Faculty of Medicine
University of Helsinki

MELANCHOLIA OR NOT; THE MYSTERIOUS DIFFERENCES IN DEPRESSION

A STUDY OF PATHOPHYSIOLOGICAL DIFFERENCES BETWEEN DEPRESSIVE SUBTYPES – FINDINGS FROM THE HELSINKI BIRTH COHORT STUDY

Mia D. Eriksson

DOCTORAL DISSERTATION

To be presented for public discussion with the permission of the Faculty of Medicine of the University of Helsinki, in Hall 107 of the Athena Building, on the 21st of April 2023 at 12 o'clock.

Helsinki 2023

University of Helsinki
Faculty of Medicine
Doctoral Programme in Population Health

Folkhälsan
Folkhälsan Research Center
Public Health Research Program

Supervised by

Associate Professor Merja Laine, MD, PhD
Department of General Practice and Primary Health Care
University of Helsinki and Helsinki University Hospital
Helsinki, Finland

Professor Päivi Korhonen, MD, PhD
Department of General Practice
University of Turku and Turku University Hospital
Turku, Finland

Reviewed by

Professor Jorma Lahtela, MD, PhD
Department of Medicine
University of Tampere
Tampere, Finland

Professor Markku Timonen, MD, PhD
Research Unit of Population Health
University of Oulu
Oulu, Finland

Opponent

Professor Peter Nilsson, MD, PhD
Faculty of medicine
Lund University
Lund, Sweden

Cover art by Mia D. Eriksson, 2023

The Faculty of Medicine uses the Ouriginal system (plagiarism recognition) to examine all doctoral dissertations.

ISBN 978-951-51-9017-8 (softcover)
ISBN 978-951-51-9018-5 (PDF)

Unigrafia
Helsinki 2023

ABSTRACT

UNIVERSITY OF HELSINKI
Faculty of Medicine
Department of General Practice and Primary Health Care
FOLKHÄLSAN
Folkhälsan Research Center
Public Health Research Program
MIA D. ERIKSSON: Melancholia or Not; The Mysterious Differences in Depression
A Study of Pathophysiological Differences Between Depressive Subtypes – Findings from The Helsinki Birth Cohort Study
Doctoral Dissertation 165 p.
Doctoral Programme in Population Health
April 2023

Depressive symptoms are behaviors and thought processes typical of depression. These symptoms can be classified into subtypes of depressive symptomatology based on established criteria. The depressive subtypes are known to differ in their presentation, but much is still unknown about their possible pathophysiologic differences.

This study aimed to shed light on some of the pathophysiologic differences between melancholic and non-melancholic depressive symptoms. The study utilized the Helsinki Birth Cohort Study population. Depressive symptoms were determined based on subtyping developed from the criteria for melancholia in the Diagnostic and Statistical Manual of Mental Disorders. Advanced glycation end products, pulse wave velocity, body composition, and mortality were analyzed for each subtype and compared.

Depressive symptoms were more common among women, were associated with less physical activity, lower likelihood of cohabitation, and lower likelihood of financial satisfaction. Comorbidities were also more common among those with depressive symptoms. Subtypes differed in regard to cholesterol, blood pressure, body mass index and fat mass.

It was shown that melancholic depressive symptoms are more closely related to advanced glycation end products and mortality, whereas non-melancholic depressive symptoms are more closely related to pulse wave velocity, body composition and impaired glucose regulation.

In conclusion, the depressive subtypes seemed to show differing pathophysiology. This may suggest that the two subtypes represent differing disease processes that present with similar symptomatology.

KEYWORDS: advanced glycation end products, Beck Depression Inventory, body composition, depressive symptoms, fat mass index, lean mass index, melancholic, mortality, non-melancholic, pulse wave velocity

ACKNOWLEDGEMENTS

During the spring of 2020, when COVID-19 was running rampant all around the globe, I was isolated in my apartment in Texas during the stay-at-home order. I graduated medical school with a doctorate in osteopathic medicine during these unprecedented times. My plans were still up in the air when an opportunity to get involved in some research presented itself. I had never planned for an academic doctorate, but the COVID pandemic changed my plans as for so many others. I hesitate to thank the pandemic, but without it this thesis may never have been written.

A sincere thank you to Dr Gary Boehm and Dr Michael Chumley for convincing me to dip my toes into the mysterious waters of research years ago, and for teaching me all the basics upon which I have been able to build what has allowed me to get to this point of my academic career. Lately I have often thought about how resistant I was at the beginning. Thank you, Gary, for that extra push I needed!

A heartfelt thank you goes out to Folkhälsan for their support and facilitation of my research endeavor. I am immensely grateful for the entire research group that has allowed me to use the data collected for the Helsinki Birth Cohort Study. The collegiality and support has been fantastic, and I am extremely appreciative of each of the individuals involved in this project. Each co-author has taught me a great deal about science and research. Thank you for your time and patience Mikaela von Bonsdorff, Johan Eriksson, Eero Kajantie, Hannu Kautiainen, Hannu Koponen, Päivi Korhonen, Merja Laine, Tuija Mikkola, Minna Salonen, and Niko Wasenius. I am also very grateful to The Finnish Medical Society Duodecim that has generously supported this project through grant funding.

I am grateful for the opportunity to carry out my thesis work as part of the Doctoral Programme in Population Health at the University of Helsinki. Thank you to my fantastic advisors Dr Merja Laine and Dr Päivi Korhonen for all their support, encouragement, and professional advice. I could not possibly have asked for two kinder and more supportive mentors for this project.

A very special thank you goes to Hannu Kautiainen for his work on the statistical aspects of this project; for his support and advice, and his numerous hours spent on helping and teaching me. I would also like to thank Hannu for his beautiful singing that always puts a smile on my face!

The reviewers of this thesis, Dr Jorma Lahtela and Dr Markku Timonen have offered their insights and support of which I am very thankful. Through their constructive criticism I have been able to produce a better thesis. I would also like to thank Dr Timo Strandberg and Dr Taisto Sarkola for their support as members of my thesis committee. Thank you to Dr Peter Nilsson for agreeing to act as the opponent for the defense of this thesis.

Completing a doctoral thesis is not something I could ever have achieved alone. In addition to the great professional support, I have also been lucky enough to have been supported by friends and family throughout the process. I am immensely appreciative of the fantastic people in my life. None of this would have been possible without them. My father has been closely involved and helped along the way. He has answered hundreds of questions and supported me each step of the way. My mother has cooked a whole number of meals and brewed too many pots of coffee to count. She has taken care of the dog, and allowed me to sleep in when I needed it the most. Thank you from the bottom of my heart to both my parents, and the rest of my family; Tove, Saku, Hanna, and Heidi. Thank you, Noor, for all the cuddles and the doggy-kisses along the way.

Thank you, Magdaline, for lending me your immense linguistic skills by proofreading my work, and for believing in me more than I could ever have asked for. Thank you, Alex, for the numerous pots of coffee, late night conversations, and the never-ending belief in my abilities. Thank you, Jessica, for always knowing when I needed a hug more than anything else. Thank you to all my fantastic friends for putting up with my intense schedule during this time!

Last but not least, I would also like to thank all of my wonderful and inspiring colleagues who have been with me on this journey.

Thank you to each and every one for the support!

Helsinki, March 2023

Mia D. Eriksson

TABLE OF CONTENTS

Abstract....2
Acknowledgements....4
Table of Contents....6
List of Original Publications....9
Abbreviations....10
1 Introduction....11
2 Review of the Literature....13
2.1 Overview of Depressive Symptoms....13
2.1.1 Subtypes of Depressive Symptoms....14
2.1.2 Grouping into Melancholic and Non-Melancholic Subgroups....16
2.2 Epidemiology of Depressive Symptoms....17
2.2.1 Prevalence and Burden of Disease....17
2.2.2 Sociodemographics of Depressive Symptoms....17
2.2.3 Epidemiology of Depressive Subtypes....20
2.3 Detection of Depressive Symptoms....21
2.3.1 Diagnostic and Statistical Manual of Mental Disorders-IV....21
2.3.2 The Beck Depression Inventory....22
2.4 Pathophysiology of Depressive Symptoms....23
2.4.1 Biological Dysregulations....23
2.4.1.1 Hypothalamic-Pituitary-Adrenal-axis....23
2.4.1.2 Glucose Metabolism....24
2.4.1.3 Body Composition....25
2.4.1.4 Inflammatory Pathways....25
2.4.1.5 Vascular Factors....26
2.4.2 Genetics....27
2.4.3 Environmental and Psychological Factors....28
2.4.4 Lifestyle choices....28
2.4.4.1 Smoking....28
2.4.4.2 Alcohol....29
2.4.4.3 Physical Activity....29
2.5 Novel Aspects of Pathophysiology of Depressive Symptoms....30
2.5.1 Depressive Symptoms and Advanced Glycation End Products....30
2.5.1.1 Advanced Glycation End Products....30
2.5.1.2 Underlying Mechanisms....31
2.5.1.3 Subtypes of Depressive Symptoms and Advanced Glycation End Products....31
2.5.2 Depressive Symptoms and Pulse Wave Velocity....33
2.5.2.1 Pulse Wave Velocity....33
2.5.2.2 Underlying Mechanisms....34

2.5.2.3 Subtypes of Depressive Symptoms and Pulse Wave Velocity 35
2.5.3 Depressive Symptoms and Body Composition 35
2.5.3.1 Body Composition 35
2.5.3.2 Underlying Mechanisms 36
2.5.3.3 Subtypes of Depressive Symptoms and Body Composition 37
2.5.4 Depressive Symptoms and Glucose Metabolism 37
2.5.4.1 Impaired Glucose Regulation 37
2.5.4.2 Underlying Mechanisms 38
2.5.4.3 Subtypes of Depressive Symptoms and Glucose Metabolism 38
2.5.5 Depressive Symptoms and Mortality 38
2.5.5.1 Depressive Symptoms and All-Cause Mortality 38
2.5.5.2 Underlying Mechanisms 39
2.5.5.3 Subtypes of Depressive Symptoms and Mortality 40
3 Aims 41
4 Materials and Methods 42
4.1 Helsinki Birth Cohort Study 42
4.1.1 Study Participants 42
4.2 Methods 44
4.2.1 Questionnaires 44
4.2.1.1 Depressive Symptoms 44
4.2.1.1.1 The Beck Depression Inventory 44
4.2.1.1.1.1 Depressive Subgroup Division 44
4.2.1.1.2 Mental Health Inventory-5 48
4.2.1.2 Sociodemographic Factors 48
4.2.1.3 Lifestyle Factors 48
4.2.1.4 Health and Medication 48
4.2.2 Physical Examination 49
4.2.2.1 Blood Pressure 49
4.2.2.2 Height, Weight, Body Mass Index 49
4.2.2.3 Advanced Glycation End Product Measurements and Analysis 50
4.2.2.4 Pulse Wave Velocity Measurements and Analysis 50
4.2.2.5 Body Composition Measurement and Analysis 51
4.2.3 Laboratory Measurements 52
4.2.4 Mortality 52
4.3 Statistical Analyses 53
4.4 Ethics 54
5 Results 55
5.1 Prevalence of Depressive Symptoms 55
5.1.1 Depressive Subgroups 55

5.2 Sociodemographic and Lifestyle Factors Associated with Depressive Symptoms 58
5.3 Advanced Glycation End Products and Depressive Symptoms (Study I) 59
5.3.1 Subtypes of Depressive Symptoms and Advanced Glycation End Products.....59
5.4 Pulse Wave Velocity and Depressive Symptoms (Study II) 61
5.4.1 Pulse Wave Velocity in Non-Melancholic Depressive Men 61
5.5 Body Composition and Depressive Symptoms (Study III) 64
5.5.1 Non-Melancholic Depressive Symptoms and Body Composition 64
5.5.2 Melancholic Depressive Symptoms and Body Composition.....65
5.6 Glucose Metabolism, Body Composition, and Depressive Symptoms (Study III) 68
5.7 All-Cause Mortality and Depressive Symptoms (Study IV) 70
5.7.1 Causes of Death.....72
5.7.2 Standardized Mortality Ratio.....72
6 Discussion.....73
6.1 Participants 73
6.2 Methods 74
6.2.1 Assessment of Depressive Symptoms 74
6.2.1.1 The Beck Depression Inventory.....74
6.2.2 Self-Reported Questionnaires 76
6.2.3 Clinical and Laboratory Measurements 76
6.2.4 Mortality.....78
6.3 Results.....79
6.3.1 Prevalence of Depressive Symptoms 79
6.3.1.1 Depressive Subgroups..... 80
6.3.2 Sociodemographic and Lifestyle Factors Associated with Depressive Symptoms..... 80
6.3.3 Advanced Glycation End Products and Depressive Symptoms (Study I) 82
6.3.4 Pulse Wave Velocity and Depressive Symptoms (Study II) 84
6.3.5 Body Composition and Depressive Symptoms (Study III) 86
6.3.6 Glucose Metabolism and Depressive Symptoms (Study III) ...87
6.3.7 All-Cause Mortality and Depressive Symptoms (Study IV) 87
6.4 Strengths and Limitations 89
6.5 Implications for Future Research..... 91
7 Conclusions 93
References 94
Original Publications 121
Appendices..... 161

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Eriksson, M. D., Eriksson, J. G., Kautiainen, H., Salonen, M. K., Mikkola, T. M., Kajantie, E., Wasenius, N., von Bonsdorff, M., & Laine, M. K. (2021). Advanced glycation end products measured by skin autofluorescence are associated with melancholic depressive symptoms - Findings from Helsinki Birth Cohort Study. *Journal of psychosomatic research*, *145*, 110488. https://doi.org/10.1016/j.jpsychores.2021.110488

II Eriksson, M. D., Eriksson, J. G., Kautiainen, H., Salonen, M. K., Mikkola, T. M., Kajantie, E., Wasenius, N., von Bonsdorff, M., Korhonen, P., & Laine, M. K. (2021). Higher carotid-radial pulse wave velocity is associated with non-melancholic depressive symptoms in men - findings from Helsinki Birth Cohort Study. *Annals of medicine*, *53*(1), 531–540. https://doi.org/10.1080/07853890.2021.1904277

III Eriksson, M. D., Eriksson, J. G., Korhonen, P., Salonen, M. K., Mikkola, T. M., Kajantie, E., Wasenius, N. S., von Bonsdorff, M., Kautiainen, H., & Laine, M. K. (2022). Non-melancholic depressive symptoms are associated with above average fat mass index in the Helsinki birth cohort study. *Scientific reports*, *12*(1), 6987. https://doi.org/10.1038/s41598-022-10592-3

IV Eriksson, M. D., Eriksson, J. G., Korhonen, P., Koponen, H., Salonen, M. K., Mikkola, T. M., Kajantie, E., Wasenius, N. S., von Bonsdorff, M., Kautiainen, H., & Laine, M. K. (2023). Depressive symptoms and mortality-findings from Helsinki birth cohort study. *Acta psychiatrica Scandinavica*, *147*(2), 175–185. https://doi.org/10.1111/acps.13512

The publications are referred to in the text by their roman numerals.

ABBREVIATIONS

AGE	advanced glycation end product
ANOVA	analysis of variance
AU	arbitrary units
BDI	Beck depression inventory
BDI-IA	Beck depression inventory version 1a
BMI	body mass index
CCI	Charlson comorbidity index
cfPWV	carotid-femoral pulse wave velocity
CI	confidence interval
CRP	C-reactive protein
crPWV	carotid-radial pulse wave velocity
CVD	cardiovascular disease
DM	diabetes mellitus
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-IV
FMI	fat mass index
HbA_{1c}	glycated hemoglobin A1c
HBCS	Helsinki Birth Cohort Study
HDL	high density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
ICD	international classification of disease
LDL	low density lipoprotein
LTPA	leisure-time physical activity
LMI	lean mass index
MAP	mean arterial pressure
MDD	major depressive disorder
MeD	melancholic depression
MET	metabolic equivalent of task
MHI-5	mental health inventory-5
MINI	Mini International Neuropsychiatric Interview
NMeD	non-melancholic depression
OGTT	oral glucose tolerance test
OR	odds ratio
PWV	pulse wave velocity
SAF	skin autofluorescence
SD	standard deviation
SF-36	Short Form-36
SMR	standardized mortality ratio
YLD	years of healthy life lost due to disability
WHO	World Health Organization

1 INTRODUCTION

Depression is a major health problem globally, with over 322 million people being affected (WHO, 2017a). In the older population depression is still far under-identified (WHO, 2017b). Depression is a major contributor to the global burden of disease (WHO, 2020), and is the most common cause of years of healthy life lost due to disability (YLD) worldwide (WHO, 2017a). It is predicted to be the leading global cause of burden of disease by the year of 2030 (Malhi & Mann, 2018). Depression is more common in the general population of Finland as compared to the global prevalence (Global Burden of Disease Collaborative Network, 2020).

Depression does not have one specific known cause, but is likely caused by a combination of multiple underlying factors presenting simultaneously to trigger depressive symptoms (Malhi & Mann, 2018; WHO, 2021b). Some known factors that may promote depression are genetics, psychological factors, physiology, environment, and lifestyle choices (Akil et al., 2018; Lamers et al., 2013; Malhi & Mann, 2018; Milano et al., 2020; Penner-Goeke & Binder, 2019; Penninx et al., 2013).

According to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) major depressive disorder (MDD) can present in different forms such as psychotic, catatonic, melancholic, atypical, or postpartum (American Psychiatric Association, 1998). Postpartum depression is set by timing, not specific symptoms (American Psychiatric Association, 1998). Psychotic depression indicates a depressive episode that contains delusions or hallucinations, but does not specify any other symptoms (American Psychiatric Association, 1998). Catatonic depression specifies depression with major psychomotor symptoms (American Psychiatric Association, 1998). Atypical depression features mood reactivity, sensitivity to interpersonal rejection, weight gain, hypersomnia, and leaden paralysis (American Psychiatric Association, 1998). Melancholic depression (MeD) displays nearly complete lack of pleasure with virtually no brightening of mood, psychomotor symptoms, weight loss, excessive guilt, morning awakenings from sleep and worse symptoms in the morning, (American Psychiatric Association, 1998). Postpartum depression and psychotic depression do not differentiate based on overall symptomatology and are therefore not used as categories in this thesis. This leaves us with MeD, and the non-melancholic depressive (NMeD) types catatonia and atypical depression. Catatonic depression is so rare that the NMeD group for all intents and purposes is the same as the atypical group (Penninx et al., 2013).

Depression is a heterogenous disorder that is still not very well understood (Akil et al., 2018; Malhi & Mann, 2018). Even though the prevalence of depression has been increasing, our ability to diagnose and treat it is still lacking (Akil et al., 2018; Malhi & Mann, 2018). It is known that different subtypes of depression exist and that these behave differently, but no objective measures to diagnose these subtypes exist (Akil et al., 2018). It has also been shown that the subtypes may behave differently in response to treatment, making it a factor of importance (Akil et al., 2018). It is known that some pathophysiological differences do exist between the depressive subtypes (Lamers et al., 2013; Penninx et al., 2013). Differences between types of depression may at least partially explain some of these unknowns surrounding depression. By studying the subtypes, one could hopefully further the understanding of depression as a disorder and in the future possibly start to focus treatments more efficiently toward specific subtypes.

This thesis conducted comparisons of factors hypothesized to affect the depressive subtypes differently. The aim was to further the understanding of differences between NMeD and MeD pathophysiology. Using the cohort participants of the Helsinki Birth Cohort Study (HBCS) the thesis focused on differences between the depressive subtypes in advanced glycation end products (AGE), pulse wave velocity (PWV), body composition, glucose metabolism, and mortality.

2 REVIEW OF THE LITERATURE

2.1 OVERVIEW OF DEPRESSIVE SYMPTOMS

Depression is a mood disorder characterized by episodes of depressed mood and lack of interest in most things (American Psychiatric Association, 1998). Depressive symptoms can be feelings of sadness or emptiness, irritability, and loss of pleasure or interest (American Psychiatric Association, 1998; WHO, 2021b). Other possible symptoms include problems with concentration, excessive guilt, low self-esteem, hopelessness, thoughts surrounding death, sleep disruptions, changes in weight and appetite, low energy and feeling tired (American Psychiatric Association, 1998; WHO, 2021b).

There are cultural differences in how depression is expressed, leading some to express more somatic symptoms such as pain and weakness rather than explicit psychological symptoms such as changes in mood (American Psychiatric Association, 1998; WHO, 2021b). Children and youth often express irritability instead of depressed mood (American Psychiatric Association, 1998). Lack in recognition of these differences may lead to under-diagnosing MDD (American Psychiatric Association, 1998).

Depressive symptoms can present as a single episode or recurrent episodes (WHO, 2021b). If an episode includes daily symptoms for most of the day during a minimum of two weeks it is considered clinical depression (WHO, 2021b). The diagnostic criteria for major depression according to the DSM-IV are presented in Table 1. Depression is more severe than mood fluctuations or emotional responses to challenges, and can cause great suffering and serious health conditions (WHO, 2021b). It is the most common mental disorder according to the American Psychological Association (American Psychological Association, 2022) and is treatable (American Psychological Association, 2022; WHO, 2021b).

Depression is a heterogenous disorder (Akil et al., 2018; Penninx et al., 2013) that can be classified as mild, moderate, or severe depending on how severe the symptoms are and how much they affect the person's ability to function in their daily life (WHO, 2021b). Symptoms can develop over days or weeks before a full depressive episode presents (American Psychiatric Association, 1998). Untreated episodes frequently last around six months or even longer, with the majority of individuals eventually achieving full remission (American Psychiatric Association, 1998). MDD can be classified as being in full remission, partial remission, a current episode, or chronic (American Psychiatric Association, 1998). Having had previous MDD episodes

is a predictor for the likelihood of having another episode (American Psychiatric Association, 1998). The severity of the initial episode is also often predictive of the persistence of the disorder (American Psychiatric Association, 1998).

Individuals in the general population with MDD have more physical illnesses and decreased functioning as compared to their counterparts (American Psychiatric Association, 1998). It has also been shown that even depressive symptoms below the level required for a clinical diagnosis of MDD can negatively affect health outcomes (Ayuso-Mateos et al., 2010; Harshfield et al., 2020). Depression has been shown to increase risks of mortality, cardiovascular disease (CVD), diabetes mellitus (DM), obesity, Alzheimer's disease, and cancer (Penninx et al., 2013).

2.1.1 SUBTYPES OF DEPRESSIVE SYMPTOMS

MDD can be classified as psychotic, with catatonic features, with melancholic features, with atypical features, or with postpartum onset (American Psychiatric Association, 1998). Postpartum onset will not be discussed here, as that has to do with timing rather than specific symptoms being displayed. A depressive episode with psychotic features is always classified as severe (American Psychiatric Association, 1998). The psychotic features are usually delusions and hallucinations that are in line with the depression, and are most often transient (American Psychiatric Association, 1998). Other than the psychosis the psychotic specifier tells us nothing about the depression and its other symptoms, which is why this type of depression will not be discussed as a separate category.

MDD with catatonic features is reserved for those with marked psychomotor symptoms (American Psychiatric Association, 1998). MeD features (Table 2) are classified by the DSM-IV as nearly complete lack of pleasure with almost no brightening of mood, depressed mood usually being worse in the morning, morning awakenings from sleep, psychomotor symptoms, weight loss, and excessive guilt (American Psychiatric Association, 1998). Melancholic features more likely present in severe depressive episodes (American Psychiatric Association, 1998). According to the DSM-IV, depression with atypical features can be recognized by mood reactivity, weight gain, leaden paralysis, hypersomnia, an sensitivity to interpersonal rejection (American Psychiatric Association, 1998).

No specific laboratory tests for depression exist. The depressive subtypes are, however, known to differ in their pathophysiology (Lamers et al., 2013; Penninx et al., 2013).

Table 1. *Diagnostic criteria of major depression according to the Diagnostic and Statistical Manual of Mental Disorders-IV. (American Psychiatric Association, 1998, p. 327)*

Criteria for Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do not include symptoms that are clearly due to general medical condition, or mood-incongruent delusions or hallucinations.

1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feeling sad or empty) or observation made by others (e.g., appears tearful). **Note:** In children and adolescents, can be irritable mood.
2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. **Note:** In children, consider failure to make expected weight gains.
4) insomnia or hypersomnia nearly every day
5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6) fatigue or loss of energy nearly every day
7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

2.1.2 GROUPING INTO MELANCHOLIC AND NON-MELANCHOLIC SUBGROUPS

The specifier of psychotic depression primarily indicates severity of symptoms, rather than type of symptoms other than the psychosis and is therefore not categorized as a separate category of depressive subtypes (American Psychiatric Association, 1998). The three remaining subtypes are melancholic, atypical, and catatonic depression (American Psychiatric Association, 1998; Penninx et al., 2013). The proportion of catatonic depressive subjects in reality is so small that it is virtually negligible (Penninx et al., 2013). This allows for classification of MDD into two categories: melancholic and atypical (Penninx et al., 2013). By using the grouping of melancholic and non-melancholic, the non-melancholic group will consist of those who do not fall into the melancholic group. There is support for dividing depression into two groups of melancholic (or typical) and atypical (or non-melancholic) based on the nature of symptoms (Lamers et al., 2010, 2012; Penninx et al., 2013).

Table 2. *Diagnostic criteria for the melancholic specifier according to the Diagnostic and Statistical Manual of Mental Disorders-IV. (American Psychiatric Association, 1998, p. 384)*

Criteria for Melancholic Features Specifier

Specify if:

With Melancholic Features (can be applied to the current or most recent Major Depressive Episode in Major Depressive Disorder and to a Major Depressive Episode in Bipolar I or Bipolar II Disorder only if it is the most recent type of mood episode)

A. Either of the following, occurring during the most severe period of the current episode:

1) loss of pleasure in all, or almost all, activities
2) lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens)

B. Three (or more) of the following:

1) distinct quality of depressed mood (i.e., the depressed mood is experienced as distinctly different from the kind of feeling experienced after the death of a loved one)
2) depression regularly worse in the morning
3) early morning awakening (at least 2 hours before usual time of awakening)
4) marked psychomotor retardation or agitation
5) significant anorexia or weight loss
6) excessive or inappropriate guilt

2.2 EPIDEMIOLOGY OF DEPRESSIVE SYMPTOMS

2.2.1 PREVALENCE AND BURDEN OF DISEASE

The lifetime risk for MDD in adults has been reported as 10-25% for women and 5-12% for men, with the point prevalence being 5-9% for women and 2-3% for men in community samples (American Psychiatric Association, 1998).

According to the Global Burden of Disease Study, the prevalence [95% confidence interval (CI)] of depression globally for both sexes (Figure 1) in 2019 was 3.76% (3.33-4.17) for all ages, and 5.41% (4.52-6.40) for ages 70 and above [women: 6.17% (5.17-7.28); men: 4.44% (3.70-5.29)] (Global Burden of Disease Collaborative Network, 2020). The World Health Organization (WHO) has estimated that approximately 7% of older individuals are affected by depression, but that it is far under-identified in the older population (WHO, 2017b).

The prevalence (mean [95% CI]) of depression in 2019 for both sexes in Finland (Figure 2) was 5.00% (4.46-5.63) for all ages, and 4.95% (4.09-6.02) for age 70 and above (Global Burden of Disease Collaborative Network, 2020). For those age 70 and above in Finland in 2019 the prevalence was 5.44% (4.44-6.57) for women, and 4.33% (3.50-5.36) for men (Global Burden of Disease Collaborative Network, 2020).

According to the WHO, depression affects over 322 million people worldwide (WHO, 2017a). It is the leading cause of YLD in the world (WHO, 2017a) and contributes massively to the overall global burden of disease (WHO, 2020). For the global population above 60 years of age depression accounts for 5.7% of YLDs (WHO, 2017b). Depression is predicted to be the global leading cause of burden of disease by the year of 2030 (Malhi & Mann, 2018).

2.2.2 SOCIODEMOGRAPHICS OF DEPRESSIVE SYMPTOMS

Depressive symptoms are associated with worse health status than that of individuals without depression, but the severity of depression has no effect on this (Ayuso-Mateos et al., 2010). It has been suggested that there is no difference in risk factors for health outcomes between subthreshold depression and clinical depression (Ayuso-Mateos et al., 2010).

