model C.

My conclusion based on AUC, is that there is very little to be gained in predictability of the model, when self rated health is added to the original model (model A) containing sex, study group, age as a category and self rated happiness. The AUC for this model (model C) was 0.72(95% CI 0.62-0.83), as opposed to AUC of 0.72 (95% CI 0.61-0.83) based on the original model with sex, study group, age as a category, self rated happiness (model A).

Hence the retained parsimonious model has 4 independent variables of sex, age as a category, study group and self rated happiness (model A).

4.4.3 Model C

Table 4.12

Multivariable logistic regression with sex, study group, age as a category, self rated happiness, self rated health

Variable	OR (95% CI) ⁵	OR (95% CI) ⁶
Sex		
Male	2.99 (0.97-9.23)	2.67 (0.85-8.36)
Female (Reference)	1.00	1.00
Study group		
Standard (Reference)	1.00	1.00
Integrative	3.64 (1.45-9.17)	3.01 (1.14-7.93)
Age categories		
32 years and less	1.31 (0.52-3.31)	1.27 (0.50-3.25)
33 years and more (Reference)	1.00	1.00
Self rated happiness		
Happy (v happy/somewhat happy)	1.56(0.58-4.19)	1.80 (0.65-4.99)
Unhappy (v unhappy/somewhat unhappy) (Reference)	1.00	1.00
Self rated health		
Good (Excellent/v good)		0.53(0.20-1.44)
Poor (Fair/poor) Reference		1.00

Self rated health was a confounder to study group (17.30 %)

Sensitivity 73.9%

Specificity 60.5 %

Positive predictive value 66.7 %

Negative predictive value 68.4 %

Percentage accuracy in classification 67.4 %

P value for this model was 0.020

OR⁵ Crude OR⁶ Adjusted

4.4.3.1 ROC for Model C

Receiver operating characteristics for model C

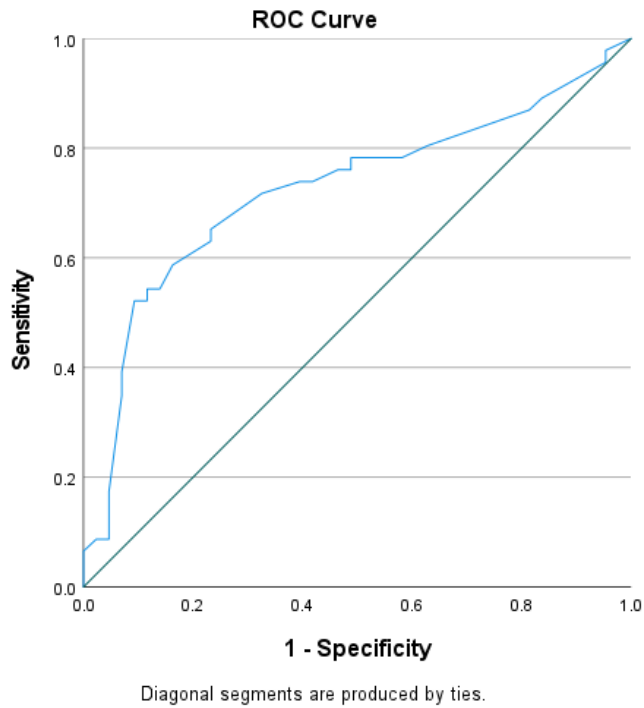


Figure 4.12

Receiver Operating Characteristics for Model C with 5 Main Effects (Sex, Age Cat, Group, self rated Happiness, and self rated Health)

4.4.3.2 AUC for Model C

Table 4.13

AUC for Model C with 5 main effects (sex, age as cat, group, self rated happiness, self rated health)

Area Under the Curve

Test Result Variable(s): Predicted probability

Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.724	.056	.000	.615	.834

The test result variable(s): Predicted probability has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

CHAPTER 5

DISCUSSION

The purpose of the study was to determine factors associated with improved depression scores at 12 months in a cohort of adults with depression. The change in the Beck Depression Inventory scores from baseline to 12 months was operationalized as the outcome variable.

A binomial logistic regression was performed to ascertain the effects of potential confounding variables such as sex, study group, age as a category, and self rated happiness, on the likelihood of predicting improvement in Beck scores over a 12-month period. The regression model was statistically significant with $p=0.018$. The model correctly classified 65.2 % of the cases.

Sensitivity was 76.1%, specificity was 53.5%, positive predictive value was 63.6% and negative predictive value was 67.7%

Of the four predictor variables, only study group was statistically significant $p=0.006$. More specifically, those in the integrative medical care group were 3.64 times more likely to show improvement in Beck scores than those in standard medical care group.

The integrative medical care showed a significant superiority compared to standard care for depression. The delivery of integrative medical care had 2 components-the therapeutic relationship with the practitioner and the carefully selected modalities of integrative care that is individualised in conjunction with the participant, in order to provide holistic care. The effects of various modalities such as dietary advice, exercise, meditation and 4-7-8 breathing techniques coming together, were more than the sum of the individual modalities.

It must be emphasised that this patient driven approach afforded opportunities for participants to pick the modalities with which they were most comfortable. Furthermore, the advice that was

given to participants about healthy living and choices were consistent with what is reported in the literature about sustained changes, leading onto better physical and mental well being in the long term(77)

The length of the first visit between the integrative care physician and participant (which was one hour long) is significant as it is a great opportunity to listen to the patient and figure out the beliefs about the issue from their perspective. In the literature, it is well known that listening to the patient's reason for consult and the meaning attributed to ill health is very helpful for the provider and the patient(78) . The approach was grounded in both physical health and mental health with active participation of patients.

In the Institute of Medicine's Quality of Health Care in America report published in 2001, it was recommended that in order to improve the quality of healthcare, the care provided should be safe, effective, person-centered, timely, efficient, and equitable(79). The same report went on to say, that patient-centered care can be defined as the provision of healthcare that respects and is representative of patients' individual preferences and needs.

At this first visit, enquiry was made about diet, sleep, and bowel movements. Participants were also provided with a paper to record specific events and details. They were asked to write down significant life events such as their birth, marriage, disease, loss, death. The purpose of this was to visualise the buildup of trauma. They were also asked to record details of the food consumed. These papers were to be brought for subsequent visits.

On subsequent visits, blood work as relevant was ordered but not limited to CRP, serum Vit D levels and tests for celiac disease. The details of diet and significant life events were also reviewed together.

Participants were encouraged to exclude dairy and gluten from their diets, to see if it was effective. Participants were also made aware of concepts regarding inflammation, and types of anti-inflammatory diets, as there is increasing recognition of the role that inflammation has to play in the pathogenesis of depression(17,23,26). At all times, participants were provided information and resources to further explore at their leisure.

Interestingly, according to a previous study (unpublished results of the same data source from my colleague Amanjot Kaur and shared with me), the mean scores were not statistically different between the 2 study arms (standard care and integrative medical care) at 3 months from baseline, therefore demonstrating equipoise between the arms. This means that in the short term (3 months) using a pharmacological approach versus an integrative medical approach was as effective. However, at 12 months, a clear superiority of the integrative medical care intervention was demonstrated. What might be the reasons for this? According to Frederic Limosin and others who studied depression in general practise, they found that there was a high likelihood of relapse in 4-6 month period even after initial symptomatic improvement. They followed up 476 depressed patients over 6 months, and found that 308(64.7%) responded to pharmacological treatment and were well, 117(24.6 %) showed no response and 51(10.7%) showed early relapse after initial improvement(80). These authors also noted a predictor of relapse or nonresponse was recurrent depression. In my study, it would appear that participants in integrative medical care arm were “bucking the trend” as described by Frederic Limosin.

Kiyomi Shinohara et al performed a meta analysis of trials with antidepressant use of more than 3 months. They attempted to answer the question which antidepressant if any should be preferred in terms of efficacy (sustained response) and the best for maintenance treatment? They classified acute use of antidepressants as 3 months and continuation/maintenance treatment as > 3 months. Unfortunately they could only conclude that there was insufficient evidence regarding efficacy of antidepressants and further could not make recommendations regarding efficacy and acceptability of maintenance treatment(81). They studied 21 antidepressants currently in use.

It would seem logical to infer that integrative medical care takes time to work and consolidate. Further, the multiple modalities customized for the participant in integrative medical care arm appear to show what might be synergies of effect with a possible boosting of response, this can only be verified in future trials with a large number of participants comparing various combinations of therapies. As a general rule, all meditative practises including 4-7-8 breathing induce a state of deep relaxation which has a calming affect in the short term, with more permanent changes in the brain if practised in the long term. Interestingly even 8 weeks of Mindfulness Based Stress Reductions (MBSR) programs result in changes in the brain as evidenced by MRI imaging. What Britta Holzel et al found in this study was that 8 weeks of

MBSR contributed to increased cortical thickening (gray matter concentration) and reduction in volume of amygdala. Thus morphological changes in the brain were associated with how the subjects actually felt(82). In view of these changes in a relatively short period of meditation, it seems likely that sustained meditative practises will contribute to sustained and profound changes in the brain.

There is a strong emphasis on patient empowerment in integrative medicine, meaning patients are encouraged to learn and understand their illness and also be aware of the treatment options available and then make decisions on their treatment in conjunction with their physician. Information on diet, exercise, meditation to name a few would foster a change in their lifestyle and hopefully become habit forming and permanent. Literature tends to support this view. In a study of mindfulness meditation program of 50 individuals with depression, anxiety, or stress as measured by the Depression Anxiety and Stress scale, were enrolled and followed up for 10 weeks(83). In view of the fact that even 8 weeks of mindfulness meditative practise result in measurable morphological changes in brain(82), it would appear that this 10 week study is sufficiently long to make valid conclusions. What was found by the authors was that the severity of all affective measures decreased by the end of the study. Further, those individuals with severe emotional difficulties at time of commencement of study showed the greatest improvement.