Individuals with overweight, and chronic disease are more likely to report depressive symptoms (van Gool et al., 2007). Compared to non-depressed individuals, the depressed population is older (Ayuso-Mateos et al., 2010; van Gool et al., 2007), more commonly women (American Psychiatric Association, 1998; Ayuso-Mateos et al., 2010; Hasin et al., 2018; Markkula et

al., 2017; van Gool et al., 2007; WHO, 2021b), less educated (Ayuso-Mateos et al., 2010; van Gool et al., 2007), and has a lower income (Hasin et al., 2018).

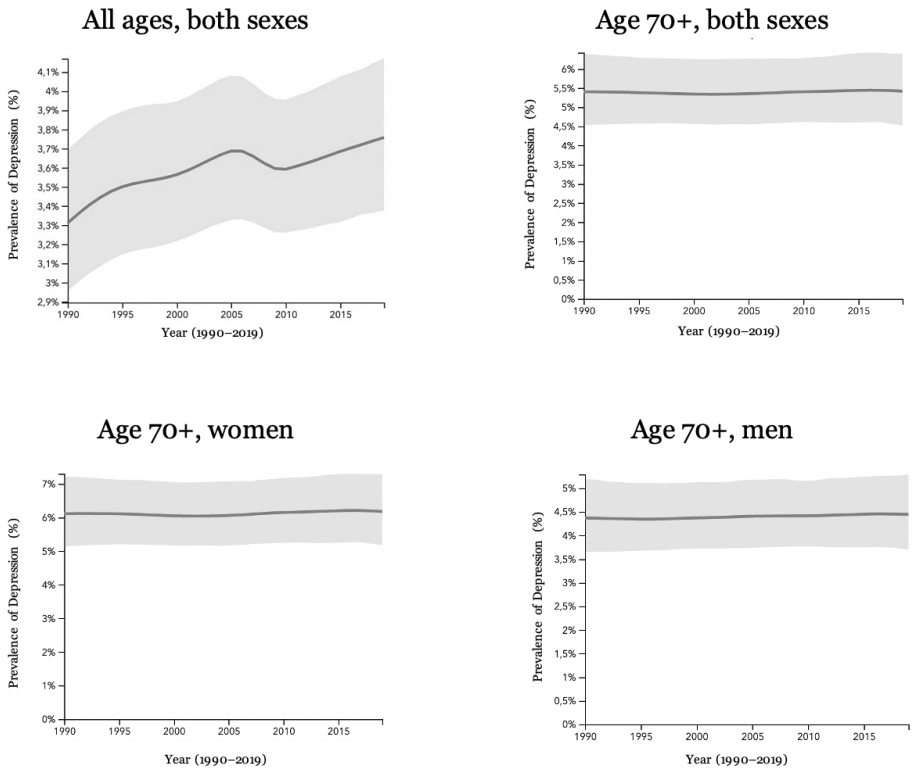


Figure 1 Prevalence of depressive disorders globally from 1990 to 2019. (Global Burden of Disease Collaborative Network, 2020)

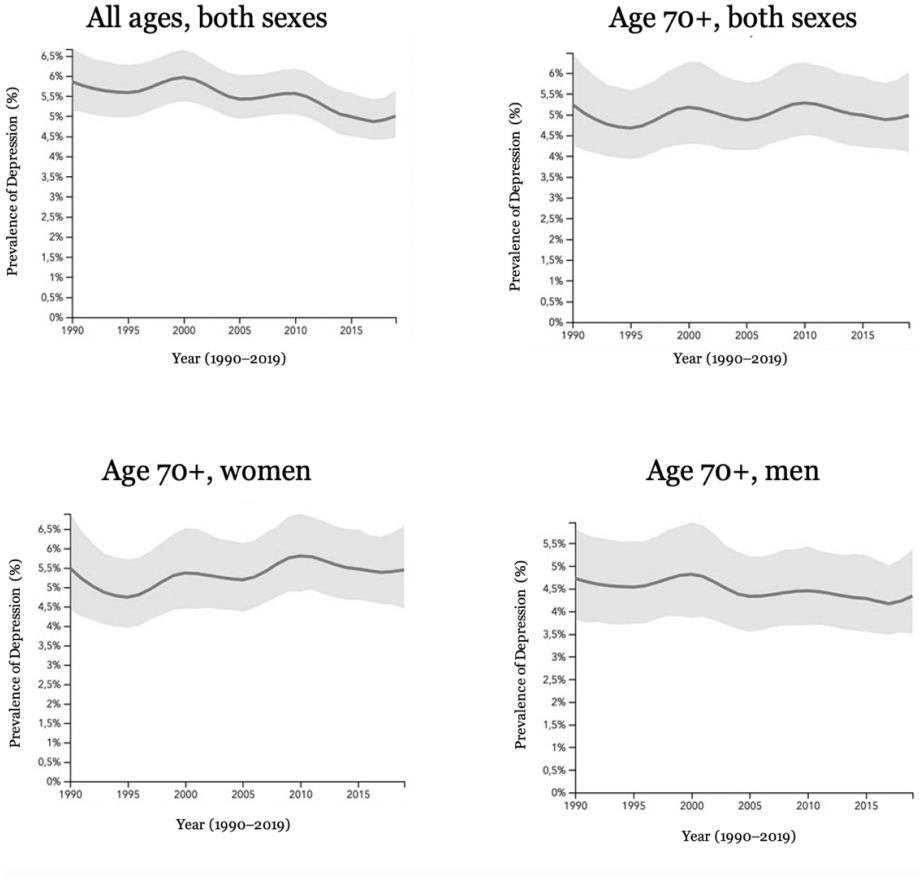


Figure 2 Prevalence of depressive disorders in Finland from 1990 to 2019. (Global Burden of Disease Collaborative Network, 2020)

On the other hand, it has also been suggested that depression may be more common among younger individuals, and that neither income nor education have any effect on depression (Markkula et al., 2017). On a global level depression has been found to be more common in high-income countries (Bromet et al., 2011). According to the DSM-IV work group neither ethnicity, education, income, nor marital status are related to prevalence of depression (American Psychiatric Association, 1998). However, a study in the United States found significant difference in depressive prevalence between ethnicities, with African American, Asian, and Hispanic adults displaying lower likelihood of MDD than Caucasians (Hasin et al., 2018).

2.2.3 EPIDEMIOLOGY OF DEPRESSIVE SUBTYPES

The prevalence of the depressive subtypes is not entirely known and depends somewhat on how the subgrouping has been done. Especially the criteria for diagnosing melancholia has significantly changed over time (M. Harris et al., 2011), making estimates of prevalence difficult. One study found individuals with MeD to account for 23.5% of individuals with depression (McGrath et al., 2008), and another reports MeD to represent 25-30% of depression (Gold & Chrousos, 2002).

Individuals with NMeD have been reported to more often be women (American Psychiatric Association, 1998; Brailean et al., 2020; Lamers et al., 2010, 2012; Rantanen et al., 2020), have higher body mass index (BMI) (Lamers et al., 2010, 2012; Rantanen et al., 2020; P. F. Sullivan et al., 2002), and have lower incomes (Brailean et al., 2020). They also have a younger onset of depression than individuals with MeD (Brailean et al., 2020; Lamers et al., 2010), and are less likely to cohabitate (P. F. Sullivan et al., 2002). Those with NMeD also reported more comorbid illnesses and more loneliness (Brailean et al., 2020).

MeD features present equally among the sexes, but are estimated by some to be more likely in older age groups (American Psychiatric Association, 1998), and by some to be more common among younger individuals (Khan et al., 2006; Parker et al., 2013).

2.3 DETECTION OF DEPRESSIVE SYMPTOMS

There is evidence for depression screening being beneficial in all adults when treatment is available (Smithson & Pignone, 2017). However, recommendations in Finland suggest that clinicians should screen for depression only when encountering patients that are likely to have depression rather than screening every patient (Working group set up by the Finnish Medical Society Duodecim and the Finnish Cardiac Society., 2022). Depression in older populations may be misinterpreted as cognitive decline or as part of normal aging (Vieira et al., 2014). Screening can significantly assist in detection of depression (Smithson & Pignone, 2017). A multitude of tests designed to screen for depression are available (Smithson & Pignone, 2017). The Beck Depression Inventory-IA (BDI-IA) has been validated for depression screening in the Finnish population (Nuevo et al., 2009).

Even though depression screening is supported by evidence, the implementation of screening remains incomplete (Smithson & Pignone, 2017). There are a variety of screening tools that can be used for depression screening. However, depression diagnostics are always based on clinical interviews by healthcare professionals and cannot be made solely based on screening results (Working group set up by the Finnish Medical Society Duodecim and the Finnish Cardiac Society., 2022).

2.3.1 DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS-IV

The DSM-IV is the fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders composed by experts in their fields for use in clinical practice, research, and educational settings both in the United States and internationally (American Psychiatric Association, 1998). The DSM-IV diagnoses are based on identification of key symptoms of each disorder (Malhi & Mann, 2018). The DSM-IV is evidence based, has taken into account ethnic and cultural differences, and has been developed under interchange with multiple different organizations, such as the WHO and the American Psychological Association (American Psychiatric Association, 1998).

The DSM together with the international classification of disease (ICD) are the two major diagnosis classification systems (Malhi & Mann, 2018). The DSM-IV is intended to be used as a guideline for clinical diagnoses to enhance agreement among professionals (American Psychiatric Association, 1998). Table 1 shows the criteria for MDD according to the DSM-IV, and Table 2 shows the criteria for the melancholic specifier.

2.3.2 THE BECK DEPRESSION INVENTORY

The BDI is an instrument developed to objectively screen for depression (Beck et al., 1961). It was originally developed to be used in an interview format and to be administered by a trained professional (Beck et al., 1961). It provides a high degree of validity and reliability in its quantitative assessment of depressive symptoms (Beck et al., 1961).

The BDI is a self-reported questionnaire consisting of 21 questions regarding behavioral manifestations of attitudes and symptoms specific to depression (Beck et al., 1961). Scores for the BDI range between 0 (low) and 63 (high), with scores of ≥10 having been validated to screen for clinical depression ranging from mild to severe (Beck et al., 1988). Anyone scoring <10 would not be considered to have shown significant enough symptoms of depression to warrant a clinical diagnosis (Beck et al., 1988).

The BDI categories per Beck et al. are mood, pessimism, sense of failure, lack of satisfaction, guilty feeling, sense of punishment, self-hate, self-accusations, self-punitive wishes, crying spells, irritability, social withdrawal, indecisiveness, body image, work inhibition, sleep disturbance, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido (Beck et al., 1961).

Table 3, in the methods section, shows the BDI-IA questions in English. The questions in Finnish that were used for Studies I-IV can be found in Appendix B.

2.4 PATHOPHYSIOLOGY OF DEPRESSIVE SYMPTOMS

The pathophysiology of depression and depressive symptoms is not fully understood. It is understood that depression stems from complex combinations of biological, psychological and social factors (WHO, 2021b). NMeD is associated with metabolic and inflammatory dysregulations, while MeD is associated with hypothalamic-pituitary-adrenal (HPA)-axis dysregulation (Lamers et al., 2013; Penninx et al., 2013).

2.4.1 BIOLOGICAL DYSREGULATIONS

2.4.1.1 Hypothalamic-Pituitary-Adrenal-axis

The HPA-axis is a network of hormonal signals that regulate and adjust the levels of the glucocorticoid stress hormone cortisol (Packard et al., 2016). The glucocorticoids produced by the HPA-axis have significant influence over human behavior (Packard et al., 2016). Both stress and depression have similar mediators and physiological circuitries in our bodies (Gold & Chrousos, 2002).

The HPA-axis can have long-term and widespread effects through changes in glucocorticoid circulation (Packard et al., 2016). When physical stress is sustained or repeated, the stress regulating system of the HPA-axis has the capacity to cause numerous long-term changes throughout our bodies (Packard et al., 2016). Long-term stress and activation of the HPA-axis causes changes in both the neural structure and function of the brain (Packard et al., 2016). Such sustained HPA-axis activation also leads to impaired negative feedback on glucocorticoid production (Packard et al., 2016). This dampened feedback loop in turn contributes to maintaining the hyperactivity of the HPA-axis (Packard et al., 2016).

Stress involves both the brain and the body of individuals and is a reflection of conflicts, life events, and burdens of everyday life (McEwen, 2012). Stress alters physiology, producing the chronic stress burden that affects disease expression (McEwen, 2012). External stressors, internal stressors, emotional memories, and recollections of abuse, failure and abandonment all factor into susceptibility to depression (Gold & Chrousos, 2002). The burden is multifaceted, comprised of genetics, epigenetic modifications, life experiences, and health behaviors interacting together (McEwen, 2012).

MeD is more closely associated with HPA-axis dysregulation than other types of depression (Lamers et al., 2013; Penninx et al., 2013). MeD symptomatology includes physiological hyperarousal such as hypercortisolism

(Gold & Chrousos, 2002). It has been suggested that MeD is associated with HPA-axis overactivity, whereas NMeD is said to be associated with HPA-axis depression (Gawlik-Kotelnicka & Strzelecki, 2021; Gold & Chrousos, 2002; Packard et al., 2016). Accurate HPA-axis assessment would require multiple parameters (Gawlik-Kotelnicka & Strzelecki, 2021), rendering any such analysis complicated. There is evidence supporting a positive association between cortisol levels and MeD (Lamers et al., 2013). Furthermore, in Cushing's syndrome a causal relationship has been suggested between cortisol and depression (Milano et al., 2020).

2.4.1.2 Glucose Metabolism

DM is a syndrome of insulin deficiency and insulin resistance (Guthrie & Guthrie, 2004) and hyperglycemia (Nouwen et al., 2011). A relationship between DM and depression has been established (Campayo et al., 2011; Roy & Lloyd, 2012). DM may not only be a risk factor for the development of depression, but also for its recurrence (for the European Depression in Diabetes (EDID) Research Consortium et al., 2010). Impaired glucose tolerance, impaired fasting glucose, or impaired glucose resistance, without a diagnosis of DM, however, do not seem to have an association with depression (Nouwen et al., 2011). However, impaired glucose metabolism has a strong connection with both obesity and body composition (Liese et al., 1998; Reaven, 1997), which in turn are also known to have associations with depression (Capuron et al., 2017; Gawlik-Kotelnicka & Strzelecki, 2021; Guh et al., 2009; Lamers et al., 2013; L. Li et al., 2017; Luppino et al., 2010; von Zimmermann et al., 2020; Wild et al., 2012; Wiltink et al., 2013; Zhu et al., 2017).

It has been suggested that the relationship between glucose metabolism and depression is mediated by inflammation and biochemical changes, or stress and psychological burden of disease (Nouwen et al., 2011; Talbot & Nouwen, 2000). However, details remain unknown and further research in the area is needed to explain the connection. (Campayo et al., 2011; Roy & Lloyd, 2012)

Some indication exists that individuals with depression exhibiting anhedonia may have a stronger relationship with impaired glucose regulation (Moreira et al., 2019). Of the depressive subtypes, specifically NMeD has an association with dysfunctional glucose metabolism (Lamers et al., 2013; Seppälä, Vanhala, et al., 2012).

2.4.1.3 Body Composition

There is an established connection between body composition and depressive symptoms (Capuron et al., 2017; Gawlik-Kotelnicka & Strzelecki, 2021; Guh et al., 2009; Lamers et al., 2013; L. Li et al., 2017; Luppino et al., 2010; von Zimmermann et al., 2020; Wild et al., 2012; Wiltink et al., 2013; Zhu et al., 2017). Both obesity and depression are among some of the most common conditions on a global level (Milano et al., 2020), and frequently co-occur (Gawlik-Kotelnicka & Strzelecki, 2021). These conditions are a serious economic burden and public health concern (Gawlik-Kotelnicka & Strzelecki, 2021; Guh et al., 2009; Milano et al., 2020). High BMI is responsible for a large part of disability-adjusted life years, and has an increasing summary exposure (Murray et al., 2020). In 2019 high BMI accounted for approximately 5 million attributable deaths globally (Murray et al., 2020).

Depression has been shown to have a positive relationship with high fat mass and with low muscle mass (von Zimmermann et al., 2020). Patients with current depressive episodes had lower muscle mass, higher fat mass, and higher visceral adipose tissue mass than controls (von Zimmermann et al., 2020). This relationship between increased body weight and depression has been suggested to be bidirectional (Luppino et al., 2010; Pereira-Miranda et al., 2017; Rooke & Thorsteinsson, 2008). Furthermore, a dose-related relationship may exist between increased body weight and depression (Luppino et al., 2010; Pereira-Miranda et al., 2017).

The suggested explanation for the connection between the two conditions is an inflammatory pathology (Gawlik-Kotelnicka & Strzelecki, 2021; Luppino et al., 2010; Milano et al., 2020; Wiltink et al., 2013). It has also been shown that there is a difference between the depressive subtypes when it comes to their relationship to weight and body composition (Lamers et al., 2013). Individuals with NMeD have larger waist circumference, a higher average number of metabolic syndrome components, and higher BMI than individuals with MeD (Lamers et al., 2013).

2.4.1.4 Inflammatory Pathways

Dysregulation of inflammatory pathways has been associated with depression (Beurel et al., 2020; Dantzer et al., 2008; Gibney & Drexhage, 2013; Kiecolt-Glaser et al., 2015; Müller, 2014; Tiemeier et al., 2003; van Sloten et al., 2014), and specifically NMeD (Lamers et al., 2013; Penninx et al., 2013). Both the innate and adaptive immune systems are dysregulated in depression (Beurel et al., 2020). When the immune system gets activated and remains activated for prolonged periods of time, the cytokines produced affect neuronal and neurotransmitter functions (Deverman & Patterson, 2009;

Elmer & McAllister, 2012; Stephan et al., 2012). This disruption of normal function affects mood and cognition (Dantzer et al., 2008).

Obesity, stress, and adversity could trigger immune responses affecting depression (Kiecolt-Glaser et al., 2015). The bidirectional relationship between depression and inflammation has the potential to propagate each other creating a hard-to-break circle of disease (Kiecolt-Glaser et al., 2015). Inflammatory markers such as interleukin-6 and C-reactive protein (CRP) have been shown to correlate with depression (Kiecolt-Glaser et al., 2015).

Infection, cancer, autoimmune diseases and other inflammatory states have the capability to activate unabated immune reactions that exacerbate sickness-behavior (Dantzer et al., 2008). Even stress has the ability to increase proinflammatory cytokine levels and contribute to long lasting pro-inflammatory states (Müller, 2014).

Low-level neuroinflammation has the ability to alter multiple different neurotransmission pathways (Müller, 2014). Infections and autoimmune states have been shown to present lifetime risk for depression (Müller, 2014). In fact, pro-inflammatory cytokines have the ability to not only induce depressive symptoms, but true MDD (Dantzer et al., 2008).

2.4.1.5 Vascular Factors

The vascular hypothesis of depression attempts to explain how vascular disease alters regional brain connectivity and function by altering local brain perfusion, and hence causing clinical symptoms down the line (Taylor et al., 2013). The cerebral microvasculature gets harmed by arterial stiffness and increased flow pulsatility (Mitchell, 2014; Mitchell et al., 2011; van Sloten et al., 2015). When arterial pulses propagate through stiff vessels from the central circulation straight into the cerebral vessels it leads to angiopathy (Thomas et al., 2019). Depression is believed to have underlying microvascular damage especially in the frontal-subcortical mood regulatory regions (Alexopoulos, 1997; Buckner, 2004; Henskens et al., 2008; Kearney-Schwartz et al., 2009; Krishnan et al., 1997; Mitchell et al., 2011; Ohmine et al., 2008; Pugh & Lipsitz, 2002). Arterial stiffness contributes to both CVD and structural changes in blood vessel walls causing increased arterial wave propagation (Thomas et al., 2019). Research has found relationships between depression or depressive symptoms and stiffness of the aorta among adult subjects (Onete et al., 2018; Tiemeier et al., 2003; van Sloten et al., 2016). PWV is a method that can be used to assess the stiffness of arteries (Elias et al., 2009; Fewlass et al., 2004; Jannasz et al., 2019; Johnson, 2006; Mancia et al., 2007; Marioni et al., 2010).

Prolonged hyperlipidemia can lead to arterial stiffness (Chen et al., 2020). Arterial stiffness is also related to hypertension and CVD (Palatini et al., 2011). Hypertension has a positive correlation with increased risk of CVD and is mediated through a complex pathway (Oparil et al., 2018). There is a strong connection between depression and CVD (WHO, 2020) or arterial stiffening (Tiemeier et al., 2003; van Sloten et al., 2014). Even at subclinical levels of depression the connection with CVD is evident (Harshfield et al., 2020). CVD, high blood pressure and dyslipidemia all fall under metabolic dysregulation (Lamers et al., 2013; Penninx et al., 2013), which means it would be reasonable to expect these vascular factors to have a closer relationship with NMeD than MeD.

One suggested connection between the vasculature and depression is the autonomic nervous system, which is closely connected to both (Kidwell & Ellenbroek, 2018; Sgoifo et al., 2015; Zanoli, Tuttolomondo, et al., 2020). The gut has also been connected to both the vascular factors and the autonomic nervous system (Zanoli, Tuttolomondo, et al., 2020). This will be further discussed in section 2.5.2.2.

2.4.2 GENETICS

Heritability of depression is not fully understood, but some degree of genetic predisposition does play a part in depressive disorders. According to the DSM-IV work group first-degree relatives of individuals with MDD are up to three times more likely to have the disorder as compared to the general population (American Psychiatric Association, 1998).

It has been established that depression is a polygenic disorder and part of the risk for depression is genetically mediated (Penner-Goeke & Binder, 2019). However, these molecular mechanisms are still poorly understood, and each genetic loci seems to only have a small effect on an individual's risk of developing depression (Penner-Goeke & Binder, 2019). Depressed individuals more likely have epigenetic changes of gene loci coding for brain-derived neurotrophic factors and serotonin transporters when measured in peripheral tissues (M. Li et al., 2019). Some loci affecting brain function and development have been found to have hypermethylated messenger ribonucleic acid in brain tissue of depressed individuals, but what drives these changes is still unknown (Penner-Goeke & Binder, 2019). Differences in epigenetic modulation of histones and microRNA between depressed individuals and controls, some reactive to antidepressant treatment, have also been found (Penner-Goeke & Binder, 2019). A study has shown that certain genetic differences are only related to depression in groups of people with specific ancestry (Jensen et al., 2014). It has also been suggested that genetic overlap between depression and

comorbidities could be affecting both conditions (Boden & Fergusson, 2011; Milaneschi et al., 2017).

There is still much that is unknown regarding the genetics-depression relationship; it is known that genetics does play a part in depression, it is just not know exactly how this happens.

2.4.3 ENVIRONMENTAL AND PSYCHOLOGICAL FACTORS

There is a connection between stress and depression (Slavich & Irwin, 2014), stress and epigenetics (Turecki & Meaney, 2016), as well as epigenetics and depression (Park et al., 2019; Penner-Goeke & Binder, 2019). It has been suggested that environmental factors could trigger epigenetic changes in individuals with depression (Park et al., 2019; Penner-Goeke & Binder, 2019). Adverse life events may trigger depressive episodes, but depression may also in turn lead to dysfunction and adversity in life (WHO, 2021b).

Childhood adversities are associated with higher likelihood of developing depression (Markkula et al., 2017). Childhood trauma, such as neglect or emotional abuse, is associated with developing depression as an adult (Mandelli et al., 2015). Both stress and social rejection have been linked to increased risk of depression through the inflammatory pathways (Slavich & Irwin, 2014). Social pressure, such as beauty standards, has also been suggested to partially mediate depressive symptoms (Milano et al., 2020).

2.4.4 LIFESTYLE CHOICES

Lifestyle factors have been shown to differ between the depressed and non-depressed populations, but the effect sizes on morbidity and mortality have been thought to be minimal (Penninx et al., 2013).

2.4.4.1 Smoking

In 2020 22.3% of the global population (over 1.3 billion individuals) used tobacco, with smoking being the most common form (WHO, 2022b). Tobacco kills over 8 million individuals every year and is considered one of the biggest public health threats by the WHO (WHO, 2022b).

There is some disagreement on whether any relationship exists between smoking and depression. Some have reported that individuals with NMeD more frequently are smokers (Brailean et al., 2020), whereas others have reported MeD individuals to more frequently be smokers (Lamers et al., 2010). Some have reported no relationship between smoking habits and depression (Rantanen et al., 2020; van Gool et al., 2007), or either type of

depressive subtypes (Rantanen et al., 2020). A meta-analysis, on the other hand, found that both current and former smokers have a higher likelihood of being depressed than those who never smoked (Luger et al., 2014).

2.4.4.2 Alcohol

Alcohol is a dependence producing psychoactive substance that has a causal effect on hundreds of diseases and injury states (WHO, 2022a). Using alcohol can affect the brain in a magnitude of ways, including cellular signaling and changes in gene expression (Egervari et al., 2021). Alcohol is responsible for over 3 million deaths every year (WHO, 2022a).

Excessive alcohol use has been associated with a higher likelihood of depression (Boden & Fergusson, 2011; van Gool et al., 2007). Those with depression also have a higher likelihood of excessive alcohol use (Boden & Fergusson, 2011). The association between alcohol consumption and depression cannot be fully explained by any confounding factors alone (Boden & Fergusson, 2011). The presence of both simultaneously is also associated with more severe expression of both (McHugh & Weiss, 2019). Some have found NMeD groups to consume more alcohol (P. F. Sullivan et al., 2002), whereas others have shown MeD groups to consume more alcohol (Rantanen et al., 2020). It has been suggested that the connection between alcohol use and depression could be due to genetics, metabolic changes, or social circumstances (Boden & Fergusson, 2011).

2.4.4.3 Physical Activity

The WHO recommends adults to spend a minimum of 150 minutes on moderate-intensity physical activity, or a minimum of 75 minutes on vigorous physical activity per week (Bull et al., 2020). Sedentary individuals with chronic conditions may benefit most from limiting sedentary behaviors (Dempsey et al., 2021). Exercising more than half an hour per day has been associated with lower prevalence of depression (van Gool et al., 2007). Between the depressive subtypes, the NMeD individuals are significantly less physically active (Brailean et al., 2020; Rantanen et al., 2020).

2.5 NOVEL ASPECTS OF PATHOPHYSIOLOGY OF DEPRESSIVE SYMPTOMS

2.5.1 DEPRESSIVE SYMPTOMS AND ADVANCED GLYCATION END PRODUCTS

2.5.1.1 Advanced Glycation End Products

AGEs are chemically modified proteins and lipids formed through the Maillard reaction, which nonenzymatically glycates sugar aldehydes into Schiff bases, Amadori products, and finally AGEs (Gaens et al., 2013). AGEs accumulate on tissue proteins and are found in for example collagen of the skin (Meerwaldt et al., 2004) and arteries (Sell & Monnier, 2012). AGEs are associated with normal aging, and accumulate over time (Fishman et al., 2018; Sell & Monnier, 2012). There are both fluorescent and non-fluorescent AGEs (Meerwaldt et al., 2004). The skin autofluorescence (SAF) measures fluorescent AGEs, but in the skin this is a good representation of total AGEs (Meerwaldt et al., 2004).

AGEs alter tissue structure and function by binding to the receptor for AGE, which in turn activates signalling pathways leading to increased oxidative stress and proinflammatory cytokines, along with endothelial dysfunction and altered glucose metabolism (Brouwers et al., 2010, 2011; Fishman et al., 2018; Gaens et al., 2013).

Traditionally AGEs were measured through fluorescence in skin biopsies (Meerwaldt et al., 2004). Immunochemical assays have successfully been used to measure both fluorescent and non-fluorescent AGEs (Meerwaldt et al., 2004). Other methods such as urine and blood samples have also been used, but these have been shown not to accurately represent tissue AGEs (Meerwaldt et al., 2004). Proteins have a higher turnover rate in the circulation compared to in tissues, which may lead plasma AGE and skin AGE measurements to not be representative of each other (Atzeni et al., 2022).

Both fluorescent and non-fluorescent AGEs have been shown to behave similarly, allowing for fluorescence to be used as a marker (Meerwaldt et al., 2004). SAF has been validated to be an alternative to invasive methods of AGE measurement (Meerwaldt et al., 2004). The Maastricht Study used both SAF and plasma AGE measurements, showing that the SAF levels are more closely related to depression, than plasma AGE levels (Meerwaldt et al., 2004).

AGE formation is non-reversible (Sell & Monnier, 2012), and 0.024 arbitrary units (AU) increase in AGE levels, as measured by SAF, is equivalent to the AGE increase caused by one year of aging (Atzeni et al., 2022).