Andrea Duarte-Diaz and others performed a secondary analysis of the INDICA study. The INDICA study was a multi arm randomized controlled study of type 2 diabetics without severe co-morbidities. Follow up was at 12, 24 months. Patient empowerment was measured with Diabetes Empowerment Scale-short form (DES-SF), depression with BDI-II and anxiety with State-Trait Anxiety-S(STAI-S). These tools were administered at baseline, 12 months and 24 months. The authors found that an increase in patient empowerment was associated with significant decrease in anxiety($p < 0.001$) and depression($p < 0.001$), furthermore there was no significant difference between follow up at 12 and 24 months(84).

A critical component of the visit to integrative care physician, was that participants were seen as frequently as needed and their appointment duration was flexible. Participants were encouraged to unpack their issues and enrich their own learning. In this author's view, this empowering of the participants was critical to establishing a fruitful and enduring therapeutic relationship. Once established, participants could be real partners journeying forward along with their physician. This has been borne out by literature too. It has been found that a common barrier to shared decision making is unsurprisingly-time(85,86). According to Lara Guedes de Pinho and other researchers, there is "increasing recognition that healthcare must be personalized and marked by shared decision making between patients and healthcare professionals. The concept of shared decision making implies that patients' preferences and cultural values influence clinical decisions"(87).

N Singh Ospina and others, performed a secondary analysis of a random sample of 112 clinical encounters recorded during trials testing efficacy of shared decision making tools(88). They found that clinicians elicited patient's agenda in only 36 % of encounters. Patient's agenda was more successfully elicited in primary care (49 %) as opposed to speciality care (20%). What was more telling was that in 67 % of encounters where clinicians elicited patient's concerns, the time to interruption was a median of 11 seconds. Considering these findings, the benefit of an unhurried consultation seems both important and relevant.

Finally in my study there was a preponderance of females. According to a study performed by Flora Matheson et al in Ontario, females with physical illnesses were 10 % more likely to seek support for their mental health than males. Further, it was reported in this study that over a 3 year window, women were on the average accessing services for mental health, 6 months before males (83). This in part may explain that the majority of participants were females in The Neural Health Project.

5.1 Strengths and limitations

5.1.1 Strengths

The main strength of The Neural Health project was that it was the *very first study of its kind in Canada*. Up to now, there has been no study comparing 2 treatment arms for depressed patients in Canada, where integrative medical care was compared with standard medical care, using BDI-II scores to determine improvement. Additionally, biomedical samples (which included saliva cortisol and peripheral blood smear for 5 biomarkers were collected). No result is available yet. My study focused on the 12 months follow up period. This was long for a cohort study on depression in Saskatchewan and I tried to tease out the factors that could explain the reduction in depression scores between baseline and 12 months. *Only the intervention arm ended up being significant. This is an especially important finding.*

5.1.1.1 Sole integrative medical care physician in study

The Neural Health Project had a sole integrative medical care physician in the study. This contrasted with multiple general practitioners who were in the standard medical care arm. In other words, participants in the integrative medical care arm always saw the same physician ensuring a consistency in the delivery of care. This was not the case for those in the standard medical care arm. Participants here, saw any general practitioner available at their follow up in the standard medical care arm.

5.2.1 Limitations

5.2.1.1 Hierarchy of evidence

Rebecca Ingham-Broomfield in her article on hierarchies of evidence, states that there are 7 levels of evidence in a form of a pyramid(89). She asserts that the base of the pyramid, and the lowest level of evidence (level 7) are ideas, opinions, and anecdotes, which are the least reliable. Hunches and gut feeling too, come under this category. She goes on to say that personal opinion may not be transferable. The other levels of evidence (in order of increasing importance), the author mentions are case controlled studies, case series, case reports (level 6); cohort studies (level 5) which can be prospective or retrospective; random control trials (level 4); critically appraised individual articles (level 3); critically appraised topics (level 2) and at the apex of the pyramid, systematic reviews and meta-analysis (level 1).

Trisha Greenhalgh and others argue that medical science has embraced whole heartedly Evidence Based Medicine(EBM) over the past few decades, without looking at it critically and being mindful of vested interests such as pharma care pushing forward their own agenda in the name of EBM(90). The authors further go onto say, that it is time to revisit EBM and make the guidelines more inclusive and individualised to the needs of the patient. Shared decision making can help in arriving at suitable holistic care with the active concurrence of patients. I would go on to argue that The Neural Health Project demonstrated the benefits of an integrated approach to patient care, despite some of its shortcomings.

The Neural Health Project was a prospective cohort study. It was not at the level of randomized, controlled trials which is considered the gold standard. There was no randomization in this study and there was no blinding. Clearly, blinding would not have been possible in the integrative medical care arm (also the intervention arm), as the kinds of therapy chosen were individualised for the participant, with inputs from the participants themselves.

5.2.1.2 Number of participants

Although 130 participants entered The Neural Health Project, only 103 completed the study at 12 months. They were seen at 3-month intervals, along with baseline there were 5 visits in total. *However, in my study which was based on changes in BDI-II scores over a 12-month period, 93 completed the BDI-II questionnaire at baseline and 90 at visit 5(end of 12 months). Effectively, this made my n=90.* This was a comparatively smaller number although there were roughly equal numbers between standard medical care and integrative medical care arms. However, females were almost 3 times the males in my study. The prevalence of depression among females is higher than males, but this cannot account for the preponderance of females in my study. Possible explanation may well be that females are more inclined to seek help for depression than males(91), consequently leading onto a larger potential pool of female participants for this study.

5.2.1.3 Improvement based on change in depression scores alone

In this study, improvement in depression was measured by reduction in Beck scores alone. As explained elsewhere, statistical significance does not always correlate with clinical significance.

This, I believe to be a limitation. Hopefully, future studies will have minimal clinically important difference, or some other method built in, in order to get round this limitation.

5.3 Implications for clinical practice

5.3.1 Sharing knowledge with family physicians and patients

Following the results of this study in favor of integrative medical care, there is a renewed sense of purpose in sharing this knowledge with both family physicians and patients. With this in mind, there have been initial steps taken in developing an app and or website available to family physicians and patients. Thus, family physicians will have all the resources available to provide integrative medical care for their depressed patients and crucially, be able to offer them a choice between standard medical care and integrative medical care for the management of depression. Similarly interested patients will have an opportunity to learn about integrative medical care and to explore it further.

Participants are eager to learn of the results. At first, meetings with donors were arranged via internet and our results shared with them. Further meetings are scheduled next year with participants in groups. It is also planned to disseminate knowledge of this study via conferences, posters and journals.

5.3.2 Team based approach for delivering integrative medical care for depression

With the current shortage of GP and other healthcare professionals, a better model in Canada maybe a multidisciplinary clinical team approach. The team could comprise doctors, nurse practitioners, physiotherapists, dietitians, mental health workers and trauma counsellors to name a few. Patients would be referred to the most appropriate health professional and team meetings could assess progress and course of treatment.

5.3.3 Cost implications of widespread adoption of integrative medical care in the treatment of adult depression

One of the anticipated criticisms of using an integrative medical care approach in the treatment of depression, are the costs involved. Yes, on the face of it, it would be more expensive than merely prescribing an antidepressant. According to the CAMH website, the annual economic cost of mental illness in Canada is \$ 50 billion(92) , this includes health care costs, loss of productivity, and reduction in health-related quality of life. I would argue that being able to return individuals

to a fulfilling and productive life, free of mental illness would actually be a cost saving in the long term. Furthermore, the taxes paid by these individuals returning to the workforce (earlier than otherwise), may well pay for the costs entailed in delivering integrative medical care for depression. A subset of these patients are those with treatment resistant depression (TRD). To this end Roger McIntyre and others studied the healthcare costs in Ontario using the database of Institute for Clinical Evaluative Sciences (ICES). They studied 277 patients with TRD with an average age of 52 years (SD 16), 53 % of whom were female. When compared with non TRD patients, they found that TRD patients had increased all cause visits to outpatients (38.2 Vs 24.2), emergency department (2.7 Vs 2.0), psychiatrist visits (5.88 Vs 1.95) and more depression related visits to GP (3.06 Vs 1.63). All had p values of < 0.05. The average 2 year cost for TRD patients was \$ 20,998(93).

5.3.4 Limitations to standard medical care for the management of depression

The recognition and understanding that not all depressed patients treated with antidepressants will go into remission. Furthermore, a sizeable number can be expected to not respond meaningfully to antidepressants. It is mentioned in the literature that up to 33 % of depressed patients may not respond to antidepressants(9). Knowing that there might be alternative pathways in the management of depression would go a long way in addressing this problem.

5.4 Implications for future research

5.4.1 Suggestion that integrative medical care is better than standard medical care alone

The Neural Health Project has suggested that integrative medical care is better than standard medical care in the management of depression among adults in Canada. This generates many questions as to why it might be so. It is hoped that other researchers in Canada will use the findings of this study to follow through and conduct their own research.