2.5.1.2 Underlying Mechanisms

AGEs are well known to be part of normal aging (Fishman et al., 2018; Sell & Monnier, 2012). Furthermore, they have been indicated in several disease processes such as depression, schizophrenia, DM, CVD, and Alzheimer's disease (Abate et al., 2017; Emanuele et al., 2011; Fishman et al., 2018; Hagen et al., 2017; Ohnuma et al., 2018; Yamagishi, 2011). Their ability to affect oxidative stress, cytokines, glucose metabolism, and endothelial dysfunction are possible ways they are involved in disease processes (Brouwers et al., 2010, 2011; Fishman et al., 2018; Gaens et al., 2013; Tiemeier et al., 2003; van Sloten et al., 2014). Many non-communicable diseases such as depression have a component of chronic low-grade inflammation (Schmidt et al., 2007) and a higher risk of autoimmune diseases with increased inflammatory markers (Roberts et al., 2018). AGE formation is accelerated by prolonged hyperglycemia (Yamagishi, 2011), and DM is known to be associated with both chronic low-grade inflammation (Schmidt et al., 2007) and depression (Campayo et al., 2011; Roy & Lloyd, 2012). Individuals with DM are also known to have higher SAF levels than individuals without DM (van Waateringe et al., 2016).

Lifestyle factors such as smoking, exercise, sleep, stress, and dietary intake are known to affect SAF levels (Isami et al., 2018; van Waateringe et al., 2016). AGE formation targets collagen and elastin that are found for example in arterial walls, causing vascular stiffening (Sell & Monnier, 2012). Arterial stiffening is a known component of depression and depressive symptomatology (Onete et al., 2018). Graphic 1 and Graphic 2 display the roles of diseases, lifestyle, and aging on AGE.

AGEs in mitochondria accumulate over time causing a self-perpetuating cycle of tissue damage which causes more AGE formation, which in turn causes even more tissue damage (Fishman et al., 2018).

2.5.1.3 Subtypes of Depressive Symptoms and Advanced Glycation End Products

To the best of the author's knowledge no prior research has been done on AGEs in relation to depressive subtypes.

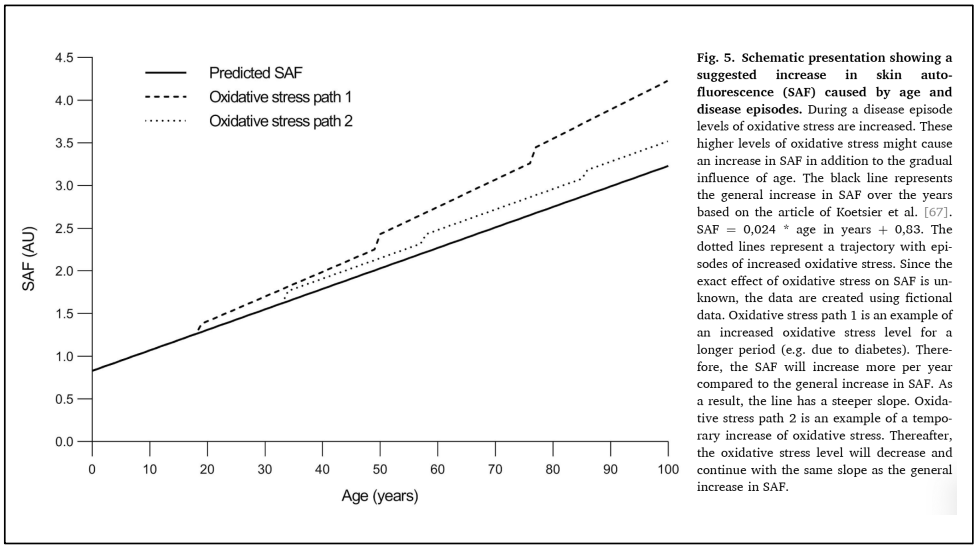


Fig. 5. Schematic presentation showing a suggested increase in skin autofluorescence (SAF) caused by age and disease episodes. During a disease episode levels of oxidative stress are increased. These higher levels of oxidative stress might cause an increase in SAF in addition to the gradual influence of age. The black line represents the general increase in SAF over the years based on the article of Koetsier et al. [67]. SAF = 0,024 * age in years + 0,83. The dotted lines represent a trajectory with episodes of increased oxidative stress. Since the exact effect of oxidative stress on SAF is unknown, the data are created using fictional data. Oxidative stress path 1 is an example of an increased oxidative stress level for a longer period (e.g. due to diabetes). Therefore, the SAF will increase more per year compared to the general increase in SAF. As a result, the line has a steeper slope. Oxidative stress path 2 is an example of a temporary increase of oxidative stress. Thereafter, the oxidative stress level will decrease and continue with the same slope as the general increase in SAF.

Graphic 1 Graphic representation of advanced glycation end product levels by age and effects of hypothetical disease processes. (Atzeni et al., 2022)

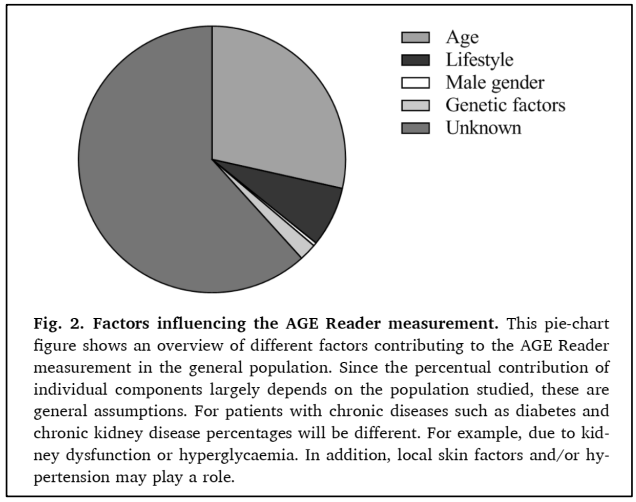


Fig. 2. Factors influencing the AGE Reader measurement. This pie-chart figure shows an overview of different factors contributing to the AGE Reader measurement in the general population. Since the percentual contribution of individual components largely depends on the population studied, these are general assumptions. For patients with chronic diseases such as diabetes and chronic kidney disease percentages will be different. For example, due to kidney dysfunction or hyperglycaemia. In addition, local skin factors and/or hypertension may play a role.

Graphic 2 Representation of factors that are estimated to influence skin autofluorescence measurements. (Atzeni et al., 2022)

2.5.2 DEPRESSIVE SYMPTOMS AND PULSE WAVE VELOCITY

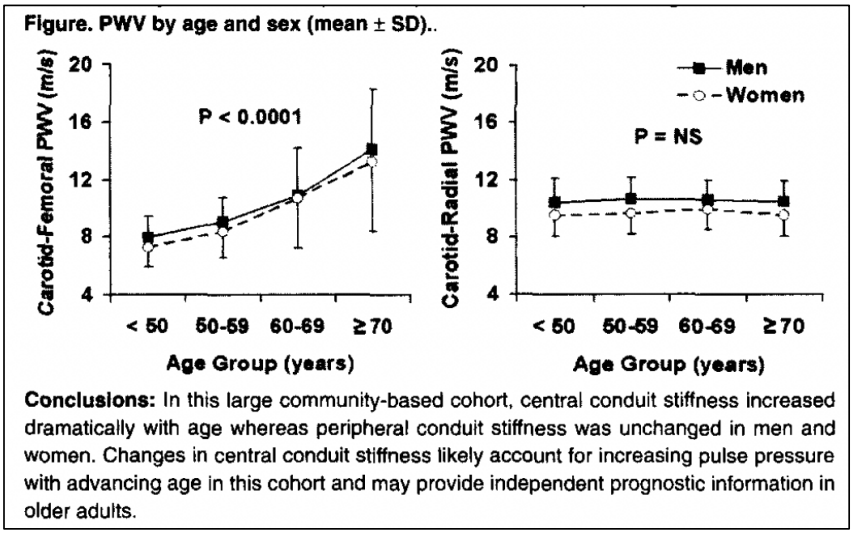
2.5.2.1 Pulse Wave Velocity

PWV is the speed of the propagation of the waves of blood pumped through the arteries of the body (Jannasz et al., 2019). The PWV is an indirect measurement of the arterial stiffness and can detect even subclinical stenosis (Elias et al., 2009; Fewlass et al., 2004; Jannasz et al., 2019; Johnson, 2006; Mancia et al., 2007; Marioni et al., 2010). Depression and depressive symptoms have been shown to be associated with arterial stiffening (Onete et al., 2018). This non-invasive method of measuring arterial stiffness may therefore work as a marker for depression (Onete et al., 2018).

PWV is commonly measured as either carotid-femoral pulse wave velocity (cfPWV) or carotid-radial pulse wave velocity (crPWV), with the former representing the PWV in the aorta and the latter the PWV in the radial artery (Mitchell et al., 2010). Peripheral arteries have smaller diameters, have more muscular structures, and less elastic wall structures than the aorta (Giannattasio et al., 1995, 2005). Endothelial function, the sympathetic branch of the autonomic nervous system, along with the renin-angiotensin system have been shown to modulate the stiffness of medium-sized peripheral arteries (Giannattasio et al., 1995, 2005). Structural changes in vessel walls, together with vasoconstriction, alter both the timing and magnitude of pulse waves being reflected (Duprez, 2004).

Research has suggested that age affects cfPWV but not crPWV (Duprez, 2004; Hickson et al., 2016). Some report the CVD and depression relationship to be stronger in younger individuals (Salaycik et al., 2007). Other research has reported no relationship between cfPWV and depression in either sex at ages above 60 years (Onete et al., 2018). With increasing age central PWV increases more than, and bypasses, peripheral PWV in magnitude (Hickson et al., 2016). An association between depression or depressive symptoms and aortic stiffness has been established in adult subjects (Onete et al., 2018; Tiemeier et al., 2003; van Sloten et al., 2016). For older adults no such association has been reported (Lewis et al., 2010; Onete et al., 2018).

Depressive symptoms have differing associations for the sexes regarding PWV (Onete et al., 2018) and cardiovascular risk (Franklin et al., 1997; Segers et al., 2007). Men ≤60 years of age have a stronger association between cfPWV and MDD than women or older individuals (Onete et al., 2018). Women have been shown to have lower cfPWV and crPWV compared to men of the same age (Graphic 3) (Mitchell et al., 2002).



Graphic 3 Graphic representation of carotid-femoral (cfPWV) and carotid-radial pulse wave velocity (crPWV) by age and sex. Sex difference was significant for both cfPWV ($p<0.01$) and for crPWV ($p<0.0001$). (Mitchell et al., 2002)

2.5.2.2 Underlying Mechanisms

The brain-gut-vascular axis has been proposed as a possible inflammatory connection between arterial stiffness and depression (Zanoli, Tuttolomondo, et al., 2020). The brain and gut are connected through both the parasympathetic and sympathetic nervous systems (Zanoli, Tuttolomondo, et al., 2020). These signals of the autonomic nervous system are also connected to the vascular and inflammatory systems, and affect for example arterial stiffness (Zanoli, Tuttolomondo, et al., 2020). Individuals with chronic inflammatory conditions may have arterial stiffness triggered through psychoneuroimmune modulation (Zanoli, Briet, et al., 2020; Zanoli, Tuttolomondo, et al., 2020). Simply put, this means that psychological states such as anxiety or depression may affect the gut vascular permeability to inflammatory factors, which in turn can affect vasculature in the long run (Zanoli, Tuttolomondo, et al., 2020). A relationship has been shown to exists between chronic inflammatory conditions and higher crPWV (Cypiene et al., 2009; Cypienė et al., 2008; Zanoli et al., 2012, 2018). Some reported young women with autoimmune disease to have higher crPWV compared to their healthy counterparts (Cypiene et al., 2009), whereas others showed crPWV to have a positive correlation with inflammatory disease duration (Zanoli et al., 2012). It has been suggested that higher PWV of early vascular disease may originate in endothelial dysfunction of smaller arteries, whereas aortic stiffening, on the other hand, is an expression of more advanced disease

(Cohn, 2006). This proposed bidirectional relationship between brain, gut, and vasculature through immune modulation and the autonomic nervous system (Zanoli, Tuttolomondo, et al., 2020) could be the explanation for these relationships described.

The vascular hypothesis of depression, as described in section 2.4.1.5, is one mechanism linking vascular stiffening and depression (Alexopoulos, 1997; Buckner, 2004; Henskens et al., 2008; Kearney-Schwartz et al., 2009; Krishnan et al., 1997; Mitchell et al., 2011; Ohmine et al., 2008; Pugh & Lipsitz, 2002).

2.5.2.3 Subtypes of Depressive Symptoms and Pulse Wave Velocity

As far as the author is aware no prior research has been done on differences between depressive subtypes and PWV. Arterial stiffness could be seen as falling under the category of metabolic dysregulation, and therefore be expected to be more closely associated with NMeD than MeD (Lamers et al., 2013; Penninx et al., 2013).

2.5.3 DEPRESSIVE SYMPTOMS AND BODY COMPOSITION

2.5.3.1 Body Mass Index and Body Composition

Body composition can be used as a determinant of health for an individual, but this information cannot be obtained from BMI (Kyle et al., 2003). Obesity and overweight are defined by BMI, which is a representation of weight in relation to height squared (kg/m^2) (Kyle et al., 2003). The WHO classifies overweight as having a BMI ≥25, and obesity as having a BMI ≥30 (WHO, 2021a). BMI alone cannot, however, adequately represent the body compositions of fat and lean mass (Kyle et al., 2003). A higher BMI is not only associated with higher fat mass, but also with higher lean mass (Kyle et al., 2003). Fat mass is the weight of fat tissue, and lean mass is the body weight excluding fat tissue. These can be represented by lean mass index (LMI) and fat mass index (FMI) that take into account these tissue weights in relation to height, which allows for height independent comparisons of these body composition measurements (Kyle et al., 2003).

Studies have suggested a bidirectional relationship for adults between depression and elevated weight (Luppino et al., 2010; Rooke & Thorsteinsson, 2008). Individuals with depression are more likely to develop obesity (Luppino et al., 2010), and individuals with overweight or obesity are more likely to develop depression (Pereira-Miranda et al., 2017). Those with obesity have a higher risk of developing depression than those with overweight,

suggesting the possible existence of a dose-related relationship between the two conditions (Luppino et al., 2010; Pereira-Miranda et al., 2017).

Both depression and obesity are related to inflammatory pathologies (Luppino et al., 2010; Milano et al., 2020). Obesity induces chronic low-grade inflammation (Milano et al., 2020). Especially visceral adipose tissue produces high levels of pro-inflammatory cytokines that play a part in both obesity and depression (Wiltink et al., 2013).

Some sex-differences have been shown in the relationship between depression and body composition (Luppino et al., 2010). Women display a significantly stronger relationship than men in this regard (L. Li et al., 2017; Milano et al., 2020; Wild et al., 2012). Specifically, obesity in women is more closely related to depressive symptoms than obesity in men (Fabricatore & Wadden, 2004; McElroy et al., 2004).

The depression-body composition relationship has been suggested to be reinforced over time (Luppino et al., 2010; Zhu et al., 2017), but others found no increases in depression rates associated with increases in either fat mass or BMI (Cameron et al., 2019).

2.5.3.2 Underlying Mechanisms

There is an established relationship between increased fat mass and depression (von Zimmermann et al., 2020). Genetics have been suggested as the link, with some genetic overlap that may possibly be driving both depressive symptoms and obesity (Milaneschi et al., 2017). Other links that have been suggested are inflammatory markers, HPA-axis dysregulation, hormonal changes, oxidative stress, or negative self-perception, stigmas, and other psychosocial mechanisms (Luppino et al., 2010; Pereira-Miranda et al., 2017; Rooke & Thorsteinsson, 2008). It has been suggested that the relationship between the two pathologies, via immunological and inflammatory pathways, is bidirectional and therefore self-perpetuating leading to increases in each symptomatology over time (Milano et al., 2020).

Brain-derived neurotrophic factor, which is known to be associated with obesity in humans, has been shown to be downregulated by inflammation driven emotional changes in animals (Milano et al., 2020). The inflammatory pathways have been described in section 2.4.1.4. The HPA-axis dysregulations have been described in section 2.4.1.1.

The differences between men and women in the relationship between depression and body composition has been suggested to exist due to sex-specific body compositions (Wiltink et al., 2013). Another suggested link is the presence of psychological sex differences related to sociocultural factors, or differences due to sex-hormones (Pereira-Miranda et al., 2017). Some psychological aspects of beauty standards may play a role in how overweight

and depressive symptoms affect each other (Milano et al., 2020). Women are more strongly affected by perceived beauty standards and other sociocultural factors, leading to a greater risk of depression due to dissatisfaction with their body-type (Pereira-Miranda et al., 2017). Decreased estrogen expression can trigger depression through reductions in serotonin levels (Pereira-Miranda et al., 2017).

2.5.3.3 Subtypes of Depressive Symptoms and Body Composition

NMeD has higher levels of inflammatory markers than MeD (Lamers et al., 2013). CRP levels and NMeD symptoms show a positive correlation (Lamers et al., 2013), with individuals having both obesity and metabolic syndrome exhibiting the highest CRP levels (Gawlik-Kotelnicka & Strzelecki, 2021). MeD, on the other hand, has been thought to be associated with changes in the HPA-axis rather than with inflammation (Lamers et al., 2013).

Higher blood pressure has been associated with both obesity and high plasma glucose concentration in depressed individuals (Penninx et al., 2013). Blood pressure has been shown to have a relationship with both lean mass and fat mass (Korhonen et al., 2021). There is evidence to support that individuals with MeD have lower systolic blood pressure than others (Lamers et al., 2013).

Having both high LMI and high FMI is a predictor for DM, and is associated with the highest cardiometabolic risk of all body composition profiles (Rehunen et al., 2021). Compared to MeD, NMeD is more closely related to higher fasting plasma glucose levels (Lamers et al., 2013; Seppälä, Koponen, et al., 2012).

2.5.4 DEPRESSIVE SYMPTOMS AND GLUCOSE METABOLISM

2.5.4.1 Impaired Glucose Regulation

Glucose is the primary metabolic fuel of mammals, and gets turned into adenosine triphosphate in the cells (Nakrani et al., 2022). After eating, if the physiological function is normal, plasma glucose rises and returns to normal within two hours (Nakrani et al., 2022). The two-hour post loading plasma glucose levels have been shown to better predict mortality than fasting plasma glucose (DECODE Study Group & European Diabetes Epidemiology Group, 2001). When blood glucose rises it causes insulin to be secreted in order to lower blood glucose (Nakrani et al., 2022). Insulin helps to move glucose into cells, but when insulin secretion is insufficient it results in DM (Nakrani et al., 2022). The rate of glucose metabolism is dependent on the amount of insulin being secreted (Nakrani et al., 2022). Type 1 DM is the result

of autoimmune destruction of the insulin secreting cells of the pancreas, whereas type 2 DM is a state where not enough insulin is produced to meet the metabolic needs of the body (Nakrani et al., 2022).

Dysfunctional glucose metabolism is a cardiovascular risk factor (DECODE Study Group & European Diabetes Epidemiology Group, 2001; Rapoport et al., 2021). Both depression and DM are related to negative quality of life, disability, and shorter life expectancy (Goetzel et al., 2003; O'Connor et al., 2009; Roy & Lloyd, 2012). A bidirectional relationship between DM and depression has been reported (Lloyd et al., 2010).

2.5.4.2 Underlying Mechanisms

DM significantly increases vascular disease risk (Ruderman et al., 1992). Hyperglycemia and sugar-derived intermediates lead to increased and more rapid AGE production (Gaens et al., 2013; Ruderman et al., 1992). AGEs also affect vasculature and vascular stiffness (Sell & Monnier, 2012). Vascular changes have been closely associated with depression (Alexopoulos, 1997; Buckner, 2004; Henskens et al., 2008; Kearney-Schwartz et al., 2009; Krishnan et al., 1997; Mitchell et al., 2011; Ohmine et al., 2008; Pugh & Lipsitz, 2002). Furthermore, both inflammation and stress have also been suggested as possible linking mechanisms between dysfunctional glucose metabolism and depression (Nouwen et al., 2011; Talbot & Nouwen, 2000).

2.5.4.3 Subtypes of Depressive Symptoms and Glucose Metabolism

Individuals that have both metabolic syndrome and obesity have the highest levels of CRP (Gawlik-Kotelnicka & Strzelecki, 2021), which in turn shows a correlation with NMeD (Lamers et al., 2013). An association between higher blood pressure and plasma glucose concentration in depressed individuals has been established (Penninx et al., 2013). Individuals with MeD present with lower systolic blood pressures than controls, and lower inflammatory markers than the NMeD group (Lamers et al., 2013). Overall, compared to MeD, NMeD is more closely related to higher fasting plasma glucose levels (Lamers et al., 2013; Seppälä, Vanhala, et al., 2012).

2.5.5 DEPRESSIVE SYMPTOMS AND MORTALITY

2.5.5.1 Depressive Symptoms and All-Cause Mortality

Many studies report a higher rate of mortality associated with depression as compared to those without depression (Schulz et al., 2002),

but others were unable to find any such association (Cuijpers et al., 2014; Schulz et al., 2002). In Finland individuals with depression have an associated two-fold risk of death as compared to non-depressed individuals (Markkula & Suvisaari, 2017). Depression has an established association with CVD-mortality (Gump et al., 2005; Saint Onge et al., 2014), cancer-mortality (Saint Onge et al., 2014) higher all-cause mortality (Cuijpers et al., 2014; Gump et al., 2005; C. Harris & Barraclough, 1998; Saint Onge et al., 2014; M. D. Sullivan et al., 2012). Some, however, report no difference in causes of death between individuals with or without depression (Pulska, 2001). It has been suggested that having a current depressive episode could even be considered life-threatening (Lasserre et al., 2016).

Studies have found clinical depression and subclinical depressive symptoms to both be associated with higher mortality (Cuijpers et al., 2014; Gump et al., 2005; Wu et al., 2020). There is a similar mortality risk for individuals that have been screened to have depression, but not diagnosed, as for individuals diagnosed with clinical depression (Christensen et al., 2017).

Those depressed individuals with the highest number of comorbidities have the highest risk of mortality, and also benefit the most in survival from depression interventions (Gallo et al., 2016). Interventions lower the risk of mortality for groups with clinical MDD but not for those with minor depression (Gallo et al., 2007, 2016) If the effects of subclinical and clinical depression on mortality could be eliminated, mortality may be reduced up to 14% (Cuijpers et al., 2013).

The increased mortality risk by depressive episodes may last for up to 20 years but decays with remission (Gilman et al., 2017). Depression in remission is associated with survival rates comparable to those seen in non-depressed individuals (Lasserre et al., 2016; Pulska, 2001).

2.5.5.2 Underlying Mechanisms

Health behavior, physical illness or socioeconomic factors cannot fully explain the higher mortality risk among individuals with depression (Markkula & Suvisaari, 2017; Saint Onge et al., 2014). Suicide does not account for the excess mortality either (Pulska, 2001).

Individuals with comorbidities such as anxiety (Wu et al., 2020) and DM displayed a greater than additive effect on mortality (M. D. Sullivan et al., 2012), suggesting the possibility of the diseases predisposing to depression causing an increased mortality rate (Pulska, 2001).

2.5.5.3 Subtypes of Depressive Symptoms and Mortality

The author is only aware of one study that has specifically looked at mortality differences between the NMeD and MeD subtypes. Said study was conducted with participants of a CVD risk group, and found non-melancholic but not MeD symptoms to be associated with a higher mortality risk (Rantanen et al., 2020). It is, however, possible that the CVD risk in these individuals could have affected the outcome.

3 AIMS

This thesis aimed at investigating whether there were differences in pathophysiologic factors between the non-melancholic depressive and melancholic depressive subtypes as part of an attempt to gain knowledge, and better understand, these depressive subtypes.

I: To assess advanced glycation end products in participants with depressive symptoms, and to assess differences in prevalence of advanced glycation end products among depressive subtypes (Study I).

II: To assess relationships between pulse wave velocity and depressive symptoms, as well as differences in pulse wave velocity between depressive subtypes (Study II).

III: To assess relationships between body composition, as lean mass or fat mass, and depressive symptoms or depressive subgroups (Study III). As well as, to assess differences in glucose metabolism among depressive subgroups (Study III).

IV: To assess relationships between depressive symptoms, as well as depressive subtypes, and all-cause mortality (Study IV).

4 MATERIALS AND METHODS

4.1 HELSINKI BIRTH COHORT STUDY

4.1.1 STUDY PARTICIPANTS

The HBCS consists of 13 345 individuals born 1934-1944 at Helsinki University Hospital or Helsinki City Maternity Hospital in Helsinki, Finland. All participants attended child welfare clinics in Helsinki, and the majority also attended school in Helsinki.

By 1971 the government of Finland had assigned unique identifying numbers to each member of the population, which allowed for reliable identification of people and their medical records. During the second half of the 1990s the original cohort participants that were born at Helsinki University Hospital were identified using these identification numbers. This study group consisted of 8760 individuals: 4630 men and 4130 women.

In 2001–2004, 2902 participants, who were identified as being alive and living in Finland, were selected from this previous group using random-number tables. Of these 2902 individuals invited, 2003 (Group 1) participated in further studies (Study III & IV). All of these participants had their depressive symptoms evaluated, body composition measured, laboratory tests drawn and evaluated, and biometric information recorded.

In 2011, 1404 individuals from the previous study group were identified as being alive and living within a 100 km radius of the study clinic in Helsinki. They were all invited to participate in further studies, which 1094 of them did.

In 2017-2018 the same criteria were used to identify and invite participants to a follow-up study. This time 815 individuals (Group 2) participated (Study I & II).

Group 1 participants (n=2003) were part of Study III and IV on body composition and mortality, respectively. For Study III 493 participants were excluded due to DM, high-sensitivity C-reactive protein (hsCRP) > 10 mg/l, or missing data. The final number of participants for this study was 1510 (56% women). For Study IV eight participants were excluded due to missing data, leaving the final number of participants at 1995 (53% women).

Group 2 (n=815, 56% women) was used in Study I. All these participants had their AGE values measured by SAF. Study II excluded 132

participants from Group 2 due to PWV measurements not having been obtained, leaving the total number of participants at 683 (55% women).

All of this has been displayed graphically in Figure 3.

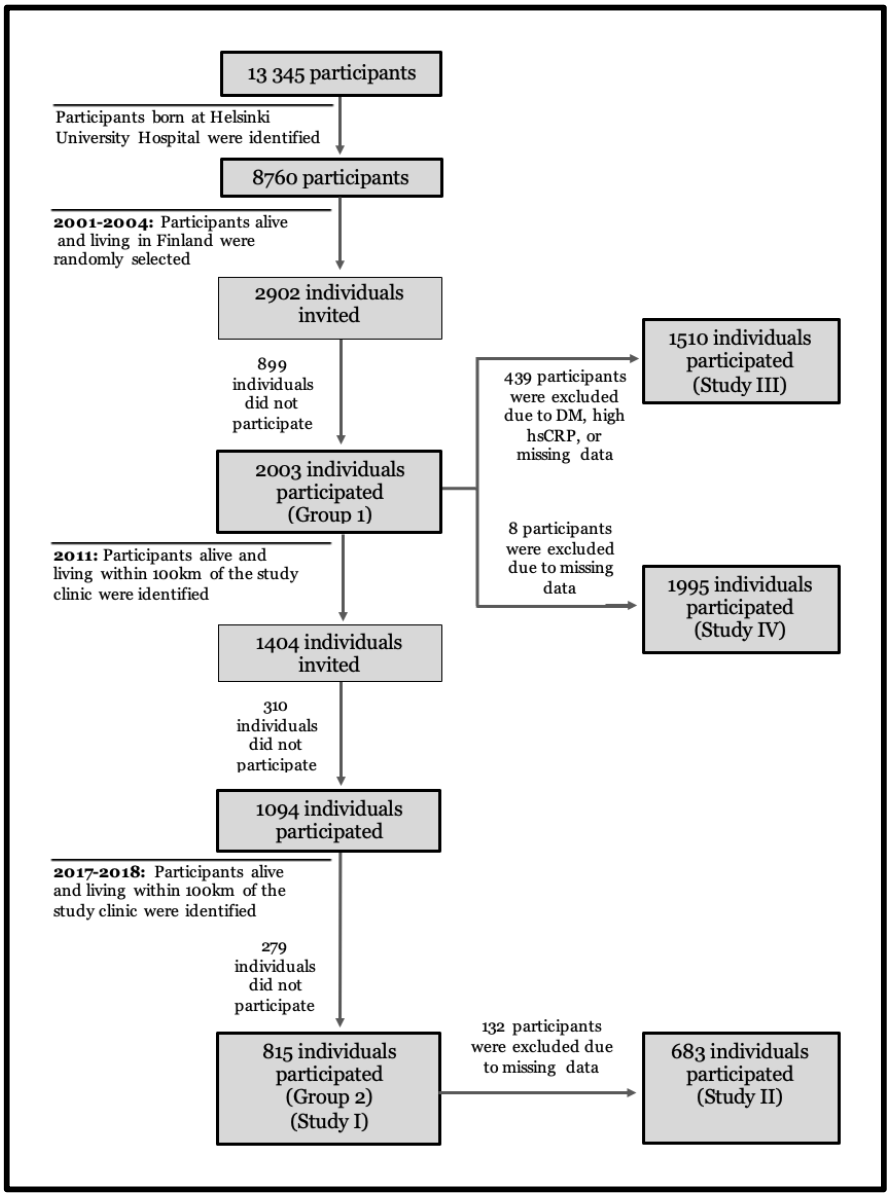


Figure 3 Participant selection over time for each study of this project. DM=diabetes mellitus, hsCRP=high sensitivity C-reactive protein

4.2 METHODS

4.2.1 QUESTIONNAIRES

Participants were asked to fill out questionnaires with a variety of questions for each of the cohort data collections throughout the years. The leisure-time physical activity (LTPA) questionnaire (Lakka et al., 1994; Lakka & Salonen, 1992), BDI-IA (ISMA, n.d.), and mental health inventory-5 (MHI-5) (Rumpf et al., 2001) that were used (in Finnish) can be found in the Appendices. The MHI-5 questions were asked as part of the mental health questions of the Short Form-36 (SF-36) questionnaire (Ware & Sherbourne, 1992).