5.4.2 Possible explanation as to why integrative medical care showed better results than standard medical care in this study

The Neural Health Project has been a pioneering study in Canada. More work needs to be done in larger, multicentred trials across Canada. A key question that I have following my study is, can the findings in favor of integrative medical care be attributed in part to the integrative medical care physician seeing patients as frequently as needed, and spending time to develop a

therapeutic relationship? Could the array of different modalities on offer to the participant be exerting a boosting effect when more than one modality is combined and tailored to fit the participant? Perhaps future studies can be designed with multiple integrative care physicians at each centre to study this in greater detail.

5.4.3 Exploring different options available for the management of adult unipolar depression using the integrative medical care approach

Future trials comparing standard medical care with integrative medical care for adult unipolar depression could explore the different treatment options available under the umbrella of integrative medical care. Provided the trial has sufficient numbers, it maybe possible to compare say 4-7-8 breathing vs anti-inflammatory diet vs health supplements and various other permutations. Such a trial would need to be sufficiently powered though.

5.4.4 Setting up trials with MCID in mind

Future trials could be designed keeping minimal clinically important difference for Beck scores in mind. These trials would have to have an anchor question asked at each visit, such as “do you feel as depressed today, as 3 months back, or more depressed, or less depressed?” Determining the MCID for BDI-II scores would be helpful in determining the minimum change in score that is clinically relevant.

5.4.5 Can improvements in depression as determined by BDI-II scores be sustained beyond 12 months?

This would entail a future trial with a follow up period in excess of 12 months. Needless to say, this would require both considerable funding and sufficient participants enrolled.

5.4.6 Lessons learned

With the benefit of hindsight, the study design could have been tweaked recognising that different components of the study generated important information. Participants could have been asked to capture the names and dosage of any drugs that participants were currently taking for their mental health. Perhaps with a view to reducing or eliminating half marks as responses in

BDI-II questionnaire, a greater emphasis could have been made to ensure only a single response per question.

It is clear that if this study were to be replicated on a larger scale in multiple centres, then it would have to be recognized that patient preference would play an important role in allocation of treatment arm. Clearly, randomization would not be possible, meaning only quasi-experimental trials could be conducted. With the added difficulty of blinding, the study design would be more in line with patient preference trials. This ties in with empowering the patients and giving them choices in the management of depression.

5.5 Conclusion

The Neural Health Project has been a pioneering study in Canada with findings suggesting that integrative medical care approach is better than standard medical care in the management of adult unipolar depression. An integrated approach centered around the patient clearly has benefits as demonstrated by the results of this study. It is hoped that future researchers will conduct further trials to answer some of the questions raised by this study.

In this author's view, the most important consideration from The Neural Health Project is that it has shown that there are other pathways to treating depression, beyond conventional standard medical care based on antidepressants alone.

Further, the findings of my study may be of interest to both physician and patients dealing with depression of varying severity, including treatment resistant depression, and help in carrying forward the conversation as to what can be done for these substantial number of individuals.

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APPENDICES

APPENDIX A: Ethics Approval



Biomedical Research Ethics Board (Bio-REB) 08-Aug-2022

Certificate of Re-Approval

Ethics Number: 17-119

Principal Investigator: Anne Leis

Department: Department of Community Health and Epidemiology

Locations Where Research

Activities are Conducted: Mediclinic, Canada
University of Saskatchewan Student Wellness Center, Canada
Health Sciences Building, Canada

Student(s): Amanjot Kaur
Chrys Henry
Joshua Allen

Funder(s): Saskatchewan Health Research Foundation

Sponsor:

Title: Impact of an Integrative Medical Approach on Depressive Symptoms in Patients Attending a Family Practice Clinic

Approval Effective Date: 12-Aug-2022

Expiry Date: 12-Aug-2023

Acknowledgment Of:

Review Type: Delegated Review

IRB Registration Number: Not Applicable

* This study, inclusive of all previously approved documents, has been re-approved until the expiry date noted above

CERTIFICATION

The University of Saskatchewan Biomedical Research Ethics Board (Bio-REB) has reviewed the above-named project. The project was found to be acceptable on scientific and ethical grounds. The principal investigator is responsible for obtaining any other administrative or regulatory approvals that may pertain to this project, and for ensuring that the authorized project is carried out according to governing law. This approval is valid for the specified period, provided there is no change to the approved project.

FIRST TIME REVIEW AND CONTINUING APPROVAL

The University of Saskatchewan Research Ethics Boards review above minimal risk projects at full-board meetings. If a project is reviewed at a full-board meeting, any subsequent projects being added with the same protocol may be reviewed through the delegated review process. Research classified as minimal risk is reviewed through the delegated review process. The initial Certificate of Approval indicates the approval period the REB has assigned to a study.

To remain in compliance, the REB must receive a status report form (renewal or closure) prior to the assigned expiry date each year. Any specific requirements of the sponsoring organizations deemed necessary for continuing ethics review (e.g., requirement for full-board review and approval) should be indicated by the researcher to the REB. Any change to the approved project must be reported to the Chair of the Bio-REB for consideration in advance of its implementation through the amendment process.

REB ATTESTATION

In respect to clinical trials, the University of Saskatchewan Bio-REB complies with the membership requirements for Research Ethics Boards defined in Part 4 of the Natural Health Products Regulations and Part C Division 5 of the Food and Drug Regulations, and carries out its functions in a manner consistent with Good Clinical Practices. The University of Saskatchewan is constituted and operates in accordance with the current version of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans - TCPS 2 (2018). If a member of the REB is named as an investigator on a project under review, the member is absent from REB deliberations and decisions regarding the project. This approval and the views of the Bio-REB have been documented in writing.

*Digitally Approved by Dr. Ildiko Badea, Ph.D.
Chair, Biomedical Research Ethics Board
University of Saskatchewan*

APPENDIX B: Centre for Epidemiological Studies Depression Scale

Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

	During the Past			
	Week	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)
1. I was bothered by things that usually don't bother me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. I did not feel like eating; my appetite was poor.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. I felt that I could not shake off the blues even with help from my family or friends.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. I felt I was just as good as other people.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. I had trouble keeping my mind on what I was doing.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. I felt depressed.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. I felt that everything I did was an effort.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. I felt hopeful about the future.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. I thought my life had been a failure.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. I felt fearful.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. My sleep was restless.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. I was happy.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. I talked less than usual.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. I felt lonely.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. People were unfriendly.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. I enjoyed life.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. I had crying spells.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. I felt sad.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. I felt that people dislike me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. I could not get "going."	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

APPENDIX C: Demographic Questionnaire

Study Number: _____

Demographic Questionnaire

1. Study Number: _____
2. Sex: Female
 Male
3. Date of Birth: Year: _____ Month: _____ Day: _____
4. How would you describe your ethnicity?

5. Where were you born?

6. Were you born vaginally or by caesarean section?
 Vaginally
 By caesarean section
 Don't know
7. Were you bottle fed or breast fed?
 Bottle fed
 Breast fed
 Don't know
8. When you were a child and teenager, did you live mostly in a city, a town, or in the country?
 Mostly in a city
 Mostly in a town
 Mostly in the country

Study Number: _____

9. In what year did you move to Saskatoon?

- I've lived in Saskatoon all my life
- I don't live in Saskatoon, I live in: _____

10. Are you currently enrolled as a full-time or part-time student?

- Yes, full-time
- Yes, part-time
- No

11. How would you describe your highest level or formal education?

- University degree
- Some university, but no degree
- College degree
- Some college, but no degree
- High school diploma (or equivalent)
- Some high school, but no diploma
- No high school

12. Which of the following best describes your current household composition?

- 1 single adult only
- 1 single adult + at least one child under 15
- Married / domestic partnership – adults only
- Married / domestic partnership – at least one child under 16
- Multiple adults aged 16+ only
- Multiple adults aged 16+ and at least one child under 16

13. Have you worked at a job or business at *any time* during the past 12 months?

- Yes
- No > go to Question 18

14. Have you worked all 12 months?

- Yes > Go to Question 16
- No

Study Number: _____

15. How many months did you work during the past 12 months? _____

16. Last week, were you working at a job or business, including self-employment?

Yes

No

17. Last week, did you have a job or business from which you were absent?

Yes, but on vacation, paid leave, ill, on strike or lock-out, or absent for other reason

Yes, but on temporary lay-off from a job and expect to return soon

No

18. Do you have definite arrangements to start a new job within the next few weeks?

Yes > Go to Question 20

No

19. If you answered "No" to question 18, what is the main reason you are not currently working at a job or business?

Your own illness or disability

Your own long-term disability

Caring for own children

Caring for elderly relatives

Other personal or family responsibilities

Vacation

School or educational leave

Retired

Believe there is no work available

Other (please specify): _____

Don't know

Decline to answer

Study Number: _____

20. Which of the following best describes your total combined family income for your household for the past 12 months? This should include income (before taxes) from all sources, wages, rent from properties, social assistance, unemployment benefits, worker's compensation, help from relatives (including child support payments and alimony), etc.?

- Less than \$25,000
- \$25,000 to \$49,999
- \$50,000 to \$74,999
- \$75,000 to \$99,999
- \$100,000 to \$149,999
- \$150,000 or greater
- Don't know

21. Generally speaking, how would you describe your overall health?

- Excellent
- Very good
- Fair
- Poor

22. Generally speaking, how happy are you with your life? Are you:

- Very happy
- Somewhat happy
- Somewhat unhappy
- Generally unhappy

Study Number: _____

23. Have you ever been diagnosed with a medical condition?

Yes No Do not know

24. Do you have any of the following medical conditions? Please check yes or no for each one. If you have the condition, please write the year you were diagnosed, if known.