4.2.1.1 Depressive symptoms

Studies I-IV assessed depression in the form of depressive symptoms as determined by the BDI-IA (ISMA, n.d.) (Table 3 and Appendix B).

4.2.1.1.1 The Beck Depression Inventory

All participants were asked to fill out the BDI-IA questionnaire (Appendix B) to assess depressive symptoms. Participants who did not fill out the BDI-IA were excluded from the current studies (Study I-IV). A cut-off of ≥10 points was used in these studies (Study I-IV) to select for increased depressive symptoms. Each question was worth 0-3 points. Any participant scoring ≥10 on the BDI-IA was placed in the depressive group. A score of <10 on the BDI-IA placed a participant in the non-depressive group.

4.2.1.1.1.1 *Depressive Subgroup Division*

Any participant scoring ≥10 points on the BDI-IA was classified as having either MeD symptoms or NMeD symptoms. This differentiation was determined based on the presence of more melancholic or non-melancholic symptoms in accordance with the DSM-IV (American Psychiatric Association, 1998). Melancholic symptoms have been determined to be sadness, past failure, loss of pleasure, guilty feelings, punishment feelings, loss of interest, irritability, changes in sleep and appetite (questions 1, 4, 7-12, 16, 18, 19). All other questions are considered as weighing toward NMeD symptomatology. DSM-IV lists eight criteria for the melancholic specifier

of mood disorders, A.1-2 and B.1-6 (Table 2). Criteria A.1 is satisfied by the questions on sadness and loss of interest, whereas criteria A.2 is represented by the question on loss of pleasure. The BDI-IA question regarding irritability satisfies criteria B.1. Criteria B.3, B.5, and B.6 are represented by the BDI-IA questions regarding changes in sleep, appetite and weight changes, and punishment feelings, respectively. Two criteria of the DSM-IV have not been represented in the BDI-IA. These are B.2 and B.4, which are diurnal variation and psychomotor symptoms. The BDI-IA questions can be seen in Table 3. The determination of placing participants in a specific subgroup was done based on factoring with different weight applied to each question, with the summary score for symptom subtype that outnumbered the other determining grouping.

Data from the Dehkon 2D study by the National Public Health Institute of Finland, and the Finnish Depression and Metabolic Syndrome in Adults study were used in creating the algorithm that categorizes participants into either depressive subtype depending on the answers on the BDI-IA questionnaire. The initial study to use this method of categorization (Seppälä et al., 2010) employed both the BDI-IA and Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Part of the MINI interview looks specifically at melancholic features. This supports the use of the BDI-IA method for categorization of depressive subtypes as its use has been validated through this comparison (Seppälä et al., 2010). These methods for subtyping depressive symptoms used in studies I-IV have also been utilized by others (Seppälä, Koponen, et al., 2012; Seppälä, Vanhala, et al., 2012; Vanhala et al., 2009).

Table 3. *Beck Depression Inventory version IA (ISMA, n.d.) questions listed according to their categorization as weighing toward melancholic or non-melancholic symptomatology.*

BDI-IA questions weighing towards melancholic depressive symptoms	BDI-IA questions weighing towards non-melancholic depressive symptoms
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.
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.	**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.
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.	**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.
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.	**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.
9. 0 I don't have any thoughts of killing myself. 1 I have thoughts of killing myself, but I would not carry them out. 2 I would like to kill myself. 3 I would kill myself if I had the chance.	**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.

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.

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.

18.
- 0 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.

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 an 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.

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.

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 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.

4.2.1.1.2 Mental Health Inventory-5

The five-question MHI-5 was used in Study I to screen for mood disorders and compared with the BDI-IA results for validity. The questions were part of a larger quality of life questionnaire (SF-36) that each participant filled out (Appendix C). The MHI-5 addresses feelings of nervousness, calmness, happiness, feeling down, and inability to cheer up (Rumpf et al., 2001). The questions are scored on a Likert scale and standardized to a 0-100 scale using linear transformation (Rumpf et al., 2001). The scores of 0-100 are inversely correlated to mood disorders (Rumpf et al., 2001). The MHI-5 results were compared to the BDI-IA results in order to validate the measurement of depressive symptoms.

4.2.1.2 Sociodemographic Factors

Participants were asked to fill out questionnaires with questions regarding marital status, income and financial satisfaction, cohabitation, quality of life, and years of education.

4.2.1.3 Lifestyle Factors

Participants were asked to fill out a questionnaire with multiple choice questions regarding smoking, alcohol consumption, and physical activity.

Physical activity was assessed as LTPA by a validated Kuopio Ischemic Heart Disease Risk Factor Study 12-month history questionnaire (Lakka et al., 1994; Lakka & Salonen, 1992). Participants were asked to report their physical activity over the past 12 months; frequency (occasions per month), average duration, and intensity of each type of activity. Metabolic equivalent of task (MET)-values were assigned to each type of activity based on available databases (1 MET = 3.5 ml O_2/kg/min) (Ainsworth et al., 2011). LTPA was reported as metabolic equivalent hours, where MET-values were multiplied by the average duration and frequency of activity per week.

4.2.1.4 Health and Medication

Participants were asked to fill out a questionnaire regarding medications, diagnosed conditions, and depression. All of these were self-reported by the participants. Participants were asked to list medications by name and dose taken. Diagnosed conditions were asked in the form of a list

of common diagnoses (Appendix D) that participants chose from whether they had said diagnosis or not. Depression was screened for through the BDI-IA (Appendix B) and the MHI-5 (Appendix C).

Charlson comorbidity index (CCI) is a mortality index that was used as an index for comorbid conditions according to existing standards (Charlson et al., 1987), with the exception that age was not included as a factor. The reason age was left out was that all participants were of similar age, and CCI was only used for comparison of comorbidities within the study population. Hence, an absolute CCI value was not necessary as mortality was not estimated based on the values.

4.2.2 PHYSICAL EXAMINATION

Each study participant was examined by a clinical study nurse according to a set schedule at the same location.

4.2.2.1 Blood Pressure

Blood pressure was measured using an Omron Intellisense M6W sphygmomanometer with cuffs of sizes 22-42 and 32-42. Measurements were taken from the right arm with participants in a seated position. Participants were instructed to sit relaxed with the right arm resting on the table, and their feet on the ground. Talking was not permitted during or between measurements. The reported values were the mean of two successive measurements one minute apart. Pulse pressure was calculated as mean diastolic pressure subtracted from the mean systolic pressure (pulse pressure = [mean systolic blood pressure] – [mean diastolic blood pressure]). Mean arterial pressure (MAP) was calculated as a third of the systolic blood pressure added to two thirds of the diastolic blood pressure (MAP = $^1/_3$ [systolic blood pressure] + $^2/_3$ [diastolic blood pressure]).

4.2.2.2 Height, Weight, Body Mass Index

Each participant had their height and weight measured without shoes in light indoor clothing. For height measurements participants were instructed to stand with their feet together, heels and back touching the wall behind them. Participants were facing forward with eyes and ears leveled. Height was recorded to the nearest 0.1cm using a Kawi stadiometer. Weight was measured using a Seca Alpha 770 scale and recorded to the nearest 0.1 kg. BMI was calculated as weight (kg) divided by height squared (m^2).

4.2.2.3 Advanced Glycation End Product Measurements and Analysis

AGE was measured by the non-invasive method of SAF using an AGE-reader (AGE Reader, Type 214B00102, DiagnOptics BV. Groningen, The Netherlands). Measurements were obtained from each participant's volar forearm of their dominant arm while seated. All participants had non-pigmented skin. SAF readings were performed on healthy skin after cleansing. Measurements were not obtained from sites of dermatological disease, birthmarks or tattoos. Participants were instructed not to apply lotion or topical solutions to the forearm for a minimum of 2 hours before the measurement.

SAF is reported as AU representing the ratio of emitted light intensity from the AGE-reader (420-600nm wavelength) and the reflected excitation light intensity (300-420nm wavelength) measured from the skin, multiplied by 100. Measurement procedures have been described by Meerwaldt et al. (Meerwaldt et al., 2004) and van Dooren et al. (van Dooren et al., 2017).

4.2.2.4 Pulse Wave Velocity Measurements and Analysis

PWV was measured using a Complior mechanotransducer sensor, and analysis program v.1.9.2 (1.0.20.0) (ALAM Medical, France). Each participant rested for 10 minutes before PWV measurements. Sensors were attached to the wrist, groin, and neck. Participants were asked to lay supine on the examination table, remain still and not to swallow during measurements. The pulse waves were observed, and three measurements were obtained. The best two measurements each for cfPWV and crPWV were recorded. PWV is calculated as distance between measurement sites divided by time between pressure wave upstrokes. These were scaled by a 0.8 factor to avoid overestimating the distance (Huybrechts et al., 2011; Van Bortel et al., 2012).

Some participants were unable to have their pulse waves measured as it required remaining completely still. Common reasons for failed measurements were tremors, heavy breathing, and inability to lay flat on the table. Those participants (n= 132) that were not able to have their PWV measured were excluded from Study II.

4.2.2.5 Body Composition Measurement and Analysis

Participants had their body composition measured using an eight-polar tactile electrode bio-impedance system (InBody 720 3.0, Biospace Co, Ltd, Seoul, Korea). Each participant was dressed in their undergarments, and the measurements took place after an overnight fast (10-12h).

FMI (kg/m²) is the measured fat mass in kg divided by the height squared in meters. LMI (kg/m²) is the participant's fat mass subtracted from the weight in kg, divided by the height squared in meters. BMI is composed of FMI in addition to LMI (BMI = FMI + LMI).

The z-scores of the FMI and the LMI were stratified by sex and combined after standardization, creating four body composition categories (Figure 4).

(A) FMI above average, LMI below average
(B) FMI above average, LMI above average
(C) FMI below average, LMI below average
(D) FMI below average, LMI above average

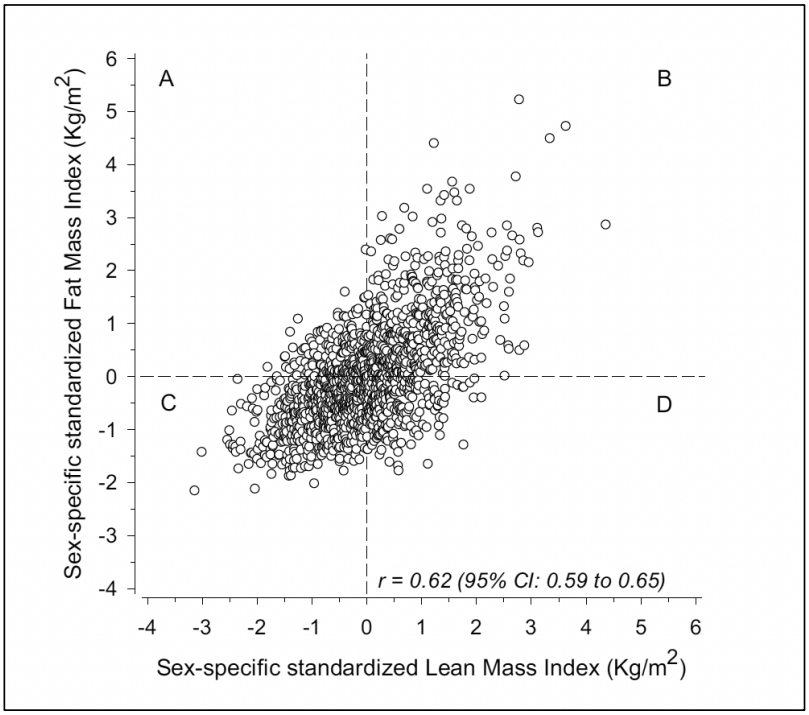


Figure 4 Sex-specific standardized body composition grouping. Axes represent z-scores, and dashed lines represent mean values. Letters represent body composition categories. (Study III)

4.2.3 LABORATORY MEASUREMENTS

Participants had their blood drawn after an overnight (10-12 hour) fast for laboratory analysis. Blood samples were analyzed for serum insulin, plasma glucose, homeostatic model assessment of insulin resistance (HOMA-IR), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, alanine transaminase, creatinine, hsCRP, and glycated hemoglobin A1c (HbA_{1c}). Each participant took part in a 75g oral glucose tolerance test (OGTT). As part of the OGTT plasma glucose measurements are obtained, after which 75g of liquid glucose is consumed orally. After the consumption of the oral glucose, plasma glucose levels are measured to evaluate the body's ability to metabolize glucose. Plasma glucose was evaluated using a hexokinase method at 0 minutes (fasting), 30 minutes and 120 minutes post consumption. Participants took their morning medication after the blood draws.

4.2.4 MORTALITY

Study participants were followed up regarding mortality for 28 044 person-years in total: 22 677 in the non-depressive group, 3 773 in the NMeD group, and 1 594 in the MeD group. The follow-up was initiated in 08/2001-03/2004 and ended December 31, 2018. The expected number of all-cause deaths, and actual deaths, were established through the official archive of death certificates in Finland (Statistics Finland). Calculations were based on sex-, age-, and calendar-period-specific mortality in the population of Finland. The standardized mortality ratio (SMR) was established by comparing observed mortality in the cohort to the expected mortality. Causes of death were categorized based on ICD-10 codes (THL, n.d.).

4.3 STATISTICAL ANALYSES

Descriptive statistics are presented as means with standard deviations (SD) for continuous variables, or as counts (*n*) with percentages for categorical variables. Statistical comparisons between groups were performed using *t*-tests, Pearson's chi-square tests, Fisher's exact test for categorical variables, generalized linear models, and analysis of variance (ANOVA).

Main effects and interactions of factors were established using ANOVAs and logistic models. For adjusted models analysis of covariance was applied. Hommel's adjustment was applied in the corrections of levels of significance for post hoc testing where appropriate. When theoretical distributions of test statistics were unknown or violating normality, the bootstrap method was used. In Study IV Monte Carlo p-values were used for small numbers as an alternative to the bootstrap method.

The possible non-linear relationships between BDI-IA and PWV (II) as well as between BDI-IA and mortality (IV) were assessed using 4-knot restricted cubic spline regression. Length of distribution of knots was at the 5th, 35th, 65th, and 95th percentiles, as recommended by Harrell (Harrell, 2001).

The Pearson method was used (I & III) for establishing correlation coefficients (95% CI). BDI-IA and body composition relationships were modeled by adjusted logistic models. Regression coefficient β was used to identify relationships between depressive groups (predictor) and AGE (outcome) in Study I.

For cumulative all-cause mortality in Study IV the Kaplan-Meier method was used, and adjusted Kaplan-Meier rates were estimated by inverse probability weighing. Hazard ratios (HR) and their 95% CIs were estimated using Cox proportional hazard regression (IV). Schoenfeld residuals and log-log plots were used in Study IV for evaluating the proportional-hazards assumption. Subject-year methods with 95% CI were used to calculate the ratio of observed to expected number of deaths for the SMR.

The normality of variables was evaluated graphically and by using the Shapiro–Wilk W test. The STATA software versions 16.1 (I & II) and 17.0 (III & IV) StataCorp LP (College Station, TX, USA) statistical packages were used for the analyses.

4.4 ETHICS

All procedures of this research project follow the ethics outlined by the Declaration of Helsinki. The study protocols (Dnro HUS/2020/2016 and 344/E3/2000) were approved by the Ethics Committee of the National Public Health Institute and the Coordinating Ethical Committee of the Hospital District of Helsinki and Uusimaa. Prior to participating in any part of the study each participant gave written informed consent. Care has been taken to conceal and protect each participant's identity. Each participant is assigned a number that is used instead of identifying personal information during the data analysis process. No participants are identifiable from the produced data.

5 RESULTS

5.1 PREVALENCE OF DEPRESSIVE SYMPTOMS

The prevalence of increased depressive symptoms in the present studies was 18-23% (Table 4). Figure 5 displays range of BDI-IA scores of study participants. Study I had a prevalence of 23%, with 66% of those with increased depressive symptoms being women. Women had higher mean BDI-IA scores (7.4, SD 5.8,) than men (5.6, SD 5.0) ($p<0.001$), and lower mean MHI-5 scores (79, SD 16) than men (84, SD 15) ($p<0.001$) indicating higher depressive symptoms among women (Study I). The BDI-IA and MHI-5 scores correlated among the participants ($r =-0.71$; 95% CI: -0.74 to -0.67).

In Study II 22% of participants, with 70% of them being women, scored in the depressive range (BDI-IA ≥10). Study III had 18% of participants scoring in the depressive range, with 70% of them being women, while Study IV had a prevalence of 20% with BDI-IA ≥10, with 67% of those in the depressive range being women.

The prevalence of increased depressive symptoms among women ranged between 23% and 28% in the four studies. The respective prevalence for men were 12-17%.

Figure 13 displays graphically how a cut-off of 10 points on the BDI-IA represents the point above which a significant increase in depressive symptoms present.

5.1.1 DEPRESSIVE SUBGROUPS

Table 4 presents the prevalence of depressive symptoms (BDI-IA ≥10) for each of the four studies. The prevalence for NMeD symptoms ranged from 14% to 19%, and from 4% to 6% for MeD symptoms (Study I-IV). Of all the participants with depressive symptoms the representation of the NMeD group was 84% (Study I), 81% (Study II), 68% (Study III), and 70%, (Study IV), respectively. Of the depressive group MeD symptoms represented 16% (Study I), 19% (Study II), 32% (Study III), and 30% (Study IV), respectively.

In Study I the distribution of depressive symptoms among the sexes (Table 4) showed a significant difference ($p = 0.003$). Of the participants scoring in the depressive range 86% of women and 79% of men were

classified as having NMeD symptoms, with 14% of women and 21% of men having MeD symptoms.

The distribution of depressive symptoms for Studies I-IV is presented in Table 4. Of the depressive women in Study II 84% were classified as NMeD, and 16% as MeD. Of the depressive men 74% were in the NMeD group, and 26% in the MeD group (Study II). Within the depressive group of Study III 75% of women and 53% of men were in the NMeD group, and 25% of women and 47% of men were in the MeD group, respectively. Among participants scoring in the depressive range in Study IV, 77% of women and 56% of men were in the NMeD group, and 23% of women and 44% of men were in the MeD group. No difference was found in sex distribution between individuals without depressive symptoms and MeD symptoms (Study III and IV).

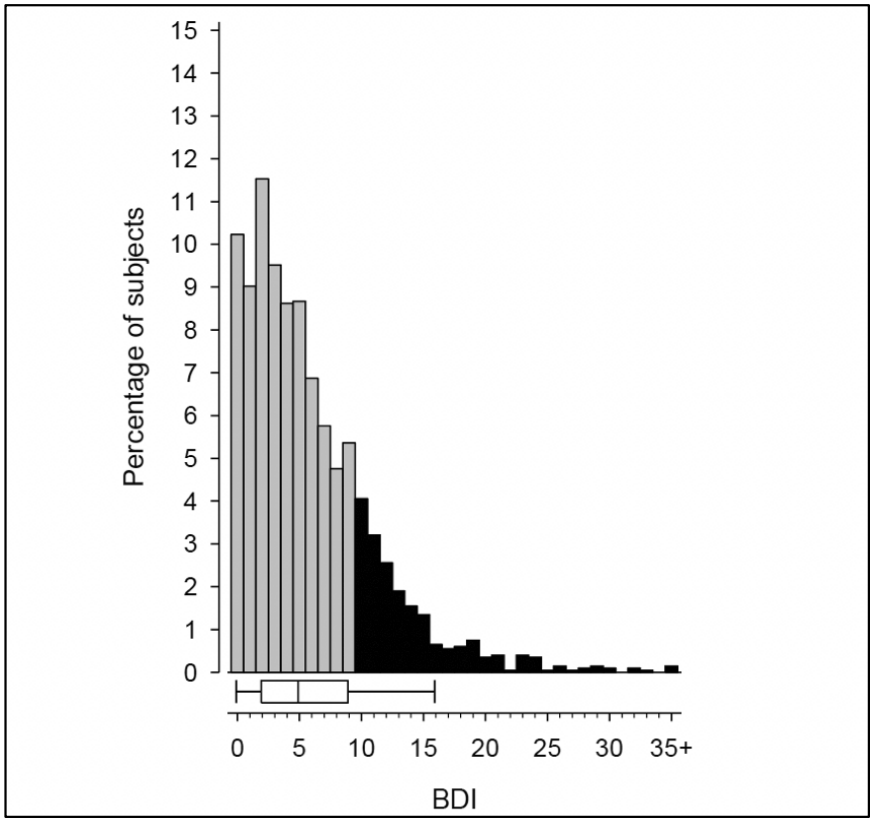


Figure 5 Distribution of Beck Depression Inventory-IA (BDI-IA) scores in the study population. Boxplot shows median and interquartile range. Whiskers indicate 5th and 95th percentiles. The black represents those scoring ≥10 on the BDI-IA. (Study IV)

Table 4. *Prevalence of depressive symptoms by type of symptoms and sex for each study. NMeD=non-melancholic depressive, MeD=melancholic depressive.*

	Study			
	I	**II**	**III**	**IV**
	n = 815 458 women, 357 men	*n* = 683 378 women, 305 men	*n* = 1510 842 women, 668 men	*n* = 1995 1067 women, 928 men
Prevalence of depressive symptoms per sex, *n* (%)				
All	185 (23)	151 (22)	274 (18)	392 (20)
Men	62 (17)	46 (15)	83 (12)	131 (14)
Women	123 (27)	105 (28)	191 (23)	261 (24)
Prevalence of NMeD symptoms per sex, *n* (%)				
All	155 (19)	122 (18)	187 (18)	273 (14)
Men	49 (14)	34 (11)	44 (7)	73 (8)
Women	106 (23)	88 (23)	143 (17)	200 (19)
Prevalence of MeD symptoms per sex, *n* (%)				
All	30 (4)	29 (4)	87 (6)	119 (6)
Men	13 (4)	12 (4)	39 (6)	58 (6)
Women	17 (4)	17 (4)	48 (6)	61 (6)

5.2 SOCIODEMOGRAPHIC AND LIFESTYLE FACTORS ASSOCIATED WITH DEPRESSIVE SYMPTOMS

There was a significant difference in depressive distribution between the sexes (Study I), with depressive symptoms being more common among women than men ($p<0.001$). The group with the highest proportion of women was the NMeD group ($p<0.001$). No difference in sex distribution was found between the MeD group and the non-depressive group. The depressive group had higher CCI scores compared to the non-depressive group ($p=0.027$). No significant differences were recorded when comparing the whole depressive group with the non-depressive group regarding blood pressure, plasma glucose, hsCRP, BMI, smoking status, and prevalence of DM (Study II). However, when separating the depressive participants into depressive subtypes Study III found that both depressive subgroups had higher prevalence of CVD than the non-depressives, and the NMeD group also had more pulmonary disease than the non-depressive group. In Study IV the NMeD group had more CVD, pulmonary disease, and DM than the non-depressive group, but no differences were found regarding cancer or between other groups.

Study II found that participants with BDI-IA ≥10 had higher triglyceride concentrations ($p=0.018$). Study IV showed that this specifically applied to the MeD group compared to the non-depressive group ($p=0.001$). There was an association between lower financial satisfaction and depressive symptoms (II). Depressive symptoms were also associated with less LTPA ($p=0.002$), lower likelihood of cohabitation ($p=0.045$), and lower likelihood of financial satisfaction ($p<0.001$). Compared to the non-depressive group, the NMeD group was less educated ($p=0.002$), less likely to cohabitate ($p<0.001$) or consume alcohol ($p=0.001$), but more likely to be current smokers ($p=0.048$), and have higher mean hsCRP levels ($p=0.045$). Compared to the other groups, participants of the NMeD group had higher BMI ($p<0.001$), and higher FMI ($p<0.001$). The NMeD participants also had lower mean LMI than the non-depressive group ($p=0.006$).

The MeD group had lower mean systolic ($p=0.004$) and mean diastolic ($p<0.001$) blood pressure, total cholesterol concentration ($p=0.005$), and LDL cholesterol concentration ($p<0.001$) than either of the other groups. There were no differences between the MeD and NMeD groups regarding LTPA, cohabitation, financial satisfaction, triglycerides or CCI scores. Study IV also established that there was no difference in mean BDI-IA scores between the NMeD and MeD groups ($p=0.62$).

5.3 ADVANCED GLYCATION END PRODUCTS AND DEPRESSIVE SYMPTOMS (STUDY I)

Women scored lower on AGE levels (mean 2.33 AU, SD 0.46) than men (mean 2.49 AU, SD 0.51) ($p < 0.001$), with a difference of 0.16 AU in crude AGE levels (95% CI: 0.10–0.24). There was no interaction between depressive groups and sex ($p=0.33$). A significant association was however established between depressive symptoms and AGE for both sexes, which remained virtually unchanged for women, and likewise significant for men, after adjusting for age, smoking, economic status, years of education, and cohabitation. After additionally adjusting for BMI, LTPA, and HbA_{1c} associations remained significant for both sexes.

A correlation was found between AGE and HbA_{1c} ($r= 0.17$; 95% CI: 0.10 to 0.23). Men had a higher prevalence of DM (21%) than women (16%) ($p = 0.033$), and women had lower CCI scores (1.0, SD 1.6) than men (1.4, SD 1.8) ($p = 0.004$).

5.3.1 SUBTYPES OF DEPRESSIVE SYMPTOMS AND ADVANCED GLYCATION END PRODUCTS

Mean AGE levels were adjusted for age, smoking status, years of education, economic status, BMI, cohabitation, DM, and HbA_{1c} while compared for between depressive groups (Figure 6). There were main effects for sex ($p<0.001$) and for depressive groups ($p=0.041$), but their interaction was not significant ($p=0.23$). The MeD group was found to have the highest crude AGE levels (2.61 AU, SD 0.57), with the NMeD following behind (2.45 AU, SD 0.45), leaving the non-depressive group with the lowest levels (2.38 AU, SD 0.49) ($p = 0.013$). After post hoc analysis the MeD group was shown to have significantly higher AGE levels than the non-depressive group ($p=0.023$).