Condition	Do you have this condition?		Year Diagnosed, if known:
	Yes	No	
Heart Disease	Yes	No	
Diabetes	Yes	No	
Cancer	Yes	No	
High Blood Pressure	Yes	No	
Asthma/Lung Disease/COPD/Emphysema	Yes	No	
Bleeding/Clots	Yes	No	
Stroke	Yes	No	
Thyroid Problems	Yes	No	
Arthritis	Yes	No	
Mental Health Problems	Yes	No	
Other, please specify:	Yes	No	

APPENDIX D: Beck Depression Inventory-II

Study Number: _____

Beck's Depression Inventory

Please circle the number which best indicates how you are currently feeling.

1.
 - 0 I do not feel sad.
 - 1 I feel sad.
 - 2 I am sad all the time and I can't snap out of it.
 - 3 I am so sad and unhappy that I can't stand it.

2.
 - 0 I am not particularly discouraged about the future.
 - 1 I feel discouraged about the future.
 - 2 I feel I have nothing to look forward to.
 - 3 I feel the future is hopeless and that things cannot improve.

3.
 - 0 I do not feel like a failure.
 - 1 I feel I have failed more than the average person.
 - 2 As I look back on my life, all I can see is a lot of failures.
 - 3 I feel I am a complete failure as a person.

4.
 - 0 I get as much satisfaction out of things as I used to.
 - 1 I don't enjoy things the way I used to.
 - 2 I don't get real satisfaction out of anything anymore.
 - 3 I am dissatisfied or bored with everything.

5.
 - 0 I don't feel particularly guilty.
 - 1 I feel guilty a good part of the time.
 - 2 I feel quite guilty most of the time.
 - 3 I feel guilty all of the time.

6.
 - 0 I don't feel I am being punished.
 - 1 I feel I may be punished.
 - 2 I expect to be punished.
 - 3 I feel I am being punished.

7.
 - 0 I don't feel disappointed in myself.
 - 1 I am disappointed in myself.
 - 2 I am disgusted with myself.
 - 3 I hate myself.

8.
 - 0 I don't feel I am any worse than anybody else.
 - 1 I am critical of myself for my weaknesses or mistakes.
 - 2 I blame myself all the time for my faults.
 - 3 I blame myself for everything bad that happens.

- 9.
- 0 I don't have any thoughts of killing myself.
 - 1 I have thoughts of killing myself, but would not carry them out.
 - 2 I would like to kill myself.
 - 3 I would kill myself if I had the chance.
- 10.
- 0 I don't cry any more than usual.
 - 1 I cry more now than I used to.
 - 2 I cry all the time now.
 - 3 I used to be able to cry, but now I can't cry even though I want to.
- 11.
- 0 I am no more irritated by things than I ever was.
 - 1 I am slightly more irritated now than usual.
 - 2 I am quite annoyed or irritated a good deal of the time.
 - 3 I feel irritated all the time.
- 12.
- 0 I have not lost interest in other people.
 - 1 I am less interested in other people than I used to be.
 - 2 I have lost most of my interest in other people.
 - 3 I have lost all of my interest in other people.
- 13.
- 0 I make decisions about as well as I ever could.
 - 1 I put off making decisions more than I used to.
 - 2 I have greater difficulty in making decisions more than I used to.
 - 3 I can't make decisions at all anymore.
- 14.
- 0 I don't feel that I look any worse than I used to.
 - 1 I am worried that I am looking old or unattractive.
 - 2 I feel there are permanent changes in my appearance that make me look unattractive.
 - 3 I believe that I look ugly.
- 15.
- 0 I can work about as well as before.
 - 1 It takes extra effort to get started at doing something.
 - 2 I have to push myself very hard to do anything.
 - 3 I can't do any work at all.
- 16.
- 0 I can sleep as well as usual.
 - 1 I don't sleep as well as I used to.
 - 2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
 - 3 I wake up several hours earlier than I used to and cannot get back to sleep.
- 17.
- 0 I don't get more tired than usual.
 - 1 I get tired more easily than I used to.
 - 2 I get tired from doing almost anything.
 - 3 I am too tired to do anything.

Study Number: _____

- 18.
- 0 My appetite is no worse than usual.
 - 1 My appetite is not as good as it used to be.
 - 2 My appetite is much worse now.
 - 3 I have no appetite at all anymore.
- 19.
- 0 I haven't lost much weight, if any, lately.
 - 1 I have lost more than five pounds.
 - 2 I have lost more than ten pounds.
 - 3 I have lost more than fifteen pounds.
- 20.
- 0 I am no more worried about my health than usual.
 - 1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
 - 2 I am very worried about my physical problems and it's hard to think of much else.
 - 3 I am so worried about my physical problems that I cannot think of anything else.
- 21.
- 0 I have not noticed any recent change in my interest in sex.
 - 1 I am less interested in sex than I used to be.
 - 2 I have almost no interest in sex.
 - 3 I have lost interest in sex completely.

Appendix E: Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long to respond: your immediate reply is best.

1. I feel tense or 'wound up': <input type="checkbox"/> Most of the time <input type="checkbox"/> A lot of the time <input type="checkbox"/> From time to time, occasionally <input type="checkbox"/> Not at all	8. I feel as if I am slowed down: <input type="checkbox"/> Nearly all the time <input type="checkbox"/> Very often <input type="checkbox"/> Sometimes <input type="checkbox"/> Not at all
2. I still enjoy the things I used to enjoy: <input type="checkbox"/> Definitely as much <input type="checkbox"/> Not quite so much <input type="checkbox"/> Only a little <input type="checkbox"/> Hardly at all	9. I get a sort of frightened feeling like 'butterflies' in the stomach: <input type="checkbox"/> Not at all <input type="checkbox"/> Occasionally <input type="checkbox"/> Quite Often <input type="checkbox"/> Very Often
3. I get a sort of frightened feeling as if something awful is about to happen: <input type="checkbox"/> Very definitely and quite badly <input type="checkbox"/> Yes, but not too badly <input type="checkbox"/> A little, but it doesn't worry me <input type="checkbox"/> Not at all	10. I have lost interest in my appearance: <input type="checkbox"/> Definitely <input type="checkbox"/> I don't take as much care as I should <input type="checkbox"/> I may not take quite as much care <input type="checkbox"/> I take just as much care as ever
4. I can laugh and see the funny side of things: <input type="checkbox"/> As much as I always could <input type="checkbox"/> Not quite so much now <input type="checkbox"/> Definitely not so much now <input type="checkbox"/> Not at all	11. I feel restless as I have to be on the move: <input type="checkbox"/> Very much indeed <input type="checkbox"/> Quite a lot <input type="checkbox"/> Not very much <input type="checkbox"/> Not at all
5. Worrying thoughts go through my mind: <input type="checkbox"/> A great deal of the time <input type="checkbox"/> A lot of the time <input type="checkbox"/> From time to time, but not too often <input type="checkbox"/> Only occasionally	12. I look forward with enjoyment to things: <input type="checkbox"/> As much as I ever did <input type="checkbox"/> Rather less than I used to <input type="checkbox"/> Definitely less than I used to <input type="checkbox"/> Hardly at all
6. I feel cheerful: <input type="checkbox"/> Not at all <input type="checkbox"/> Not often <input type="checkbox"/> Sometimes <input type="checkbox"/> Most of the time	13. I get sudden feelings of panic: <input type="checkbox"/> Very often indeed <input type="checkbox"/> Quite often <input type="checkbox"/> Not very often <input type="checkbox"/> Not at all
7. I can sit at ease and feel relaxed: <input type="checkbox"/> Definitely <input type="checkbox"/> Usually <input type="checkbox"/> Not Often <input type="checkbox"/> Not at all	14. I can enjoy a good book or radio or TV program: <input type="checkbox"/> Often <input type="checkbox"/> Sometimes <input type="checkbox"/> Not often <input type="checkbox"/> Very seldom

Appendix F: Child Experience Questionnaire

Childhood Experience Questionnaire

Please answer yes or no to the following questions.

While you were growing up, during your first 18 years of life:

1. Did a parent or other adult in the household often ... Swear at you, insult you, put you down, or humiliate you? or Act in a way that made you afraid that you might be physically hurt?	Yes	No
2. Did a parent or other adult in the household often ... Push, grab, slap, or throw something at you? or Ever hit you so hard that you had marks or were injured?	Yes	No
3. Did an adult or person at least 5 years older than you ever ... Touch or fondle you or have you touch their body in a sexual way? or Try to or actually have oral, anal, or vaginal sex with you?	Yes	No
4. Did you often feel that ... No one in your family loved you or thought you were important or special? or Your family didn't look out for each other, feel close to each other, or support each other?	Yes	No
5. Did you often feel that ... You didn't have enough to eat, had to wear dirty clothes, and had no one to protect you? or Your parents were too drunk or high to take care of you or take you to the doctor if you needed it?	Yes	No
6. Were your parents ever separated or divorced?	Yes	No
7. Was your mother or stepmother: Often pushed, grabbed, slapped, or had something thrown at her? or Sometimes or often kicked, bitten, hit with a fist, or hit with something hard? or Ever repeatedly hit over at least a few minutes or threatened with a gun or knife?	Yes	No
8. Did you live with anyone who was a problem drinker or alcoholic or who used street drugs?	Yes	No
9. Was a household member depressed or mentally ill or did a household member attempt suicide?	Yes	No
10. Did a household member go to prison?	Yes	No