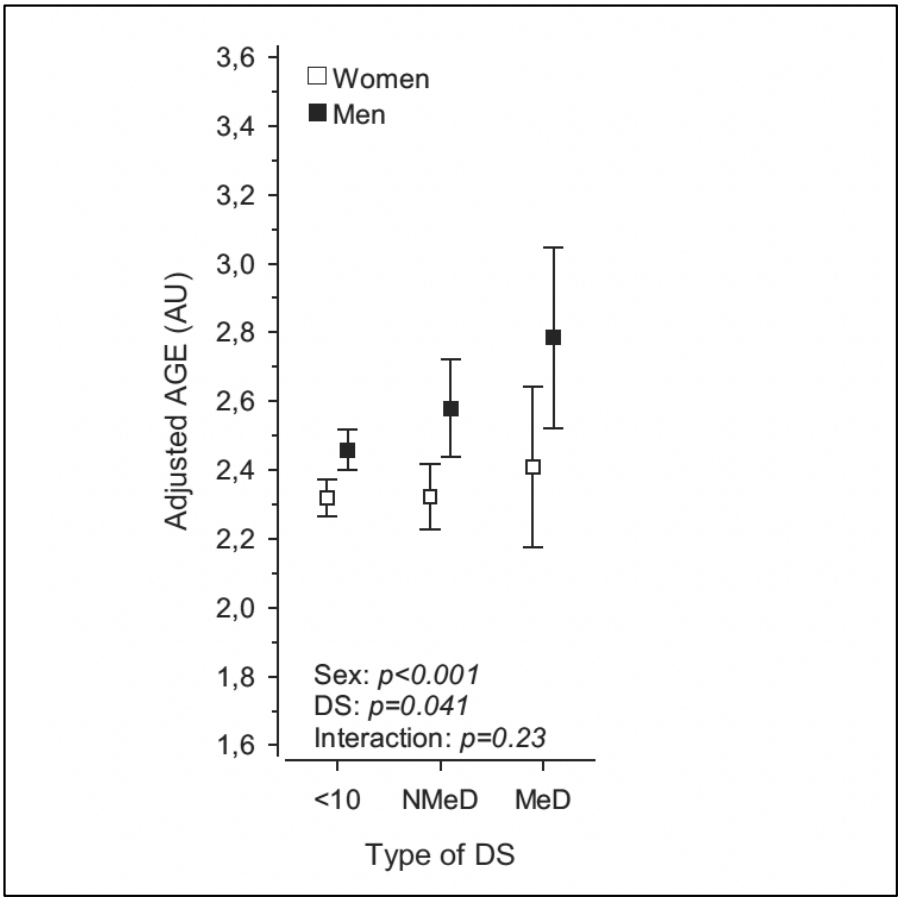


Figure 6 Advanced glycation end product (AGE) values by sex and depressive subtypes (DS). AGE readings are adjusted for age, smoking status, years of education, economic status, cohabitation status, diabetes mellitus, glycated hemoglobin, body mass index, and leisure-time physical activity. P-values were derived from a two-way ANOVA of sex and depressive subtype related to AGE. Sex = comparison of AGEs by sex; DS = comparison of AGEs by depressive subtypes; Interaction = the interaction of sex and DS in relation to AGEs. (Study I)

5.4 PULSE WAVE VELOCITY AND DEPRESSIVE SYMPTOMS (STUDY II)

Mean crPWV was lower for women (10.01 m/s, SD 1.59) than for men (10.69 m/s, SD 2.98) ($p<0.001$). There was no difference between mean cfPWV for women (12.75 m/s, SD 4.25) and for men (12.87 m/s, SD 4.53) ($p=0.71$)

The relationship between BDI-IA and PWV according to sex (adjusted for age, CCI, MAP, smoking status, and years of education) is displayed in Figure 7. The study found no relationship between BDI-IA and cfPWV ($p=0.47$) or crPWV ($p=0.50$) for women. For men there was no relationship between BDI-IA and cfPWV ($p=0.30$). However, a significant relationship was found between BDI-IA and crPWV for men ($p<0.001$).

5.4.1 PULSE WAVE VELOCITY IN NON-MELANCHOLIC DEPRESSIVE MEN

The relationship between PWV and depressive symptoms per sex is shown in Figure 8. Data has been adjusted for age, CCI, MAP, smoking status, and years of education. No differences were found between NMeD and MeD for cfPWV ($p= 0.82$). There was, however, a significant difference in crPWV between NMeD and MeD ($p<0.001$). Differences between sexes were found for crPWV ($p=0.020$), but not for cfPWV ($p=0.58$). For interactions between sex and type of depressive symptoms it was significant for crPWV ($p=0.009$), but not for cfPWV ($p=0.76$). Men in the NMeD group had the highest crPWV.

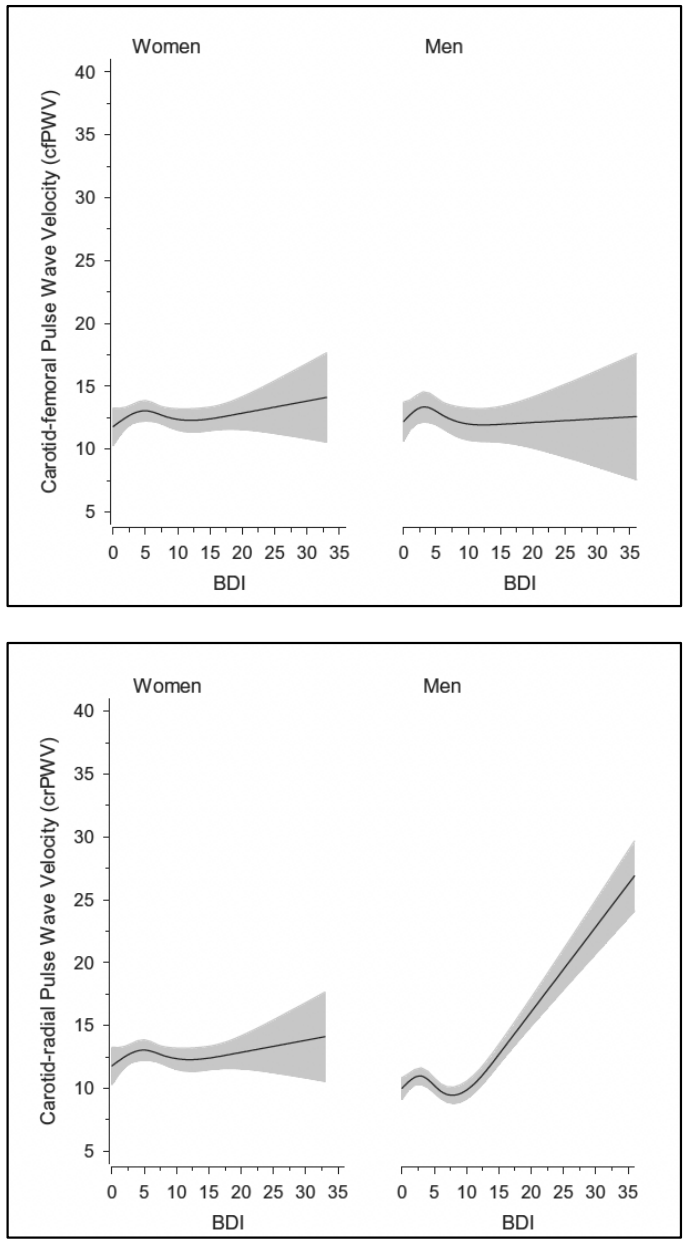


Figure 7 Relationships of PWV as the function of the BDI-IA in men and women. All curves have been derived from 4-knot-restricted cubic splines regression models. The models have been adjusted for age, CCI, MAP, smoking status, and years of education. Grey areas represent a 95% CI. BDI=Beck Depressive Inventory-IA, CCI=Charlson comorbidity index, MAP=mean arterial pressure, PWV=pulse wave velocity. (Study II)

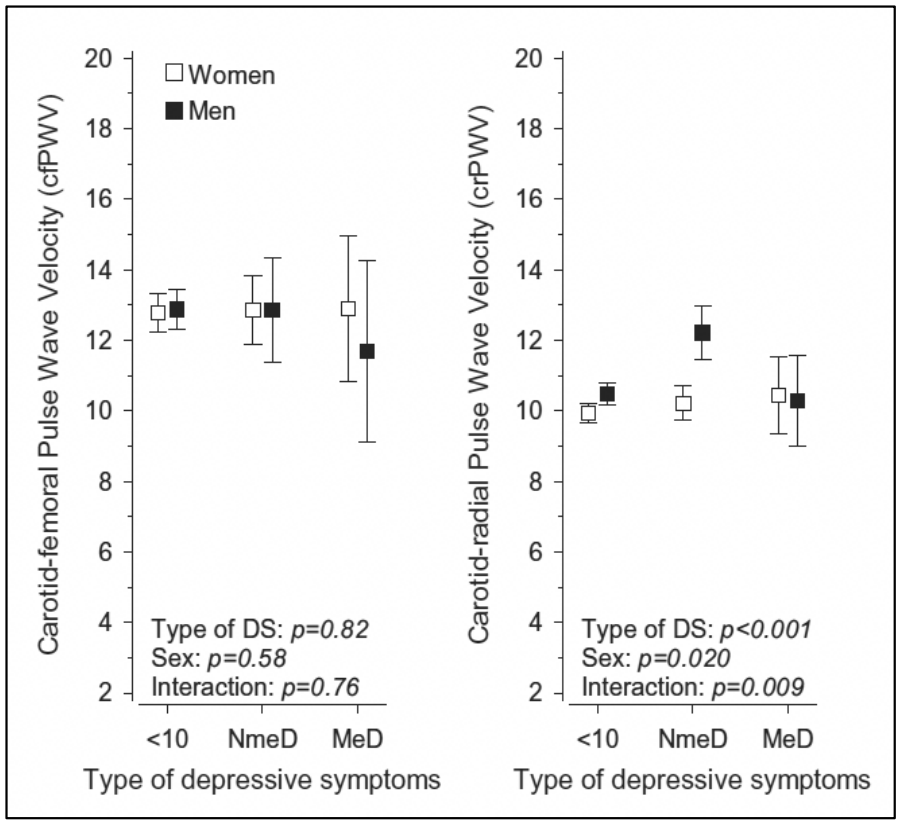


Figure 8 cfPWV and crPWV in men and women based on type of depressive subtype. Data has been adjusted for age, CCI, MAP, smoking status, and years of education. CCI=Charlson comorbidity index, cfPWV=carotid-femoral pulse wave velocity, crPWV=carotid-radial pulse wave velocity, DS=depressive subtypes, NMeD=non-melancholic depressive, MAP=mean arterial pressure, MeD=melancholic depressive, <10= <10 BDI-IA points= non-depressive. (Study II)

5.5 BODY COMPOSITION AND DEPRESSIVE SYMPTOMS (STUDY III)

Study III found that it was more common for women to be in groups B and C (high FMI–high LMI, and low FMI–low LMI) than groups D and A (low LMI–high FMI, and high LMI–low FMI). It was established that there was an interaction between FMI, LMI and sex ($p<0.001$). Participants with high FMI had lower HDL cholesterol, and higher triglycerides, higher hsCRP, higher heart rate, and higher blood pressure compared to those with low FMI. They also had higher BDI-IA scores. On the other hand, participants with high LMI also had higher blood pressure and triglycerides along with lower HDL cholesterol and heart rate compared to their counterparts with low LMI. No differences in hsCRP or BDI-IA were found related to the different LMI groups.

A higher FMI was associated with higher probability of scoring in the depressive range (mean 20.2 %, 95% CI: 17.2–23.2) compared to low FMI (mean 16.3%, 95% CI: 13.8–18.9) after adjusting for age, sex, years of education, and fasting plasma glucose concentration (Figure 9). No effect for LMI ($p=0.49$), nor any interaction ($p=0.26$) was found.

Participants with higher FMI had a higher likelihood of having depressive symptoms (odds ratio [OR] per 1 SD, FMI = 1.37, 95% CI 1.13–1.65). Those with higher LMI were less likely to have depressive symptoms (OR per 1 SD, LMI = 0.76, 95% CI 0.64–0.91). This has been represented visually in Figure 10.

5.5.1 NON-MELANCHOLIC DEPRESSIVE SYMPTOMS AND BODY COMPOSITION

NMeD participants had higher mean BMI (28.2 kg/m², 5.4 SD) than either of the other two groups (MeD: 26.8 kg/m², 4.6 SD; BDI-IA<10: 26.9 kg/m², 3.9 SD) ($p<0.001$), and higher FMI (mean 9.6 kg/m², SD 4.1) than either of the other groups (BDI-IA<10: mean 7.7 kg/m², SD 3.1; MeD: mean 7.9 kg/m², SD 3.6) ($p<0.001$). Compared to the non-depressive individuals, the NMeD group had lower LMI (NMeD: mean 18.6, SD 2.2; BDI-IA<10: mean 19.1, SD 2.1) ($p=0.006$), higher hsCRP (NMeD: mean 2.49, SD 2.25; BDI-IA<10: mean 2.11, SD 2.08) ($p=0.045$) and higher 2-h glucose concentration (NMeD: mean 7.21 mmol/l, SD 1.65; BDI-IA<10: mean 6.78 mmol/l, SD 1.70) ($p=0.005$).

Those participants with high FMI more frequently had NMeD symptoms (mean 14.7%, 95% CI: 11.8-17.7) than those with low FMI (mean 9.7%, 95% CI: 7.6-11.9) regardless of LMI levels (Figure 11).

5.5.2 MELANCHOLIC DEPRESSIVE SYMPTOMS AND BODY COMPOSITION

Compared to the non-depressive and NMeD groups, the participants of the MeD group had lower blood pressure, LDL cholesterol, and total cholesterol. There were no differences in frequency of MeD symptoms between the body composition groups (FMI p=0.83, LMI p=0.93), and there was no interaction either (p=0.52).

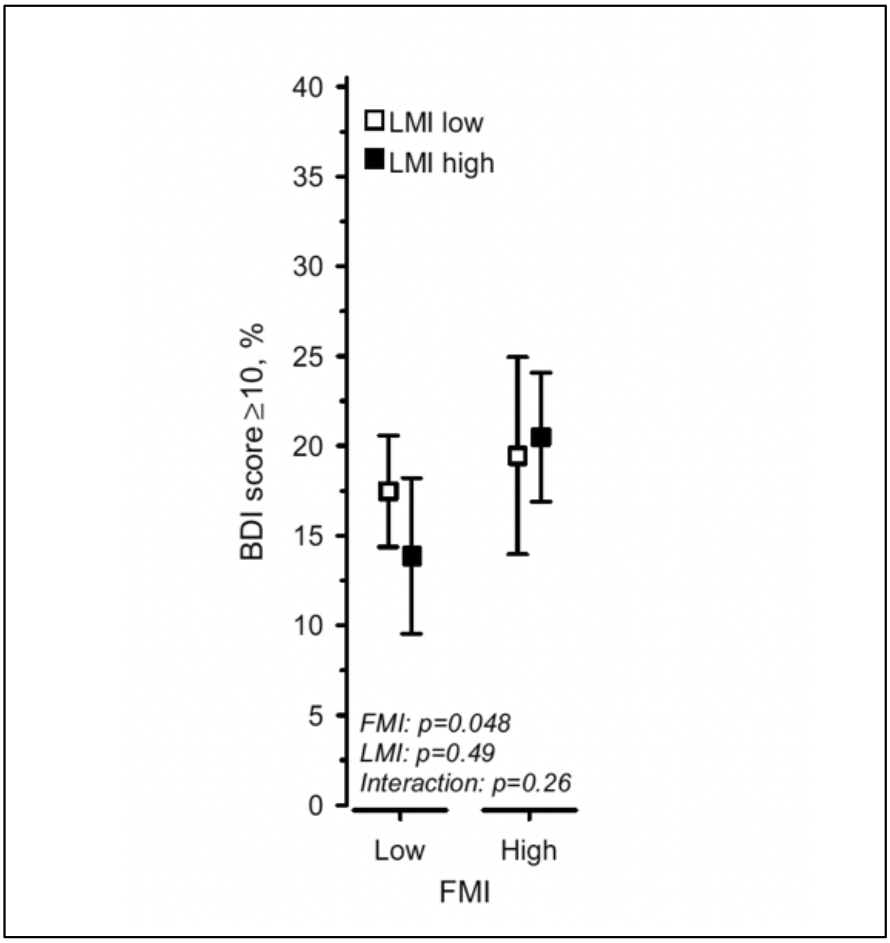


Figure 9 Percentage of BDI-IA scores in the depressive range per body composition group. Data has been adjusted for age, sex, years of education, and fasting plasma glucose concentration. BDI=Beck Depression Inventory-IA, FMI= fat mass index, LMI=lean mass index. (Study III)

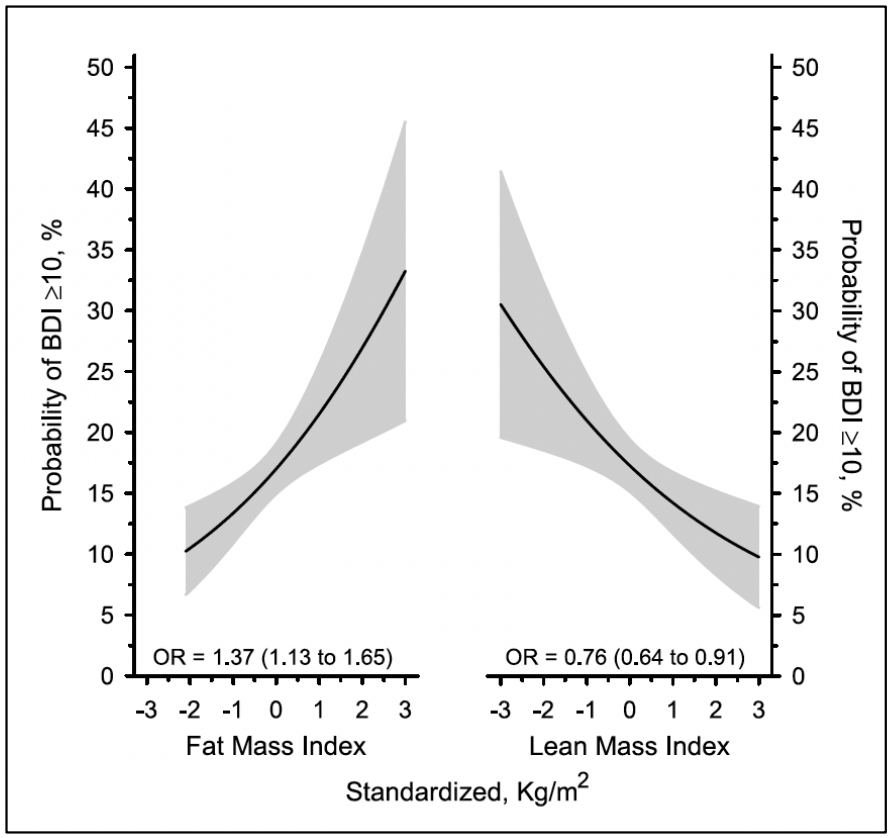


Figure 10 Relationship between scoring in the depressive range of the BDI-IA, and body composition. Odds ratio (OR) is presented per 1 SD. Data has been adjusted for age, sex, years of education, and fasting plasma glucose concentration. BDI=Beck Depression Inventory-IA. (Study III)

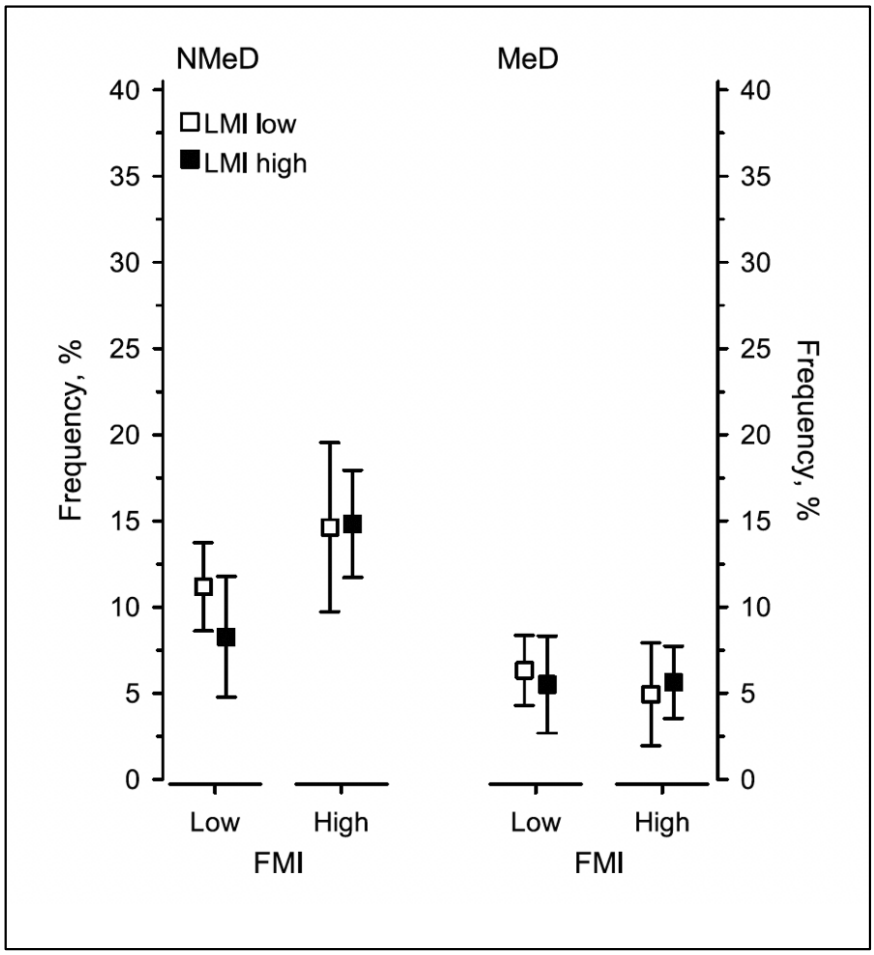


Figure 11 Frequency in terms of body composition (mean, SD) per depressive subtype. Data has been adjusted for age, sex, years of education, and fasting plasma glucose concentration. NMeD: FMI p = 0.008, LMI p = 0.38, interaction p = 0.31. MeD: FMI p = 0.83, LMI p = 0.93, interaction p = 0.52. FMI=fat mass index, LMI=lean mass index, NMeD=non-melancholic depressive, MeD=melancholic depressive. (Study III)

5.6 GLUCOSE METABOLISM, BODY COMPOSITION, AND DEPRESSIVE SYMPTOMS (STUDY III)

A main effect was found for high FMI on both fasting glucose concentrations and post load (75g OGTT) glucose concentrations (Table 5). High FMI also had a main effect on fasting insulin concentration ($p<0.001$) and HOMA-IR ($p<0.001$). High LMI had a main effect on fasting glucose ($p<0.001$), as well as fasting insulin ($p=0.008$) and HOMA-IR ($p=0.003$), but no relation to post-load (75g OGTT) glucose concentrations.

NMeD participants had higher mean post load glucose concentrations at 120 min compared to the BDI-IA<10 group (Table 6). No other differences were found for depressive subtypes for fasting insulin, HOMA-IR, or glucose levels.

Table 5. *Glucose and insulin concentrations per body composition group after a 75 g oral glucose tolerance test. FMI= fat mass index, LMI= lean mass index. (Study III)*

	High FMI		Low FMI		p-value		
	Low LMI	High LMI	Low LMI	High LMI	Main effect		Interaction
	A n = 197	**B** n = 470	**C** n = 580	**D** n = 263	FMI	LMI	
Glucose (mmol/l), mean (SD)							
0 min	5.51 (0.57)	5.63 (0.56)	5.37 (0.54)	5.48 (0.53)	< 0.001	< 0.001	0.93
30 min	9.17 (1.69)	9.27 (1.52)	8.80 (1.73)	8.81 (1.60)	< 0.001	0.57	0.62
120 min	7.22 (1.67)	7.25 (1.65)	6.50 (1.65)	6.59 (1.75)	< 0.001	0.53	0.78
Fasting insulin (µU/ml) mean (SD)	11.1 (14.8)	13.8 (16.5)	7.2 (4.2)	7.8 (4.1)	< 0.001	0.008	0.10
HOMA-IR, mean (SD)	2.74 (3.51)	3.52 (4.48)	1.73 (1.08)	1.92 (1.07)	< 0.001	0.003	0.073

Table 6. *Glucose measurements per depressive group after a 75 g oral glucose tolerance test. *Hommel's multiple comparison procedure was used to correct the significance level for post hoc testing (p < 0.05). BDI-IA<10= non depressive, NMeD=non-melancholic depressive, MeD=melancholic depressive. (Study III)*

	BDI -IA < 10 [**X**]	NMeD [**Y**]	MeD [**Z**]	
	N = 1236	N = 187	N = 87	p-value [multiple comparison]
Glucose (mmol/l), mean (SD)				
0 min	5.49 (0.54)	5.49 (0.61)	5.50 (0.62)	0.96
30 min	8.95 (1.62)	9.22 (1.69)	9.13 (1.98)	0.10
120 min	6.78 (1.70)	7.21 (1.65)	6.94 (1.72)	0.005 [**X/Y**] *
Fasting insulin (μU/ml), mean (SD)	9.8 (11.8)	11.2 (11.3)	8.4 (5.1)	0.15
HOMA-IR, (mean (SD)	2.43 (3.12)	2.80 (2.86)	2.10 (1.34)	0.16

5.7 ALL-CAUSE MORTALITY AND DEPRESSIVE SYMPTOMS (STUDY IV)

A total of 357 participants (273 non-depressive, 55 NMeD, 29 MeD) died during the follow-up period. The crude mortality rate was 19.2% (95% CI: 17.0-21.6), 21.7% (95% CI: 16.9-27.5), and 24.4% (95% CI: 17.7-33.2) for the non-depressive group, NMeD group, and MeD group, respectively (p=0.051). After adjusting the mortality data for age, sex, years of education, systolic blood pressure, smoking status, CVD, BMI, DM and dyslipidemia there was no difference between the three groups (p=0.11).

There was no difference in adjusted cumulative mortality between the non-depressive and NMeD groups (Figure 12). Study IV also showed that the HR for mortality increases along with increasing BDI-IA scores. A BDI-IA above 10 is associated with a HR that is significantly higher than for a BDI-IA of zero (Figure 13).

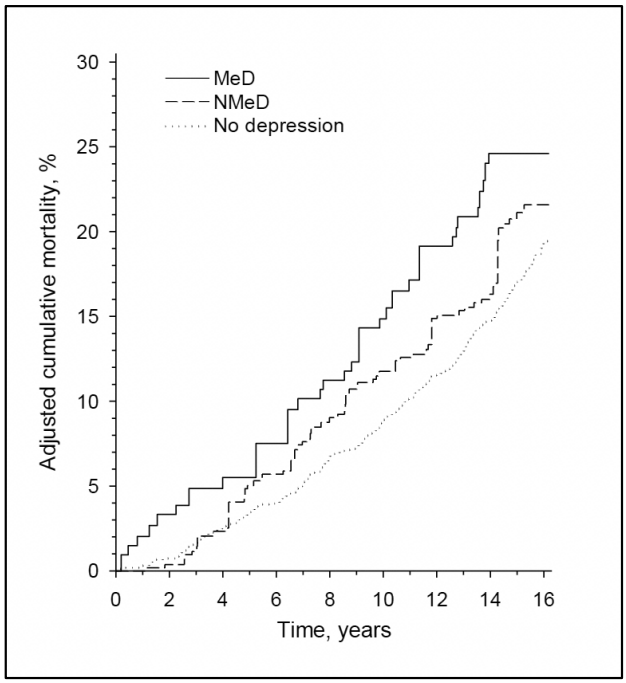


Figure 12 All-cause mortality over time according to depressive symptoms. Adjusted for diabetes mellitus, age, sex, years of education, systolic blood pressure, smoking status, cardiovascular disease, body mass index, and dyslipidemia. NMeD=non-melancholic depressive, MeD=melancholic depressive. (Study IV)

When using the mortality HR of the non-depressive group as the comparison point, it showed that there is no increase in mortality risk for the NMeD in either crude or adjusted data models. There is, however, a higher risk for the MeD group in the crude model (HR 1.53, 95% CI: 1.04-2.42) and the adjusted (DM, age, sex, years of education, systolic blood pressure, smoking status, CVD, BMI, and dyslipidemia) model (HR 1.49, 95% CI: 1.02-2.20).

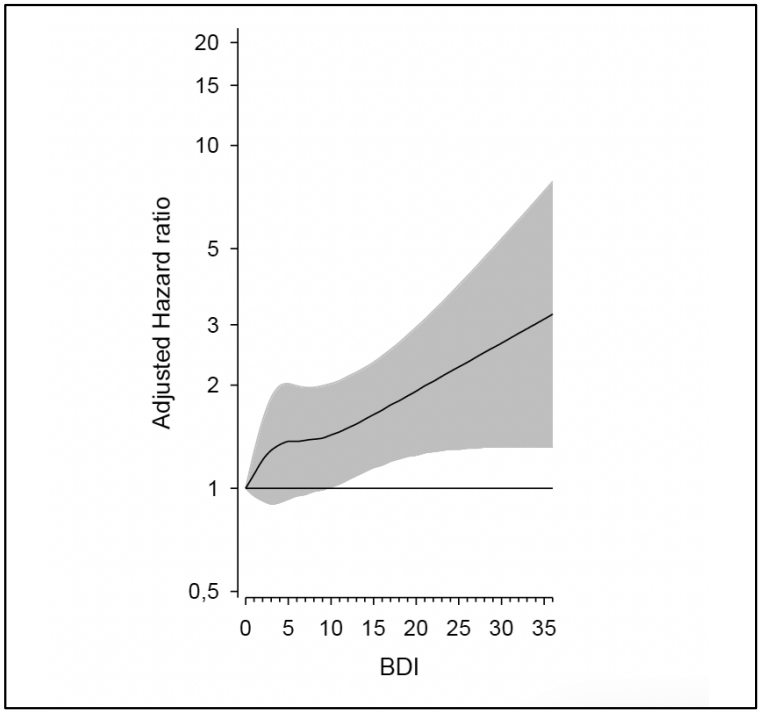


Figure 13 All-cause mortality HR in relation to BDI-IA scores. Data has been adjusted for age, sex, years of education, smoking status, DM, systolic blood pressure, CVD, BMI, and dyslipidemia. The grey area represents the 95% confidence interval. BDI=Beck Depression Inventory-IA, BMI=body mass index, CVD=cardiovascular disease, DM=diabetes mellitus.
The reference point (HR 1.00) is set at a BDI-IA score of zero. (Study IV)

5.7.1 CAUSES OF DEATH

The highest percentage of death is caused by neoplasms (C00-D48) both when looking at each depressive subgroup separately and overall. The same applies for diseases of the circulatory system (I00-I99), which is the second most common cause of death. The other categories for causes of death were certain infectious and parasitic diseases (A00-B99), diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89), endocrine, nutritional and metabolic diseases (E00-E90), mental, behavioral and neurodevelopmental disorders (F00-F99), diseases of the nervous system (G00-G99), diseases of the respiratory system (J00-J99), diseases of the digestive system (K00-K93), symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99), and external causes of morbidity (V01-Y98).

5.7.2 STANDARDIZED MORTALITY RATIO

The mortality of the study population was compared to that of the general population and no difference was found in SMR between NMeD (1.11, 95% CI: 0.85-1.44) or MeD (1.26, 95% CI: 0.87-1.81) and the general population. However, SMR for the non-depressive group (0.82, 95% CI: 0.73-0.93) was significantly lower than that of the general population. It was also found that mortality ratios in the NMeD group (p=0.044) and the MeD group (p=0.031) were significantly higher than in the non-depressive group.

6 DISCUSSION

This thesis examined some differences between individuals displaying NMeD and MeD symptoms. Focusing on AGEs, PWV, body composition, glucose metabolism, and mortality in individuals from the HBCS certain differences between the two depressive subtypes were established. MeD symptoms seem to be more closely related to AGE and mortality, whereas NMeD symptoms seem to have a closer relationship with PWV, body composition and glucose metabolism. The differences in pathophysiology may suggest that the depressive subtypes are caused by differing pathology or even represent different disease processes presenting with similar depressive symptoms.

6.1 PARTICIPANTS

All participants were part of the original cohort of 13 345 individuals born in Helsinki between 1934 and 1944. The HBCS-cohort has been extensively phenotyped, adding to the strengths of these studies. It is possible that since these individuals have taken part in studies for such a long time that their salience toward health behaviors differs from other individuals', which may be reflected in comparisons between the cohort and the general population. It is also possible that those with the most severe health conditions either opted not to participate in the studies or had already passed away.

When the cohort data gathering started in 1995 the youngest of the individuals would have been over 50 years old, and the oldest over 60 years old. All participants are of a similar age, which may limit the applicability of the findings to this specific age group.

Another factor possibly affecting the participants is that only people born in Helsinki, with the majority still living there, were part of the studies. Lifestyles in other parts of the country may vastly differ, possibly affecting health and health outcomes. Without doubt, differences may also exist between countries and areas of the world, possibly limiting global applicability of any findings.

However, for the clinical studies the study participants were randomly selected from the large cohort without discrimination or exclusions. This ensures that the participants are as representative as possible of the population they represent.

6.2 METHODS

6.2.1 ASSESSMENT OF DEPRESSIVE SYMPTOMS

Depression can be assessed using a variety of validated screening tools. In this cohort the BDI-IA has been used. In Study I the MHI-5 was also used to show the validity of the BDI-IA as a screening tool in the population at hand.

Studies I-IV have been based on DSM-IV even though a more updated version, the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), does exist. There are very few changes made to the sections on major depression between the DSM-IV and the DSM-5, with the significant one being the removal of bereavement as an exclusion criteria for MDD in the updated version (Black & Grant, 2014). Bereavement has, however not been utilised as an exclusion criteria in the studies (Study I-IV), and therefore this update would not have significantly affected the symptomatic criteria used. The DSM-5 is not discussed in any more detail here since it has not been part of the studies at hand. The cohort data gathering began before the time of the DSM-5, and in order to keep things consistent throughout the studies the DSM-IV continues to be used in the HBCS.

6.2.1.1 The Beck Depression Inventory

The studies of the thesis used the BDI (Beck et al., 1961), specifically the BDI-IA version (Beck et al., 1996) to screen for depressive symptoms. The BDI-IA has been validated as a screening tool both internationally and for the Finnish population (Beck et al., 1996; Nuevo et al., 2009). The BDI has previously been used to differentiate between depressive subtypes as well (Järvimäki et al., 2016; Ovaskainen et al., 2009; Rantanen et al., 2020; Seppälä, Koponen, et al., 2012; Seppälä, Vanhala, et al., 2012; Vanhala et al., 2009), making it suitable for the purpose of this project. The BDI has been shown to possibly over-estimate depression when used for screening purposes with a low cut-off (Bautovich et al., 2018; Vasegh & Baradaran, 2014; Zich et al., 1990). Hence, it is possible that the depressive subgroups in the current studies are estimated to be larger than they are in reality. The screening cut-off point of ≥10 was set by Beck himself to include all severities of depression (Beck et al., 1988). However, Figure 13 shows that in this population the cut-off of 10 points on the BDI-IA is representative of when significantly increased depressive symptoms present.

The BDI was originally intended to be used as a tool by professionals (Beck et al., 1961). However, here individuals answered the questions in the form of a questionnaire, which could possibly affect the results. A professional using the BDI-IA would have the opportunity to ask further questions and narrow down the appropriate response based on clinical expertise. Eliminating the professional opinion may allow for differing interpretations regarding symptom severity making responses less objective. However, the aim for these studies was never to screen for clinically diagnosable depression, but to allow for even mild symptoms to be included. Allowing for the subjective severity to be reflected in the responses, and keeping the cut-off score low, the intention was to include all individuals showing any type of depressive symptoms rather than restricting the groups and only allowing for more severe symptomatology. Furthermore, it has been noted that when using BDI as a screening tool for depression other psychiatric symptoms such as anxiety are found as well (Kotiaho et al., 2019). It is unclear whether this is due to the frequent occurrence of comorbidities or whether the BDI questions themselves pick up symptoms of other psychiatric diagnoses than just depression.

As discussed in the Methods section, the BDI-IA does leave out two of the DSM-IV criteria for the melancholic specifier. Psychomotor retardation or psychomotor symptoms (DSM-IV criteria B.4) are virtually impossible for individuals to assess themselves (Tamada et al., 2021). Considering that depressive symptoms in studies I-IV are determined based on self-reports, it would not be expected for self-reported psychomotor symptoms to be accurately reported even if they would have been screened for. Therefore, having this criterion included would unlikely add any further value to screening process. The second DSM-IV criteria (B.2) that has been omitted is diurnal variation. It would be of value to have this variable included. However, even the DSM-IV does not require all criteria to be satisfied for any specifier to be applicable. Hence, even though this criterion is absent in the categorization of depressive subtypes, it does not render the method invalid.

Finland having two official languages, Finnish and Swedish (Oikeusministeriö, n.d.), means that participants may have either one as their primary language. All BDI-IA questionnaires were in Finnish, which eliminates the possibility of translation errors or differing wording which could have resulted in differing results between the questionnaires in each language. However, since some of the participants do not have Finnish as their primary language it may lead to differences in how questions are interpreted. Most people in Finland speak Finnish fluently, especially in the Helsinki region, even if it is not their primary language, and therefore it was opted for as the best option to minimize any room for error. It may, however, be of

interest to investigate whether language affects the scores on the BDI-IA questionnaire in this population.

6.2.2 SELF-REPORTED QUESTIONNAIRES

All information regarding health, medication, lifestyle, habits, and exercise was gathered through participants reporting this through questionnaires. The first obvious question is whether this information can be trusted to be reliable. People may forget to report something, may not be aware of everything they should be mentioning, may feel shame and try to hide certain information, or for any other reason not report things accurately. Research shows that people do not always accurately self-report lifestyle habits such as smoking (Gorber et al., 2009), physical activity (Tucker et al., 2011), and alcohol consumption (Del Boca & Darkes, 2003).

However, gathering all required information through health records or databases would not be feasible either since there is no centralized database containing all the information. Neither would laboratory tests and continuous tracking regarding tobacco, alcohol, drugs, and exercise be realistic options. Furthermore, gathering information pertaining to the entire lives of these individuals would be impossible as much information only exists in paper format if at all.

The LTPA is slightly problematic in the sense that it requires extensive memory. It asks for an assessment of the past year, which can prove hard for anyone to remember accurately. However, tracking people for long periods of time to assess physical activity requires both additional technology and analysis of such data.

Due to the factors mentioned above, first-person accounts by each participant would be the only feasible way to gather this information. Each participant has been de-identified so as not to connect their health information to their personal information. This gives the participants a certain level of anonymity which hopefully encourages a level of honesty regarding responses.

6.2.3 CLINICAL AND LABORATORY MEASUREMENTS

All measurements were obtained by a trained nurse at the same clinic in Helsinki. This eliminates the risk of variance in procedures between locations. Professionally measured parameters of blood pressure, glucose concentrations, and weight for example are more reliable due to the fact that these have been shown to be portrayed in a bias manner when self-reported (Maukonen et al., 2018; Peterson et al., 2016).

In some cases, people who were unaware of, for example, having impaired glucose metabolism or high blood pressure gained valuable insights into their health through these clinic visits. In some ways this could be viewed as resulting in the study participants being more aware and possibly in better health than their peers. However, most of the findings were no different than what their own physician could have told them at a check-up. For these studies (I-III) subjects also received their own results for AGE, PWV, and body composition measurements. It is possible that these results may have made subjects more aware of their health, but it is unlikely that knowing these results by themselves would have resulted in any direct medical interventions.

SAF measurements of AGEs have been validated for use by previous studies (Meerwaldt et al., 2004; van Dooren et al., 2017). Every participant in Study I had non-pigmented skin as recommended for SAF readings (Meerwaldt et al., 2004). This, however, limits the ability to utilize said technique in populations with pigmented skin.

PWV measurements required participants to lay supine on an examination table for the duration of the measurements. This proved challenging for some participants due to age and health problems. It is possible that having to eliminate these individuals due to missing data could have affected the results. One could think that those with the worst health may have problems participating, leading the participants of Study II to possible represent a slightly healthier than average population. Each measurement was taken by the same nurse as to limit user variability and aiding in reliability of the results.

Body composition was presented as LMI and FMI, which is a more accurate representation of body composition than BMI alone. The ability to separate these parameters allows for more detailed analysis and categorization. Participants were separated into four groups based on combinations of LMI and FMI in order to be able to compare said groups amongst themselves. Furthermore, LMI and FMI values were stratified by sex in order to eliminate sex specific differences in body composition as a confounder. This strategy allowed for having men and women in the same body composition groups and compare effects of depressive symptoms on each group rather than analyzing each sex separately which would have made the depressive subgroups so small as to not have the power to analyze and report any differences.

Glucose metabolism was studied through an OGTT. Plasma glucose levels and insulin levels were measured before and after glucose loading. Study III, which studied glucose metabolism specifically, eliminated all participants with previously known DM and who were diagnosed with DM based on the OGTT. In other studies participants with DM were not excluded. Excluding participants with DM was necessary in order to control for effects by other factors than depressive symptoms. Measurements at different time points

allows for analysis of glucose metabolism on a wider scale than simply measuring fasting levels. Furthermore, glucose levels 2h post-loading are better representations of mortality risk than fasting glucose levels (DECODE Study Group & European Diabetes Epidemiology Group, 2001).

6.2.4 MORTALITY

Mortality rates of the population were obtained through official government records. The number of deaths and causes of death among the study participants are likewise verified through official records. Hence, the accuracy of mortality rates, times of death, and causes of death for both the general population and the study participants have been ensured.

6.3 RESULTS

6.3.1 PREVALENCE OF DEPRESSIVE SYMPTOMS

Depression prevalence rising globally means that burden of disease will also be on the rise, making the study of depression of utter importance on many levels. The prevalence of depressive symptoms increases with age, but according to the WHO is still far under-estimated for older individuals (WHO, 2017b). As the Global Burden of Disease Collaborative Network graphics (Figure 1) show depression is on the rise globally. However, the prevalence for populations above the age of 70 has remained stable for both sexes, with women having a higher prevalence than men. According to the Global Burden of Disease Collaborative Network (Figure 2) the prevalence of depression has decreased in Finland compared to the 1990s. However, the prevalence for women above the age of 70 has increased (Global Burden of Disease Collaborative Network, 2020). Since the last few years depression prevalence is increasing for all age groups and both sexes in Finland (Global Burden of Disease Collaborative Network, 2020). The age group above 70 for both sexes have lower prevalence in Finland than globally (Global Burden of Disease Collaborative Network, 2020). The prevalence for men in this age group is similar in Finland and globally, but for women the prevalence in Finland is lower (Global Burden of Disease Collaborative Network, 2020). It is unclear why there is such a difference between the global numbers and Finland.

Depression prevalence among the Finnish population is more variable than the global values throughout the years, which can probably be explained partially by the smaller population of Finland allowing for smaller changes to create larger changes graphically. Looking at the graphs from Finland it seems as if every 10 years (1990, 2000, 2010) there is a rise in cases, and every 10 years (1995, 2005, 2015) there is a decrease in cases. This type of rise and fall is not visible in the global prevalence. That may indicate some sort of local events in Finland affecting the prevalence rates.

Table 4 shows that the prevalence for depressive symptoms in the study cohort is much higher than depression in the general population. Each sub-study had a higher prevalence of depression among women as was expected. It is possible that the higher estimates of depressive symptoms are simply due to the fact that the BDI-IA was used with a low cut-off to screen for symptomatic individuals rather than true clinical depression. However, research has shown that the severity of depressive symptomatology is not the important factor when looking at connections to health outcomes (Ayuso-Mateos et al., 2010; Harshfield et al., 2020). This means that the purpose of the studies (I-IV) is still valid even though using the depressive-symptom-approach leads to a larger depressive group than if only using clinical depression as the criteria.

6.3.1.1 Depressive Subgroups

Even though there are more than two depressive subtypes, this thesis has focused on the two main ones: NMeD and MeD. In practice the catatonic depressive group is virtually nonexistent and hence negligible (Penninx et al., 2013), so for the purposes of this thesis it was determined not to be include as a category. This means that for these purposes the non-melancholic group will represent the atypical depressive subtype.

The distribution between depressive subtypes can be seen in Table 4. There is no difference in MeD between sexes, as expected (Bogren et al., 2018). MeD is more common among younger individuals (Khan et al., 2006; Parker et al., 2013). This explains why Studies III and IV have a higher percentage of MeD symptoms (6%) as this data was gathered over a decade before Studies I and II (4%). This also applies for overall depressive symptoms being more prevalent in Studies I and II compared to III and IV. This, however, is not true for NMeD symptoms where Studies II and III display equal levels of NMeD symptoms among the participants. The overall percentages of MeD participants were equal between the sexes in each study. However, of those participants that showed depressive symptoms, MeD was more common among men than women. This could be explained by the fact that the total number of depressive participants was much higher among women, leading to men having lower numbers of NMeD symptoms and hence resulting in a larger MeD proportion. It is known that there are sex differences in depressive symptoms, with females showing symptoms related to eating habits and anxiety, while men experience more substance abuse (Marcus et al., 2008).

6.3.2 SOCIODEMOGRAPHIC AND LIFESTYLE FACTORS ASSOCIATED WITH DEPRESSIVE SYMPTOMS

It has been shown that the effect of lifestyle factors on depressive symptoms is minimal (Penninx et al., 2013). It cannot be ruled out that a combined effect of many factors could have some significant effect. It may also be the case that the opposite findings in different studies represent the fact that there is no true effect.

The relationship between tobacco use and depression is highly debated and has not been agreed upon among researchers. No difference between depressed and non-depressed individuals in regard to smoking status was found, but when comparing only the NMeD group to the non-depressive group the NMeD group was much more likely to be smokers. Some of these relationships may be culturally influenced, but there is also a chance that the type of depressive symptoms may have a relationship with certain lifestyle factors. Since causality has not been established, it is even possible that a third confounding factor exists.

There is a known association between alcohol use and depression (Boden & Fergusson, 2011; McHugh & Weiss, 2019; van Gool et al., 2007). It has even been suggested that some cases of alcohol use disorder may lead to depression, and treating the alcohol use disorder in these cases may result in remission of the depression (Boden & Fergusson, 2011). It was determined that NMeD participants had a lower likelihood of consuming alcohol than their non-depressive counterparts. These studies did not, however, take into account a longer history of alcohol use. It is also known that self-reports, such as used in this case, are not always reliable in this matter (Del Boca & Darkes, 2003).

Study II showed higher CCI among those with depressive symptoms. This is in line with the fact that depression is associated with several comorbidities (Boden & Fergusson, 2011; Campayo et al., 2011; Capuron et al., 2017; Gawlik-Kotelnicka & Strzelecki, 2021; Guh et al., 2009; Harshfield et al., 2020; Lamers et al., 2013; L. Li et al., 2017; Luppino et al., 2010; McHugh & Weiss, 2019; Müller, 2014; Roy & Lloyd, 2012; Tiemeier et al., 2003; van Gool et al., 2007; van Sloten et al., 2014; von Zimmermann et al., 2020; WHO, 2017b, 2020; Wild et al., 2012; Wiltink et al., 2013; Zhu et al., 2017).

There is some evidence for exercise having a relationship with depression. Participants with depressive symptoms were found to engage in less exercise than those without depressive symptoms. This shows that a relationship may exist at subclinical levels of depression and does not necessarily require the clinical level of depression for this relationship to exist. One theory is that exercise through for example endorphins is protective against depression (Dinas et al., 2011), whereas another option may be that the lack of energy that may be part of the depressive symptomatology may prevent individuals from exercising (Stein, 2005). As with so many things associated with depression it could go either way.

Depressive individuals were found to be less likely to cohabitate and be less likely to be financially satisfied. Both of these findings, like previously, could go either way. Loneliness and financial stressors could lead to depressive symptoms. It is also possible that having depressive symptoms may lead to individuals ending up alone either voluntarily or due to trouble finding a partner. Being depressed or experiencing depressive symptoms may also affect productivity, work performance, or motivation, through which their financial situation may be affected.

As is evident with all the sociodemographic and lifestyle factors mentioned, causality cannot be determined without doubt, or even directionality of these relationships. Since it is known that the effect is small, it may even be worth focusing on other factors than these when looking for relationships and what separates people with depressive symptoms from those without depressive symptoms.

6.3.3 ADVANCED GLYCATION END PRODUCTS AND DEPRESSIVE SYMPTOMS (STUDY I)

Study I focused on AGE, evaluated through SAF, in relation to depressive symptoms. The study found significant connections between depressive symptoms and AGE. It was shown that women had lower AGE levels than men in this cohort. Previous research suggests that the sex difference exists but is very small (Atzeni et al., 2022), which may indicate that the sex difference in this study is strengthened by the older age of the participants. The present study showed that AGE has an association with depressive symptoms for both sexes, just as was hypothesized. Furthermore, melancholic symptoms have an association with higher AGE levels.

Melancholic symptoms being associated with higher AGE levels has, to the best of the author's knowledge, never been reported before. This novel finding most likely represents the fact that no other studies looking at AGE in depressive subtypes has been performed, as far as the author knows. This shows that the emerging understanding of depressive subtyping may be of importance in understanding pathophysiology of depression.

Sex differences show that women used more antidepressants, which could affect results. Antidepressants could affect the BDI-IA and MHI-5 scores by affecting severity of depressive symptoms. Since women were more likely to be affected by this possible confounder there is a possibility that if antidepressant use was eliminated as a factor that sex differences could be limited. Men having lower depressive levels but more comorbidities may indicate that the higher AGE levels in men is caused by somatic disease rather than depressive symptoms. Research has indicated that women may have more reactive AGE levels in response to factors such as smoking (Koetsier et al., 2010), which may also affect sex differences and indicate a possible need for different controls used for the sexes. In Study I men were more likely to be smokers, which may have played a part in men having higher AGE levels.

Both the BDI-IA and MHI-5 were used to screen for depression, showing a strong agreement on depressive symptoms among participants. This way it was possible to validate the use of the BDI-IA in the population for this thesis, and ensure that the differentiation between depressives and non-depressives is as accurate as possible. Since the BDI-IA focuses on many physical symptoms it could be possible that certain comorbidities or somatic conditions could cause higher BDI-IA scores, artificially causing an inflated depressive group. However, the fact that the correlation between the BDI-IA and MHI-5 scores is so strong indicates that BDI-IA can be used as a valid screening tool for depressive symptoms for this thesis.

The relationship between AGE and HbA_{1c} was expected, as it has been reported that extended hyperglycemia increases AGE (Yamagishi, 2011) and individuals with DM have higher SAF levels (van Waateringe et al., 2016). It was, however, surprising that the association was not stronger. It may be

possible that since AGE was higher in men, and men also had a higher prevalence of DM that sex may be a confounding factor in this connection. It is also possible that the relationship was not stronger because the majority of participants had well controlled glucose values.

AGEs can accumulate in various tissues including the brain. Prior research has found that SAF, as opposed to plasma AGEs, is a better representation of brain AGE (Spauwen et al., 2015). This method was chosen for this specific reason as it could be expected that depression would have a closer relationship to brain AGE. It has been suggested that vascular factors and depression both affect AGEs (Spauwen et al., 2015). AGE formation causes vascular stiffening (Sell & Monnier, 2012), which in turn has a known association with depression and depressive symptoms (Onete et al., 2018). Considering the vascular hypothesis and how depression may affect vascular tissue elsewhere in the body AGE all over the body may have some associations with depression. Research has, however, suggested that SAF levels are associated with cognitive and somatic depressive symptoms, but that plasma AGEs do not have any such relationship (van Dooren et al., 2017).

Surprisingly, all SAF readings in the study were fairly low compared to both the manufacturer reports (Koetsier et al., 2010) and the Maastricht Study (van Dooren et al., 2017), which used the same SAF reader as Study I. One significant difference in participants of Study I was the age. Validations and standards have not been set for SAF in the older age range (Koetsier et al., 2010) that participants of this study would fall into. It is possible that factors such as overall health, genetics, or some other factors may lay behind the lower SAF readings. It cannot be excluded that this population has some confounding factor that affects these readings and would need to be addressed in order for findings to be generalizable to other populations.

AGEs are known to accumulate with age leading to a self-perpetuating cycle of AGEs causing more AGE and further damage (Fishman et al., 2018). It has however been suggested that as a measure of comorbidities it is significantly more reliable in younger individuals (Emmerink et al., 2018). This opens up the question regarding reliability of AGE readings in participants of older age with comorbidities. There may be a possibility that the effects of age on AGEs could mask some of the effects of any depressive symptoms. This brings up the possibility that connections between depressive symptoms and AGEs may have to be studied differently in different age groups.

AGE levels could also be affected by a variety of factors other than depression. Known confounders are dietary intake, exercise, smoking, stress, and sleep (Isami et al., 2018; van Waateringe et al., 2016). This means that the findings of Study I could possibly be affected by any of these factors since controlling for them all was not possible.

Based on prior research it can be estimated that one year of aging equals an increase in AGE of 0.024 AU (Atzeni et al., 2022). The difference in AGE levels between the sexes in Study I was equivalent to 6.7 years of aging. When comparing participants with BDI-IA <10 and the MeD group, the latter had AGE levels equivalent to 9.6 years of additional aging. The NMeD group only had 2.9 years' worth of increased AGE compared to the non-depressive group.

In summation, higher AGE levels correlate with depressive symptoms, and especially in men and those with melancholic symptoms. No conclusions can be drawn based on these findings alone, and inferring directionality, causality, or effect is impossible without further studies. This study suggests that AGEs are a part of the multifactorial process affecting both depression and possibly other disorders. Further research on the matter would be indicated.

6.3.4 PULSE WAVE VELOCITY AND DEPRESSIVE SYMPTOMS (STUDY II)

Men had higher PWV values than women. An association was found between BDI-IA and crPWV for men, but not for women. No associations were found for either sex or either depressive subtype for cfPWV. However, crPWV was significantly higher for NMeD men.

It was hypothesized that since arterial stiffness falls under the category of metabolic dysregulation (Lamers et al., 2013; Penninx et al., 2013), PWV would be more closely related to NMeD symptoms. The findings of Study II support this hypothesis.

The participants of the study had higher cfPWV than crPWV, which is in agreement with aging causing more increase in central PWV than peripheral PWV (Hickson et al., 2016). Human peripheral arteries are smaller, less elastic, and more muscular than the central ones (Giannattasio et al., 1995, 2005). Endothelial function, renin–angiotensin system, and the sympathetic nervous system modulates the stiffness of the peripheral arteries (Giannattasio et al., 1995, 2005). Any structural changes in arterial walls as well as vasoconstriction affects the reflected waves that are measured as part of PWV (Duprez, 2004).

Research indicates that age affects central PWV but not peripheral PWV (Hickson et al., 2016; Mitchell et al., 2002). This may explain why Study II found no relationship between depressive symptoms and central PWV. It has been suggested that no differences in cfPWV exist between depressive groups for either sex at ages above 60 years (Onete et al., 2018). Study II findings support this, but open up the question of whether there may have been further findings had the participants of the study been younger. It has been reported that the association between depression and CVD is stronger in

younger individuals (Salaycik et al., 2007). It is also known that there are sex differences between depression and both PWV (Onete et al., 2018) and cardiovascular risks (Franklin et al., 1997; Segers et al., 2007). The age of the population of this study lowers the possibility of any sex differences being caused by hormonal effects since female participants are post-menopausal. Furthermore, other studies (Mitchell et al., 2002; Onete et al., 2018) have found sex differences between PWV and depression in younger populations as well. This may suggest that any sex differences could be a result of factors as far back as intrauterine effects on the cardiovascular system (Eriksson et al., 2010).

One proposed connection between depression and arterial stiffness is the inflammatory connection through the brain-gut-vascular axis (Zanoli, Tuttolomondo, et al., 2020). Chronic inflammatory conditions may result in triggering of arterial stiffness through psychoneuroimmune modulation (Zanoli, Briet, et al., 2020). Chronic inflammation is also known to be associated with higher crPWV (Cypiene et al., 2009; Cypienė et al., 2008; Zanoli et al., 2012, 2018), which suggests that depression may be able to cause arterial stiffening through similar pathways. Aging has been suggested to enhance the relationship between PWV and inflammation (Zanoli et al., 2018). However, some findings suggest that crPWV is higher in young women (Cypiene et al., 2009) or those with prolonged inflammation (Zanoli et al., 2012).

If cfPWV increases with age and crPWV decreases with age it is reasonable to also consider that the two may react differently to inflammation as well, or even the combination of aging and inflammation. This also goes along with the findings implying stiffening of the peripheral arteries having an association with increased depressive symptoms.

Elevated PWV of small arteries is often caused by endothelial dysfunction and is a marker for early vascular disease (Cohn, 2006). Aortic stiffening on the other hand is a marker for advanced CVD (Cohn, 2006). CVD developing later in women may partly explain the sex differences of the findings in Study II. Less LTPA, higher triglycerides, and higher CCI-scores among depressive participants may also affect the differences in arterial stiffening between groups.

In summary, Study II presented novel findings regarding depressive subtypes and their relationship to PWV. As far as the author is aware, no other research has looked at PWV in relation to depressive subtypes and sex. No directionality or causality can be inferred based solely on the findings of this study, but the findings support the need for further research in this field. Based on these findings, it is likely that arterial stiffness is part of the multifactorial pathophysiology of depression and its subtypes.

6.3.5 BODY COMPOSITION AND DEPRESSIVE SYMPTOMS (STUDY III)

Study III showed that both participants with high FMI, and high LMI had higher blood pressure and triglycerides, but lower HDL cholesterol than their counterparts. This finding is interesting, as having high LMI would in general be considered a good quality. However, this finding suggests that too much of either fat or lean mass may come with certain detriments to one's health.

High FMI was associated with high BDI-IA scores and high hsCRP. This goes along with what one would expect based on the current understanding of how obesity and overweight is related to inflammation, and how inflammation in turn is related to depression. However, it was also showed that high LMI was related to a lesser likelihood of depressive symptoms. It is unclear what the etiology is behind the protective nature of high LMI against depressive symptoms. It could possibly have something to do with metabolism as muscle tissue is known to increase metabolism. Interestingly, as mentioned above, the high LMI is associated with factors not considered particularly healthy, such as high triglycerides and high blood pressure. This may suggest that it is not weight nor body mass but specifically fat tissue that affects the level of depressive symptoms. Fat tissue may alter hormonal signals that could affect mood (Borgland, 2021). Alternatively, hormonal signals, such as cortisol, may affect both fat mass and mood (Borgland, 2021; Mann & Thakore, 1999)

As expected, the NMeD participants had higher BMI than the others. This makes sense as it is known that metabolism has a closer connection with NMeD (Lamers et al., 2013; Penninx et al., 2013). The BMI difference more specifically is due to FMI. The NMeD group has the closest relationship with FMI, and presented with higher FMI than either the MeD or the non-depressive groups. It was also showed that high FMI compared to low FMI was more closely related to NMeD regardless of LMI levels, which indicates that a relationship exists despite any protective factor of LMI. This suggests that the stronger effect comes from fat mass.

The NMeD group had low LMI and high hsCRP. This is in line with the findings indicating high LMI to be a partially protective factor against depression, and that an inflammatory relationship exists.

The MeD group had no relationship with body composition. This finding is in agreement with prior research that has indicated that metabolic factors are more closely related to NMeD symptoms (Lamers et al., 2013). However, it should be noted that it was not just a weaker association between MeD symptoms and body composition compared to NMeD symptoms, but there was in fact no relationship at all between body composition and MeD symptoms.

6.3.6 GLUCOSE METABOLISM AND DEPRESSIVE SYMPTOMS (STUDY III)

FMI was found to be related to both fasting and post-load glucose concentrations, along with fasting insulin and HOMA-IR. The fact that the participants with high FMI, compared to the ones with low FMI, had higher glucose concentrations suggests that body composition, and specifically fat mass, does affect glucose metabolism. High LMI having a relationship with fasting glucose and insulin, but not post-load glucose levels indicate that the worse glucose metabolism is not due to a lack of LMI but a presence of more FMI. It should be noted that all of the glucose levels do fall within a normal range. However, the fact that even after elimination of participants with DM there is a clear difference between body composition groups speaks to the strength of the effect on glucose metabolism. HOMA-IR reflects the insulin sensitivity of participants. Those with high FMI had significantly reduced insulin sensitivity compared to those with low FMI. Interestingly also those with high LMI had reduced insulin sensitivity compared to those with low LMI. The relationship with FMI was, however, stronger than with LMI indicating that having a high FMI has a greater effect on glucose metabolism than having a high LMI. The fasting insulin levels follow the same pattern as HOMA-IR. The high LMI having no effect on post-load glucose may be a reflection of lean mass having the capacity to metabolize glucose and react to insulin, but that the increased mass overall affects the fasting levels by requiring more insulin to keep the balance.

The only difference in glucose metabolism for the depressive subtypes was for NMeD at 2h post loading. This indicates that the NMeD group may have a slightly impaired glucose regulation, with glucose levels not returning to fasting levels as fast as for the MeD participants and the non-depressive participants.

6.3.7 ALL-CAUSE MORTALITY AND DEPRESSIVE SYMPTOMS (STUDY IV)

Study IV showed a relationship between increasing BDI-IA and greater mortality. The BDI-IA scores did not differ between the MeD and the NMeD groups. This tells us that the participants with depressive symptoms have a higher risk of mortality than those in the non-depressive group. Compared to the non-depressive group the MeD group had a higher risk of mortality, but the NMeD group did not. This indicates that the increased mortality among depressive subjects may be due to the effect of individuals with MeD. This finding does not rule out that NMeD individuals may have a higher mortality risk if larger samples were studied even though no such findings were evident based on the data of Study IV.

The most common cause of death was neoplasms, and the second most common one was diseases of the circulatory system. This was the case for each subgroup separately, and for the study population overall. This finding is in line with prior research reporting no differences in causes of death between depressed and non-depressed individuals (Pulska, 2001). The novel finding here, which is of importance, is that there is no difference in causes of death between the depressive subtypes. However, the subgroups were small, so greater differences may possibly be present in larger samples.

Study IV found that compared to the mortality rate of the population of Finland there was no difference in SMR for the NMeD and the MeD groups. This would suggest that the depressive groups had no increased mortality compared to the general population. However, the non-depressive group had a lower SMR than the general population. Based on this it is likely the case that the cohort overall has some survival bias and is overall healthier than the general population. This also suggests that if all groups of the cohort are healthier than their counterparts in the general population, the depressive individuals in the population may still have a higher rate of mortality. Study IV showed that the SMR for both NMeD and MeD were higher than for the non-depressive group. Unfortunately, it is impossible to evaluate the survival bias among the cohort and look for any possible differences in survival among the depressive groups as the information for such analysis do not exist. This means that there is a chance that the difference found between the groups is itself a reflection of the survival bias. If this is true, the findings may not represent the general population but be an artificially created difference due to the nature of the cohort.

6.4 STRENGTHS AND LIMITATIONS

Some of the strengths of this thesis includes the utilization of an extensively phenotyped cohort, including a large pool of participants, and novel research aims. This thesis presents novel findings, regarding differences between depressive subtypes. To the best of the author's knowledge this is the first study to look at depressive subtypes and associated pathophysiology in this age group.

Having used a second method (MHI-5) to verify the validity of BDI-IA in this population can be seen as a strength of the thesis. Furthermore, having used a longitudinal study cohort for the thesis is a strength since it allows for pooling the results from each separate study more reliably than if having had different populations of participants for each study of the thesis. This allows for forming a better overall picture of each depressive subtype without having to worry that profiles could be affected by population differences.

There are a limited number of studies in Nordic populations that have measured AGE by SAF, which means that the findings of Study I are of importance in building understanding and gathering data on this.

Some of the limitations of the thesis is the narrow focus on a few specific pathophysiologic factors when there are likely many more that could be of interest. The cross-sectional nature of Study I-III is a limitation. The age of the cohort participants, specifically the homogeneity in age, limits applicability. Findings of this thesis may therefore not be fully applicable across different age groups. The same applies for the heritage of participants of this thesis. All participants being of Caucasian, north European descent, possibly limits applicability of findings in regard to other ethnicities or heritages. Another limitation is not having clinical diagnoses of depression, or even severity of depression as part of the thesis. There is a chance that severity of symptoms or a clinical diagnosis as a differential could affect the results and give one power to draw more definitive conclusions based on any results.

Concerning lifestyle factors, self-reported consumption of tobacco and alcohol raise some concern. However, as discussed previously in the thesis this may limit our understanding of their effect on depression, but no other feasible options are available either. Regarding exercise it could have been more desirable to have actual continuous objective tracking of physical activity instead of questionnaires based of subjective memory. This does limit the strength of any connections that can be found between depressive subtypes and exercise. Theoretically it is possible that depression could affect for example the ability to estimate performed exercise rather than the actual amount of exercise itself. The way FMI and LMI are determined through bioimpedance could also be viewed as a limitation since the measurements represent estimates rather than absolute values.

It is possible that some level of survival bias presents in the population of the thesis. The participants are all older, and some of the unhealthiest individuals may already have passed away or chosen not to participate due to poor health. This opens the door to the possibility that the study participants may be healthier than the average person. Furthermore, survival bias may differ between the depressive groups. There is no way to evaluate, eliminate, or control for this possibility. Individual studies eliminated people based on inability to obtain the measurements. This too could mean that some of the people who were in the poorest health were not able to have their AGEs or PWVs measured, and were hence eliminated due to missing data.

A major factor that has to be brought up is the determination of depressive subtypes. The nature of the grouping is complicated as there is no exact or globally agreed upon way to categorize individuals into these subtypes. The methods used in the thesis have been extensively used in the HBCS as well as other studies in Finland. However, if others were to categorize individuals using the same diagnostics and same symptoms, they may decide to place more weight behind some factors than others, possibly leading to slightly differing categorization than used in this thesis. The fact that the method used in this thesis has been extensively used in different populations does lend it some strength. However, the lack of any global precise method that eliminates subjective views does limit the study of depressive subtypes not only when it comes to this thesis, but overall.

6.5 IMPLICATIONS FOR FUTURE RESEARCH

Due to these findings being the first of their kind a multitude of options for further research presents itself. The field of depressive subtypes overall need to be studied much further to obtain a proper fundamental understanding of the differences. Research separating participants further into groups by depressive severity may also be of relevance to understanding the depth of each connection.

The findings of Study I brings up the possibilities of being able to study depression in the context of both AGE and systemic inflammatory markers simultaneously. Looking into effects of exercise and sleep on AGE and depression, and further information on diet may also be warranted. Furthermore, to eliminate confounding factors it may be valuable to look at the AGE and depressive symptom association in populations without participants who smoke or participants with DM. Lastly, longitudinal studies focusing on determination of causality between AGE and depressive symptoms could be of value.

Further studies relating to PWV and depressive symptoms are certainly indicated. Studying the relationship between PWV and depressive symptoms, or depression, in participants with and without prior vascular stenosis or CVD may aid in furthering the understanding of this connection. Being able to simultaneously measure intra-arterial PWV and non-invasive PWV could possibly aid in understanding differences between cfPWV and crPWV when it comes to depression. Further studies to verify and explain the sex differences could be highly valuable.

Further studies focusing on time as a factor in the relationship between depressive symptoms and body composition would be indicated since time has been reported to possibly reinforce this relationship. Lifetime follow-up regarding body composition and depressive symptoms may provide valuable information about directionality and timing of depressive episodes in relation to changes in body composition. Most importantly, further research into the effects of fat mass on depression and depressive symptoms would be valuable to further the understanding of how fat tissue affects the relationship between obesity and depression, and specifically depressive subtypes.

When focusing on mortality it would be of interest to have a larger sample to see if any differences between the depressive group and the general population present in regard to causes of death. Likewise, it would be valuable to begin the follow-up at a younger age to be able to see the variety of causes of death at different ages and to study potential differences.

Lastly, looking at AGE, PWV and body composition at the same time, and evaluating possible interactions and relationships would give us further depth of understanding when it comes to the pathophysiology of depressive symptoms. Likewise, being able to compare findings to longer follow-up and

mortality in order to determine how much AGE, PWV and body composition affect time of death and cause of death in different depressive subgroups would be of value for understanding the bigger picture.

7 CONCLUSIONS

This thesis concludes that the depressive subtypes do play a significant role in the depressive profile when it comes to AGE, PWV, body composition, glucose metabolism, and mortality.

I. Depressive symptoms, measured by either BDI-IA or MHI-5, are associated with higher AGE levels for both men and women. AGE levels are most closely related to MeD symptoms. (Study I)

II. Higher crPWV has a relationship with NMeD men. No relationship exists for MeD symptoms, or for cfPWV. (Study II)

III. High LMI was associated with lower likelihood of depressive symptoms. High FMI was associated with higher likelihood of depressive symptoms, and specifically with NMeD symptoms. MeD symptoms had no association with body composition. (Study III)

IV. Impaired glucose regulation is related to high FMI both at fasting and post-load times, but to high LMI only at fasting. Glucose metabolism has a relationship with NMeD symptoms. (Study III)

V. Increasing BDI-IA scores, and specifically MeD symptoms, are associated with greater mortality. (Study IV)

REFERENCES

Abate, G., Marziano, M., Rungratanawanich, W., Memo, M., & Uberti, D. (2017). Nutrition and AGE-ing: Focusing on Alzheimer's Disease. *Oxidative Medicine and Cellular Longevity*, *2017*, 1–10. https://doi.org/10.1155/2017/7039816

Ainsworth, B. E., Haskell, W. L., Herrmann, S. D., Meckes, N., Bassett, D. R., Tudor-Locke, C., Greer, J. L., Vezina, J., Whitt-Glover, M. C., & Leon, A. S. (2011). 2011 Compendium of Physical Activities: A Second Update of Codes and MET Values. *Medicine & Science in Sports & Exercise*, *43*(8), 1575–1581. https://doi.org/10.1249/MSS.0b013e31821ece12

Akil, H., Gordon, J., Hen, R., Javitch, J., Mayberg, H., McEwen, B., Meaney, M. J., & Nestler, E. J. (2018). Treatment resistant depression: A multi-scale, systems biology approach. *Neuroscience & Biobehavioral Reviews*, *84*, 272–288. https://doi.org/10.1016/j.neubiorev.2017.08.019

Alexopoulos, G. S. (1997). "Vascular Depression" Hypothesis. *Archives of General Psychiatry*, *54*(10), 915. https://doi.org/10.1001/archpsyc.1997.01830220033006

American Psychiatric Association (Ed.). (1998). *Diagnostic and statistical manual of mental disorders: DSM-IV ; includes ICD-9-CM codes effective 1. Oct. 96* (4. ed., 7. print).

American Psychological Association. (2022). *Depression*. American Psychological Association. https://www.apa.org/topics/depression

Atzeni, I. M., van de Zande, S. C., Westra, J., Zwerver, J., Smit, A. J., & Mulder, D. J. (2022). The AGE Reader: A non-invasive method to assess long-term tissue damage. *Methods*, *203*, 533–541. https://doi.org/10.1016/j.ymeth.2021.02.016

Ayuso-Mateos, J. L., Nuevo, R., Verdes, E., Naidoo, N., & Chatterji, S. (2010). From depressive symptoms to depressive disorders: The relevance of thresholds. *British Journal of Psychiatry*, *196*(5), 365–371. https://doi.org/10.1192/bjp.bp.109.071191

Bautovich, A., Katz, I., Loo, C. K., & Harvey, S. B. (2018). Beck Depression Inventory as a screening tool for depression in chronic haemodialysis patients. *Australasian Psychiatry*, *26*(3), 281–284. https://doi.org/10.1177/1039856218758582

Beck, A. T., Steer, R. A., Ball, R., & Ranieri, W. F. (1996). Comparison of Beck Depression Inventories-IA and-II in Psychiatric Outpatients. *Journal of Personality Assessment*, *67*(3), 588–597. https://doi.org/10.1207/s15327752jpa6703_13

Beck, A. T., Steer, R. A., & Carbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, *8*(1), 77–100. https://doi.org/10.1016/0272-7358(88)90050-5

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry*, *4*(6), 561. https://doi.org/10.1001/archpsyc.1961.01710120031004

Beurel, E., Toups, M., & Nemeroff, C. B. (2020). The Bidirectional Relationship of Depression and Inflammation: Double Trouble. *Neuron*, *107*(2), 234–256. https://doi.org/10.1016/j.neuron.2020.06.002

Black, D. W., & Grant, J. E. (2014). *DSM-5 guidebook: The essential companion to the Diagnostic and statistical manual of mental disorders, fifth edition* (First edition). American Psychiatric Publishing. https://search-ebscohost-com.libproxy.helsinki.fi/login.aspx?direct=true&db=e000xww&AN=1610168&site=ehost-live&scope=site

Boden, J. M., & Fergusson, D. M. (2011). Alcohol and depression: Alcohol and depression. *Addiction*, *106*(5), 906–914. https://doi.org/10.1111/j.1360-0443.2010.03351.x

Bogren, M., Brådvik, L., Holmstrand, C., Nöbbelin, L., & Mattisson, C. (2018). Gender differences in subtypes of depression by first incidence and age of onset: A follow-up of the Lundby population. *European Archives of Psychiatry and Clinical Neuroscience*, *268*(2), 179–189. https://doi.org/10.1007/s00406-017-0778-x

Borgland, S. L. (2021). Can treatment of obesity reduce depression or vice versa? *Journal of Psychiatry & Neuroscience*, *46*(2), E313–E318. https://doi.org/10.1503/jpn.210036

Brailean, A., Curtis, J., Davis, K., Dregan, A., & Hotopf, M. (2020). Characteristics, comorbidities, and correlates of atypical depression: Evidence from the UK Biobank Mental Health Survey. *Psychological Medicine*, *50*(7), 1129–1138. https://doi.org/10.1017/S0033291719001004

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., de Girolamo, G., de Graaf, R., Demyttenaere, K., Hu, C., Iwata, N., Karam, A. N., Kaur, J., Kostyuchenko, S., Lépine, J.-P., Levinson, D., Matschinger, H., Mora, M. E. M., Browne, M. O., Posada-Villa, J., … Kessler, R. C. (2011). Cross-national epidemiology of DSM-IV major depressive episode. *BMC Medicine*, *9*(1), 90. https://doi.org/10.1186/1741-7015-9-90

Brouwers, O., Niessen, P. M., Ferreira, I., Miyata, T., Scheffer, P. G., Teerlink, T., Schrauwen, P., Brownlee, M., Stehouwer, C. D., & Schalkwijk, C. G. (2011). Overexpression of Glyoxalase-I Reduces Hyperglycemia-induced Levels of Advanced Glycation End Products and Oxidative Stress in Diabetic Rats. *Journal of Biological Chemistry*, *286*(2), 1374–1380. https://doi.org/10.1074/jbc.M110.144097

Brouwers, O., Niessen, P. M., Haenen, G., Miyata, T., Brownlee, M., Stehouwer, C. D., De Mey, J. G., & Schalkwijk, C. G. (2010). Hyperglycaemia-induced impairment of endothelium-dependent vasorelaxation in rat mesenteric arteries is mediated by intracellular methylglyoxal levels in a pathway dependent on oxidative stress. *Diabetologia*, *53*(5), 989–1000. https://doi.org/10.1007/s00125-010-1677-0

Buckner, R. L. (2004). Memory and Executive Function in Aging and AD. *Neuron*, *44*(1), 195–208. https://doi.org/10.1016/j.neuron.2004.09.006

Bull, F. C., Al-Ansari, S. S., Biddle, S., Borodulin, K., Buman, M. P., Cardon, G., Carty, C., Chaput, J.-P., Chastin, S., Chou, R., Dempsey, P. C., DiPietro, L., Ekelund, U., Firth, J., Friedenreich, C. M., Garcia, L., Gichu, M., Jago, R., Katzmarzyk, P. T., … Willumsen, J. F. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *British Journal*

of Sports Medicine, *54*(24), 1451–1462. https://doi.org/10.1136/bjsports-2020-102955

Cameron, N., Godino, J. G., Skipper, T., Dillon, L., Waalen, J., Hill, L., & Patrick, K. (2019). Associations between reliable changes in depression and changes in BMI, total body fatness and visceral adiposity during a 12-month weight loss trial. *International Journal of Obesity*, *43*(9), 1859–1862. https://doi.org/10.1038/s41366-018-0272-1

Campayo, A., Gómez-Biel, C. H., & Lobo, A. (2011). Diabetes and Depression. *Current Psychiatry Reports*, *13*(1), 26–30. https://doi.org/10.1007/s11920-010-0165-z

Capuron, L., Lasselin, J., & Castanon, N. (2017). Role of Adiposity-Driven Inflammation in Depressive Morbidity. *Neuropsychopharmacology*, *42*(1), 115–128. https://doi.org/10.1038/npp.2016.123

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases*, *40*(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Chen, H., Liu, F., Pang, L., Liu, F., Fang, T., Wen, Y., Chen, S., Xie, Z., Zhang, X., Zhao, Y., & Gu, X. (2020). Are You Tired of Working amid the Pandemic? The Role of Professional Identity and Job Satisfaction against Job Burnout. *International Journal of Environmental Research and Public Health*, *17*(24), 9188. https://doi.org/10.3390/ijerph17249188

Christensen, G. T., Maartensson, S., & Osler, M. (2017). The association between depression and mortality – a comparison of survey- and register-based measures of depression. *Journal of Affective Disorders*, *210*, 111–114. https://doi.org/10.1016/j.jad.2016.12.024

Cohn, J. N. (2006). Arterial Stiffness, Vascular Disease, and Risk of Cardiovascular Events. *Circulation*, *113*(5), 601–603. https://doi.org/10.1161/CIRCULATIONAHA.105.600866

Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., & Penninx, B. W. (2013). Differential mortality rates in major and subthreshold depression: Meta-analysis of studies that measured both. *British Journal of Psychiatry*, *202*(1), 22–27. https://doi.org/10.1192/bjp.bp.112.112169

Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., & Penninx, B. W. (2014). Comprehensive Meta-Analysis of Excess Mortality in Depression in the General Community Versus Patients With Specific Illnesses. *American Journal of Psychiatry*, *171*(4), 453–462. https://doi.org/10.1176/appi.ajp.2013.13030325

Cypiene, A., Kovaite, M., Venalis, A., Dadoniene, J., Rugiene, R., Petrulioniene, Z., Ryliskyte, L., & Laucevicius, A. (2009). Arterial wall dysfunction in systemic lupus erythematosus. *Lupus*, *18*(6), 522–529. https://doi.org/10.1177/0961203308099625

Cypienė, A., Laucevicius, A., Venalis, A., Dadonienė, J., Ryliskytė, L., Petrulionienė, Z., Kovaitė, M., & Gintautas, J. (2008). The impact of systemic sclerosis on arterial wall stiffness parameters and endothelial function. *Clinical Rheumatology*, *27*(12), 1517–1522. https://doi.org/10.1007/s10067-008-0958-1

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*, *9*(1), 46–56. https://doi.org/10.1038/nrn2297

DECODE Study Group, & European Diabetes Epidemiology Group. (2001). Glucose Tolerance and Cardiovascular Mortality: Comparison of Fasting and 2-Hour Diagnostic Criteria. *Archives of Internal Medicine*, *161*(3), 397. https://doi.org/10.1001/archinte.161.3.397

Del Boca, F. K., & Darkes, J. (2003). The validity of self-reports of alcohol consumption: State of the science and challenges for research: The validity of self-reports of alcohol consumption. *Addiction*, *98*, 1–12. https://doi.org/10.1046/j.1359-6357.2003.00586.x

Dempsey, P. C., Friedenreich, C. M., Leitzmann, M. F., Buman, M. P., Lambert, E., Willumsen, J., & Bull, F. (2021). Global Public Health Guidelines on Physical Activity and Sedentary Behavior for People Living With Chronic Conditions: A Call to Action. *Journal of Physical Activity and Health*, *18*(1), 76–85. https://doi.org/10.1123/jpah.2020-0525

Deverman, B. E., & Patterson, P. H. (2009). Cytokines and CNS Development. *Neuron*, *64*(1), 61–78. https://doi.org/10.1016/j.neuron.2009.09.002

Dinas, P. C., Koutedakis, Y., & Flouris, A. D. (2011). Effects of exercise and physical activity on depression. *Irish Journal of Medical Science*, *180*(2), 319–325. https://doi.org/10.1007/s11845-010-0633-9

Duprez, D. (2004). Determinants of radial artery pulse wave analysis in asymptomatic individuals. *American Journal of Hypertension*, *17*(8), 647–653. https://doi.org/10.1016/j.amjhyper.2004.03.671

Egervari, G., Siciliano, C. A., Whiteley, E. L., & Ron, D. (2021). Alcohol and the brain: From genes to circuits. *Trends in Neurosciences*, *44*(12), 1004–1015. https://doi.org/10.1016/j.tins.2021.09.006

Elias, M. F., Robbins, M. A., Budge, M. M., Abhayaratna, W. P., Dore, G. A., & Elias, P. K. (2009). Arterial Pulse Wave Velocity and Cognition With Advancing Age. *Hypertension*, *53*(4), 668–673. https://doi.org/10.1161/HYPERTENSIONAHA.108.126342

Elmer, B. M., & McAllister, A. K. (2012). Major histocompatibility complex class I proteins in brain development and plasticity. *Trends in Neurosciences*, *35*(11), 660–670. https://doi.org/10.1016/j.tins.2012.08.001

Emanuele, E., Martinelli, V., Carlin, M. V., Fugazza, E., Barale, F., & Politi, P. (2011). Serum levels of soluble receptor for advanced glycation endproducts (sRAGE) in patients with different psychiatric disorders. *Neuroscience Letters*, *487*(1), 99–102. https://doi.org/10.1016/j.neulet.2010.10.003

Emmerink, D., Bakker, S., Van Bemmel, T., Noorthoorn, E. O., & Naarding, P. (2018). Skin autofluorescence assessment of cardiovascular risk in people with severe mental illness. *BJPsych Open*, *4*(4), 313–316. https://doi.org/10.1192/bjo.2018.34

Eriksson, J. G., Kajantie, E., Osmond, C., Thornburg, K., & Barker, D. J. P. (2010). Boys live dangerously in the womb. *American Journal of Human Biology*, *22*(3), 330–335. https://doi.org/10.1002/ajhb.20995

Fabricatore, A. N., & Wadden, T. A. (2004). Psychological aspects of obesity. *Clinics in Dermatology*, *22*(4), 332–337. https://doi.org/10.1016/j.clindermatol.2004.01.006

Fewlass, D. C., Noboa, K., Pi-Sunyer, F. X., Johnston, J. M., Yan, S. D., & Tezapsidis, N. (2004). Obesity-related leptin regulates Alzheimer's Aβ. *The FASEB Journal*, *18*(15), 1870–1878. https://doi.org/10.1096/fj.04-2572com

Fishman, S. L., Sonmez, H., Basman, C., Singh, V., & Poretsky, L. (2018). The role of advanced glycation end-products in the development of coronary artery disease in patients with and without diabetes mellitus: A review. *Molecular Medicine*, *24*(1), 59. https://doi.org/10.1186/s10020-018-0060-3

for the European Depression in Diabetes (EDID) Research Consortium, Nouwen, A., Winkley, K., Twisk, J., Lloyd, C. E., Peyrot, M., Ismail, K., & Pouwer, F. (2010). Type 2 diabetes mellitus as a risk factor for the onset of depression: A systematic review and meta-analysis. *Diabetologia*, *53*(12), 2480–2486. https://doi.org/10.1007/s00125-010-1874-x

Franklin, S. S., Gustin, W., Wong, N. D., Larson, M. G., Weber, M. A., Kannel, W. B., & Levy, D. (1997). Hemodynamic Patterns of Age-Related Changes in Blood Pressure: The Framingham Heart Study. *Circulation*, *96*(1), 308–315. https://doi.org/10.1161/01.CIR.96.1.308

Gaens, K. HJ., Stehouwer, C. DA., & Schalkwijk, C. G. (2013). Advanced glycation endproducts and its receptor for advanced glycation endproducts in obesity: *Current Opinion in Lipidology*, *24*(1), 4–11. https://doi.org/10.1097/MOL.0b013e32835aea13

Gallo, J. J., Bogner, H. R., Morales, K. H., Post, E. P., Lin, J. Y., & Bruce, M. L. (2007). The Effect of a Primary Care Practice–Based Depression Intervention on Mortality in Older Adults: A Randomized Trial. *Annals of Internal Medicine*, *146*(10), 689. https://doi.org/10.7326/0003-4819-146-10-200705150-00002

Gallo, J. J., Hwang, S., Joo, J. H., Bogner, H. R., Morales, K. H., Bruce, M. L., & Reynolds, C. F. (2016). Multimorbidity, Depression, and Mortality in Primary Care: Randomized Clinical Trial of an Evidence-Based Depression Care Management Program on Mortality Risk. *Journal of General Internal Medicine*, *31*(4), 380–386. https://doi.org/10.1007/s11606-015-3524-y

Gawlik-Kotelnicka, O., & Strzelecki, D. (2021). Adiposity in Depression or Depression in Adiposity? The Role of Immune-Inflammatory-Microbial Overlap. *Life*, *11*(2), 117. https://doi.org/10.3390/life11020117

Giannattasio, C., Failla, M., Lucchina, S., Zazzeron, C., Scotti, V., Capra, A., Viscardi, L., Bianchi, F., Vitale, G., Lanzetta, M., & Mancia, G. (2005). Arterial Stiffening Influence of Sympathetic Nerve Activity: Evidence From

Hand Transplantation in Humans. *Hypertension*, *45*(4), 608–611. https://doi.org/10.1161/01.HYP.0000157368.09939.88

Giannattasio, C., Failla, M., Stella, M. L., Mangoni, A. A., Turrini, D., Carugo, S., Pozzi, M., Grassi, G., & Mancia, G. (1995). Angiotensin-Converting Enzyme Inhibition and Radial Artery Compliance in Patients With Congestive Heart Failure. *Hypertension*, *26*(3), 491–496. https://doi.org/10.1161/01.HYP.26.3.491

Gibney, S. M., & Drexhage, H. A. (2013). Evidence for a Dysregulated Immune System in the Etiology of Psychiatric Disorders. *Journal of Neuroimmune Pharmacology*, *8*(4), 900–920. https://doi.org/10.1007/s11481-013-9462-8

Gilman, S. E., Sucha, E., Kingsbury, M., Horton, N. J., Murphy, J. M., & Colman, I. (2017). Depression and mortality in a longitudinal study: 1952–2011. *Canadian Medical Association Journal*, *189*(42), E1304–E1310. https://doi.org/10.1503/cmaj.170125

Global Burden of Disease Collaborative Network. (2020). *Global Burden of Disease Study 2019 (GBD 2019) Results*. Seattle, United States: Institute for Health Metrics and Evaluation (IHME). https://vizhub.healthdata.org/gbd-results/.

Goetzel, R. Z., Hawkins, K., Ozminkowski, R. J., & Wang, S. (2003). The Health and Productivity Cost Burden of the "Top 10" Physical and Mental Health Conditions Affecting Six Large U.S. Employers in 1999: *Journal of Occupational and Environmental Medicine*, *45*(1), 5–14. https://doi.org/10.1097/00043764-200301000-00007

Gold, P. W., & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: High vs low CRH/NE states. *Molecular Psychiatry*, *7*(3), 254–275. https://doi.org/10.1038/sj.mp.4001032

Gorber, S. C., Schofield-Hurwitz, S., Hardt, J., Levasseur, G., & Tremblay, M. (2009). The accuracy of self-reported smoking: A systematic review of the relationship between self-reported and cotinine-assessed smoking status. *Nicotine & Tobacco Research*, *11*(1), 12–24. https://doi.org/10.1093/ntr/ntn010

Guh, D. P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C. L., & Anis, A. H. (2009). The incidence of co-morbidities related to obesity and overweight: A

systematic review and meta-analysis. *BMC Public Health*, *9*(1), 88. https://doi.org/10.1186/1471-2458-9-88

Gump, B. B., Matthews, K. A., Eberly, L. E., & Chang, Y. (2005). Depressive Symptoms and Mortality in Men: Results From the Multiple Risk Factor Intervention Trial. *Stroke*, *36*(1), 98–102. https://doi.org/10.1161/01.STR.0000149626.50127.d0

Guthrie, R. A., & Guthrie, D. W. (2004). Pathophysiology of Diabetes Mellitus: *Critical Care Nursing Quarterly*, *27*(2), 113–125. https://doi.org/10.1097/00002727-200404000-00003

Hagen, J. M., Sutterland, A. L., Koeter, M. W., Lutter, R., Cohen, D., & de Haan, L. (2017). Advanced Glycation End Products in Recent-Onset Psychosis Indicate Early Onset of Cardiovascular Risk. *The Journal of Clinical Psychiatry*, *78*(9), 1395–1401. https://doi.org/10.4088/JCP.16m10972

Harrell, F. E. (2001). *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. Springer.

Harris, C., & Barraclough, B. (1998). Excess mortality of mental disorder. *British Journal of Psychiatry*, *173*(1), 11–53. https://doi.org/10.1192/bjp.173.1.11

Harris, M., Farquhar, F., Healy, D., Le Noury, J., Baker, D., Whitaker, C., Linden, S., Green, P., & Roberts, A. P. (2011). The incidence and prevalence of admissions for melancholia in two cohorts (1875–1924 and 1995–2005). *Journal of Affective Disorders*, *134*(1–3), 45–51. https://doi.org/10.1016/j.jad.2011.06.015

Harshfield, E. L., Pennells, L., Schwartz, J. E., Willeit, P., Kaptoge, S., Bell, S., Shaffer, J. A., Bolton, T., Spackman, S., Wassertheil-Smoller, S., Kee, F., Amouyel, P., Shea, S. J., Kuller, L. H., Kauhanen, J., van Zutphen, E. M., Blazer, D. G., Krumholz, H., Nietert, P. J., … Emerging Risk Factors Collaboration. (2020). Association Between Depressive Symptoms and Incident Cardiovascular Diseases. *JAMA*, *324*(23), 2396. https://doi.org/10.1001/jama.2020.23068

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of Adult *DSM-5* Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry*, *75*(4), 336. https://doi.org/10.1001/jamapsychiatry.2017.4602

Henskens, L. H. G., Kroon, A. A., van Oostenbrugge, R. J., Gronenschild, E. H. B. M., Fuss-Lejeune, M. M. J. J., Hofman, P. A. M., Lodder, J., & de Leeuw, P. W. (2008). Increased Aortic Pulse Wave Velocity Is Associated With Silent Cerebral Small-Vessel Disease in Hypertensive Patients. *Hypertension*, *52*(6), 1120–1126. https://doi.org/10.1161/HYPERTENSIONAHA.108.119024

Hickson, S. S., Nichols, W. W., Yasmin, McDonnell, B. J., Cockcroft, J. R., Wilkinson, I. B., & McEniery, C. M. (2016). Influence of the central-to-peripheral arterial stiffness gradient on the timing and amplitude of wave reflections. *Hypertension Research*, *39*(10), 723–729. https://doi.org/10.1038/hr.2016.64

Huybrechts, S. A. M., Devos, D. G., Vermeersch, S. J., Mahieu, D., Achten, E., de Backer, T. L. M., Segers, P., & van Bortel, L. M. (2011). Carotid to femoral pulse wave velocity: A comparison of real travelled aortic path lengths determined by MRI and superficial measurements. *Journal of Hypertension*, *29*(8), 1577–1582. https://doi.org/10.1097/HJH.0b013e3283487841

Isami, F., West, B. J., Nakajima, S., & Yamagishi, S. (2018). Association of advanced glycation end products, evaluated by skin autofluorescence, with lifestyle habits in a general Japanese population. *Journal of International Medical Research*, *46*(3), 1043–1051. https://doi.org/10.1177/0300060517736914

ISMA. (n.d.). *Beck's Depression Inventory*. Indiana State Medical Association. Retrieved September 30, 2022, from https://www.ismanet.org/doctoryourspirit/pdfs/Beck-Depression-Inventory-BDI.pdf

Jannasz, I., Sondej, T., Targowski, T., Dobrowolski, A., & Olszewski, R. (2019). [Pulse wave velocity—A useful tool in assessing the stiffness of the arteries]. *Polski Merkuriusz Lekarski: Organ Polskiego Towarzystwa Lekarskiego*, *46*(276), 257–262.

Järvimäki, V., Kautiainen, H., Haanpää, M., Koponen, H., Spalding, M., Alahuhta, S., & Vakkala, M. (2016). Depressive symptoms are associated with poor outcome for lumbar spine surgery. *Scandinavian Journal of Pain*, *12*(1), 13–17. https://doi.org/10.1016/j.sjpain.2016.01.008

Jensen, K. P., Kranzler, H. R., Stein, M. B., & Gelernter, J. (2014). The effects of a *MAP2K5* microRNA target site SNP on risk for anxiety and depressive disorders. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *165*(2), 175–183. https://doi.org/10.1002/ajmg.b.32219

Johnson, T. E. (2006). Recent results: Biomarkers of aging. *Experimental Gerontology*, *41*(12), 1243–1246. https://doi.org/10.1016/j.exger.2006.09.006

Kearney-Schwartz, A., Rossignol, P., Bracard, S., Felblinger, J., Fay, R., Boivin, J.-M., Lecompte, T., Lacolley, P., Benetos, A., & Zannad, F. (2009). Vascular Structure and Function Is Correlated to Cognitive Performance and White Matter Hyperintensities in Older Hypertensive Patients With Subjective Memory Complaints. *Stroke*, *40*(4), 1229–1236. https://doi.org/10.1161/STROKEAHA.108.532853

Khan, A. Y., Carrithers, J., Preskorn, S. H., Lear, R., Wisniewski, S. R., Rush, A. J., Stegman, D., Kelley, C., Kreiner, K., Nierenberg, A. A., & Fava, M. (2006). Clinical and Demographic Factors Associated With DSM-IV Melancholic Depression. *Annals of Clinical Psychiatry*, *18*(2), 91–98. https://doi.org/10.1080/10401230600614496

Kidwell, M., & Ellenbroek, B. A. (2018). Heart and soul: Heart rate variability and major depression. *Behavioural Pharmacology*, *29*(2 and 3), 152–164. https://doi.org/10.1097/FBP.0000000000000387

Kiecolt-Glaser, J. K., Derry, H. M., & Fagundes, C. P. (2015). Inflammation: Depression Fans the Flames and Feasts on the Heat. *American Journal of Psychiatry*, *172*(11), 1075–1091. https://doi.org/10.1176/appi.ajp.2015.15020152

Koetsier, M., Lutgers, H. L., de Jonge, C., Links, T. P., Smit, A. J., & Graaff, R. (2010). Reference Values of Skin Autofluorescence. *Diabetes Technology & Therapeutics*, *12*(5), 399–403. https://doi.org/10.1089/dia.2009.0113

Korhonen, P. E., Mikkola, T., Kautiainen, H., & Eriksson, J. G. (2021). Both lean and fat body mass associate with blood pressure. *European Journal of Internal Medicine*, S0953620521001485. https://doi.org/10.1016/j.ejim.2021.04.025

Kotiaho, S., Korniloff, K., Vanhala, M., Kautiainen, H., Koponen, H., Ahonen, T., & Mäntyselkä, P. (2019). Psychiatric diagnosis in primary care patients with increased depressive symptoms. *Nordic Journal of Psychiatry*, *73*(3), 195–199. https://doi.org/10.1080/08039488.2019.1584240

Krishnan, K. R., Hays, J. C., & Blazer, D. G. (1997). MRI-defined vascular depression. *American Journal of Psychiatry*, *154*(4), 497–501. https://doi.org/10.1176/ajp.154.4.497

Kyle, U. G., Schutz, Y., Dupertuis, Y. M., & Pichard, C. (2003). Body composition interpretation. *Nutrition*, *19*(7–8), 597–604. https://doi.org/10.1016/S0899-9007(03)00061-3

Lakka, T. A., & Salonen, J. T. (1992). Intra-Person Variability of Various Physical Activity Assessments in the Kuopio Ischaemic Heart Disease Risk Factor Study. *International Journal of Epidemiology*, *21*(3), 467–472. https://doi.org/10.1093/ije/21.3.467

Lakka, T. A., Venalainen, J. M., Rauramaa, R., Salonen, R., Tuomilehto, J., & Salonen, J. T. (1994). Relation of Leisure-Time Physical Activity and Cardiorespiratory Fitness to the Risk of Acute Myocardial Infarction in Men. *New England Journal of Medicine*, *330*(22), 1549–1554. https://doi.org/10.1056/NEJM199406023302201

Lamers, F., Burstein, M., He, J., Avenevoli, S., Angst, J., & Merikangas, K. R. (2012). Structure of major depressive disorder in adolescents and adults in the US general population. *British Journal of Psychiatry*, *201*(2), 143–150. https://doi.org/10.1192/bjp.bp.111.098079

Lamers, F., de Jonge, P., Nolen, W. A., Smit, J. H., Zitman, F. G., Beekman, A. T. F., & Penninx, B. W. J. H. (2010). Identifying Depressive Subtypes in a Large Cohort Study: Results From the Netherlands Study of Depression and Anxiety (NESDA). *The Journal of Clinical Psychiatry*, *71*(12), 1582–1589. https://doi.org/10.4088/JCP.09m05398blu

Lamers, F., Vogelzangs, N., Merikangas, K. R., de Jonge, P., Beekman, A. T. F., & Penninx, B. W. J. H. (2013). Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Molecular Psychiatry*, *18*(6), 692–699. https://doi.org/10.1038/mp.2012.144

Lasserre, A. M., Marti-Soler, H., Strippoli, M.-P. F., Vaucher, J., Glaus, J., Vandeleur, C. L., Castelao, E., Marques-Vidal, P., Waeber, G., Vollenweider, P., & Preisig, M. (2016). Clinical and course characteristics of depression and all-cause mortality: A prospective population-based study. *Journal of Affective Disorders*, *189*, 17–24. https://doi.org/10.1016/j.jad.2015.09.010

Lewis, T. T., Sutton-Tyrrell, K., Penninx, B. W., Vogelzangs, N., Harris, T. B., Vaidean, G. D., Ayonayon, H. N., Kim, L., Lakatta, E. G., & Newman, A. B. (2010). Race, Psychosocial Factors, and Aortic Pulse Wave Velocity: The Health, Aging, and Body Composition Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *65A*(10), 1079–1085. https://doi.org/10.1093/gerona/glq089

Li, L., Gower, B. A., Shelton, R. C., & Wu, X. (2017). Gender-Specific Relationship between Obesity and Major Depression. *Frontiers in Endocrinology*, *8*, 292. https://doi.org/10.3389/fendo.2017.00292

Li, M., D'Arcy, C., Li, X., Zhang, T., Joober, R., & Meng, X. (2019). What do DNA methylation studies tell us about depression? A systematic review. *Translational Psychiatry*, *9*(1), 68. https://doi.org/10.1038/s41398-019-0412-y

Liese, A. D., Mayer-Davis, E. J., & Haffner, S. M. (1998). Development of the multiple metabolic syndrome: An epidemiologic perspective. *Epidemiologic Reviews*, *20*(2), 157–172. https://doi.org/10.1093/oxfordjournals.epirev.a017978

Lloyd, C. E., Pambianco, G., & Orchard, T. J. (2010). Does diabetes-related distress explain the presence of depressive symptoms and/or poor self-care in individuals with Type 1 diabetes? *Diabetic Medicine*, *27*(2), 234–237. https://doi.org/10.1111/j.1464-5491.2009.02896.x

Luger, T. M., Suls, J., & Vander Weg, M. W. (2014). How robust is the association between smoking and depression in adults? A meta-analysis using linear mixed-effects models. *Addictive Behaviors*, *39*(10), 1418–1429. https://doi.org/10.1016/j.addbeh.2014.05.011

Luppino, F. S., de Wit, L. M., Bouvy, P. F., Stijnen, T., Cuijpers, P., Penninx, B. W. J. H., & Zitman, F. G. (2010). Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. *Archives of*

General Psychiatry, *67*(3), 220–229. https://doi.org/10.1001/archgenpsychiatry.2010.2

Malhi, G. S., & Mann, J. J. (2018). Depression. *Lancet (London, England)*, *392*(10161), 2299–2312. https://doi.org/10.1016/S0140-6736(18)31948-2

Mancia, G., De Backer, G., Dominiczak, A., Cifkova, R., Fagard, R., Germano, G., Grassi, G., Heagerty, A. M., Kjeldsen, S. E., Laurent, S., Narkiewicz, K., Ruilope, L., Rynkiewicz, A., Schmieder, R. E., Boudier, H. A. S., & Zanchetti, A. (2007). 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Journal of Hypertension*, *25*(6), 1105–1187. https://doi.org/10.1097/HJH.0b013e3281fc975a

Mandelli, L., Petrelli, C., & Serretti, A. (2015). The role of specific early trauma in adult depression: A meta-analysis of published literature. Childhood trauma and adult depression. *European Psychiatry*, *30*(6), 665–680. https://doi.org/10.1016/j.eurpsy.2015.04.007

Mann, J. N., & Thakore, J. H. (1999). Melancholic Depression and Abdominal Fat Distribution: A Mini-Review. *Stress*, *3*(1), 1–15. https://doi.org/10.3109/10253899909001108

Marcus, S. M., Kerber, K. B., Rush, A. J., Wisniewski, S. R., Nierenberg, A., Balasubramani, G. K., Ritz, L., Kornstein, S., Young, E. A., & Trivedi, M. H. (2008). Sex differences in depression symptoms in treatment-seeking adults: Confirmatory analyses from the Sequenced Treatment Alternatives to Relieve Depression study. *Comprehensive Psychiatry*, *49*(3), 238–246. https://doi.org/10.1016/j.comppsych.2007.06.012

Marioni, R. E., Strachan, M. W. J., Reynolds, R. M., Lowe, G. D. O., Mitchell, R. J., Fowkes, F. G. R., Frier, B. M., Lee, A. J., Butcher, I., Rumley, A., Murray, G. D., Deary, I. J., & Price, J. F. (2010). Association Between Raised Inflammatory Markers and Cognitive Decline in Elderly People With Type 2 Diabetes. *Diabetes*, *59*(3), 710–713. https://doi.org/10.2337/db09-1163

Markkula, N., Marola, N., Nieminen, T., Koskinen, S., Saarni, S. I., Härkänen, T., & Suvisaari, J. (2017). Predictors of new-onset depressive disorders – Results

from the longitudinal Finnish Health 2011 Study. *Journal of Affective Disorders*, *208*, 255–264. https://doi.org/10.1016/j.jad.2016.08.051

Markkula, N., & Suvisaari, J. (2017). Prevalence, risk factors and prognosis of depressive disorders. *Duodecim; Laaketieteellinen Aikakauskirja*, *133*(3), 275–282.

Maukonen, M., Männistö, S., & Tolonen, H. (2018). A comparison of measured versus self-reported anthropometrics for assessing obesity in adults: A literature review. *Scandinavian Journal of Public Health*, *46*(5), 565–579. https://doi.org/10.1177/1403494818761971

McElroy, S. L., Kotwal, R., Malhotra, S., Nelson, E. B., Keck, P. E., & Nemeroff, C. B. (2004). Are Mood Disorders and Obesity Related? A Review for the Mental Health Professional. *The Journal of Clinical Psychiatry*, *65*(5), 634–651. https://doi.org/10.4088/JCP.v65n0507

McEwen, B. S. (2012). Brain on stress: How the social environment gets under the skin. *Proceedings of the National Academy of Sciences*, *109*(supplement_2), 17180–17185. https://doi.org/10.1073/pnas.1121254109

McGrath, P. J., Khan, A. Y., Trivedi, M. H., Stewart, J. W., Morris, D. W., Wisniewski, S. R., Miyahara, S., Nierenberg, A. A., Fava, M., & Rush, A. J. (2008). Response to a Selective Serotonin Reuptake Inhibitor (Citalopram) in Major Depressive Disorder With Melancholic Features: A STAR*D Report. *The Journal of Clinical Psychiatry*, *69*(12), 1847–1855. https://doi.org/10.4088/JCP.v69n1201

McHugh, K., & Weiss, R. (2019). Alcohol Use Disorder and Depressive Disorders. *Alcohol Research: Current Reviews*, *40*(1), arcr.v40.1.01. https://doi.org/10.35946/arcr.v40.1.01

Meerwaldt, R., Graaff, R., Oomen, P. H. N., Links, T. P., Jager, J. J., Alderson, N. L., Thorpe, S. R., Baynes, J. W., Gans, R. O. B., & Smit, A. J. (2004). Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia*, *47*(7), 1324–1330. https://doi.org/10.1007/s00125-004-1451-2

Milaneschi, Y., Lamers, F., Peyrot, W. J., Baune, B. T., Breen, G., Dehghan, A., Forstner, A. J., Grabe, H. J., Homuth, G., Kan, C., Lewis, C., Mullins, N., Nauck, M., Pistis, G., Preisig, M., Rivera, M., Rietschel, M., Streit, F.,

Strohmaier, J., … CHARGE Inflammation Working Group and the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. (2017). Genetic Association of Major Depression With Atypical Features and Obesity-Related Immunometabolic Dysregulations. *JAMA Psychiatry*, *74*(12), 1214–1225. https://doi.org/10.1001/jamapsychiatry.2017.3016

Milano, W., Ambrosio, P., Carizzone, F., De Biasio, V., Di Munzio, W., Foia, M. G., & Capasso, A. (2020). Depression and Obesity: Analysis of Common Biomarkers. *Diseases (Basel, Switzerland)*, *8*(2). https://doi.org/10.3390/diseases8020023

Mitchell, G. F. (2014). Arterial Stiffness and Hypertension. *Hypertension*, *64*(1), 13–18. https://doi.org/10.1161/HYPERTENSIONAHA.114.00921

Mitchell, G. F., Benjamin, E. J., Kupka, M. J., Larson, M. G., & Lew, D. (2002). Differential changes in central and peripheral conduit vessel stiffness with advancing age in a community-based cohort: The NHLBI framingham heart study. *Journal of the American College of Cardiology*, *39*, 139. https://doi.org/10.1016/S0735-1097(02)80610-6

Mitchell, G. F., Hwang, S.-J., Vasan, R. S., Larson, M. G., Pencina, M. J., Hamburg, N. M., Vita, J. A., Levy, D., & Benjamin, E. J. (2010). Arterial Stiffness and Cardiovascular Events: The Framingham Heart Study. *Circulation*, *121*(4), 505–511. https://doi.org/10.1161/CIRCULATIONAHA.109.886655

Mitchell, G. F., van Buchem, M. A., Sigurdsson, S., Gotal, J. D., Jonsdottir, M. K., Kjartansson, Ó., Garcia, M., Aspelund, T., Harris, T. B., Gudnason, V., & Launer, L. J. (2011). Arterial stiffness, pressure and flow pulsatility and brain structure and function: The Age, Gene/Environment Susceptibility – Reykjavik Study. *Brain*, *134*(11), 3398–3407. https://doi.org/10.1093/brain/awr253

Moreira, F. P., Jansen, K., Cardoso, T. de A., Mondin, T. C., Vieira, I. S., Magalhães, P. V. da S., Kapczinski, F., Souza, L. D. de M., da Silva, R. A., Oses, J. P., & Wiener, C. D. (2019). Metabolic syndrome, depression and anhedonia among young adults. *Psychiatry Research*, *271*, 306–310. https://doi.org/10.1016/j.psychres.2018.08.009

Müller, N. (2014). Immunology of Major Depression. *Neuroimmunomodulation*, *21*(2–3), 123–130. https://doi.org/10.1159/000356540

Murray, C. J. L., Aravkin, A. Y., Zheng, P., Abbafati, C., Abbas, K. M., Abbasi-Kangevari, M., Abd-Allah, F., Abdelalim, A., Abdollahi, M., Abdollahpour, I., Abegaz, K. H., Abolhassani, H., Aboyans, V., Abreu, L. G., Abrigo, M. R. M., Abualhasan, A., Abu-Raddad, L. J., Abushouk, A. I., Adabi, M., … Lim, S. S. (2020). Global burden of 87 risk factors in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*(10258), 1223–1249. https://doi.org/10.1016/S0140-6736(20)30752-2

Nakrani, M. N., Wineland, R. H., & Anjum, F. (2022). Physiology, Glucose Metabolism. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK560599/

Nouwen, A., Nefs, G., Caramlau, I., Connock, M., Winkley, K., Lloyd, C. E., Peyrot, M., Pouwer, F., & European Depression in Diabetes Research Consortium. (2011). Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: A systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. *Diabetes Care*, *34*(3), 752–762. https://doi.org/10.2337/dc10-1414

Nuevo, R., Lehtinen, V., Reyna-Liberato, P. M., & Ayuso-Mateos, J. L. (2009). Usefulness of the Beck Depression Inventory as a screening method for depression among the general population of Finland. *Scandinavian Journal of Public Health*, *37*(1), 28–34. https://doi.org/10.1177/1403494808097169

O'Connor, P. J., Crain, A. L., Rush, W. A., Hanson, A. M., Fischer, L. R., & Kluznik, J. C. (2009). Does Diabetes Double the Risk of Depression? *The Annals of Family Medicine*, *7*(4), 328–335. https://doi.org/10.1370/afm.964

Ohmine, T., Miwa, Y., Yao, H., Yuzuriha, T., Takashima, Y., Uchino, A., Takahashi-Yanaga, F., Morimoto, S., Maehara, Y., & Sasaguri, T. (2008). Association between Arterial Stiffness and Cerebral White Matter Lesions in Community-Dwelling Elderly Subjects. *Hypertension Research*, *31*(1), 75–81. https://doi.org/10.1291/hypres.31.75

Ohnuma, T., Nishimon, S., Takeda, M., Sannohe, T., Katsuta, N., & Arai, H. (2018). Carbonyl Stress and Microinflammation-Related Molecules as Potential Biomarkers in Schizophrenia. *Frontiers in Psychiatry*, *9*, 82. https://doi.org/10.3389/fpsyt.2018.00082

Oikeusministeriö. (n.d.). *Suomen ja ruotsin kieli*. Oikeusministeriö. Retrieved July 9, 2022, from https://oikeusministerio.fi/suomen-ja-ruotsin-kieli

Onete, V., Henry, R. M., Sep, S. J. S., Koster, A., van der Kallen, C. J., Dagnelie, P. C., Schaper, N., Köhler, S., Reesink, K., Stehouwer, C. D. A., & Schram, M. T. (2018). Arterial stiffness is associated with depression in middle-aged men—The Maastricht Study. *Journal of Psychiatry & Neuroscience*, *43*(2), 111–119. https://doi.org/10.1503/jpn.160246

Oparil, S., Acelajado, M. C., Bakris, G. L., Berlowitz, D. R., Cífková, R., Dominiczak, A. F., Grassi, G., Jordan, J., Poulter, N. R., Rodgers, A., & Whelton, P. K. (2018). Hypertension. *Nature Reviews Disease Primers*, *4*(1), 18014. https://doi.org/10.1038/nrdp.2018.14

Ovaskainen, Y., Koponen, H., Jokelainen, J., Keinänen-Kiukaanniemi, S., Kumpusalo, E., & Vanhala, M. (2009). Depressive symptomatology is associated with decreased interleukin-1 beta and increased interleukin-1 receptor antagonist levels in males. *Psychiatry Research*, *167*(1–2), 73–79. https://doi.org/10.1016/j.psychres.2007.12.004

Packard, A. E. B., Egan, A. E., & Ulrich-Lai, Y. M. (2016). HPA Axis Interactions with Behavioral Systems. In R. Terjung (Ed.), *Comprehensive Physiology* (1st ed., pp. 1897–1934). Wiley. https://doi.org/10.1002/cphy.c150042

Palatini, P., Casiglia, Gasowski, J., Gluszek, J., Jankowski, Narkiewicz, Saladini, Stolarz-Skrzypek, Tikhonoff, Van Bortel, Wojciechowska, & Kawecka-Jaszcz, K. (2011). Arterial stiffness, central hemodynamics, and cardiovascular risk in hypertension. *Vascular Health and Risk Management*, 725. https://doi.org/10.2147/VHRM.S25270

Park, C., Rosenblat, J. D., Brietzke, E., Pan, Z., Lee, Y., Cao, B., Zuckerman, H., Kalantarova, A., & McIntyre, R. S. (2019). Stress, epigenetics and depression: A systematic review. *Neuroscience & Biobehavioral Reviews*, *102*, 139–152. https://doi.org/10.1016/j.neubiorev.2019.04.010

Parker, G., Hyett, M. P., Friend, P., & Hadzi-Pavlovic, D. (2013). Does age impact on rating melancholic and non-melancholic depressive symptoms? *Journal of Affective Disorders*, *147*(1–3), 318–324. https://doi.org/10.1016/j.jad.2012.11.031

Penner-Goeke, S., & Binder, E. B. (2019). Epigenetics and depression. *Dialogues in Clinical Neuroscience*, *21*(4), 397–405. https://doi.org/10.31887/DCNS.2019.21.4/ebinder

Penninx, B. W., Milaneschi, Y., Lamers, F., & Vogelzangs, N. (2013). Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. *BMC Medicine*, *11*(1), 129. https://doi.org/10.1186/1741-7015-11-129

Pereira-Miranda, E., Costa, P. R. F., Queiroz, V. A. O., Pereira-Santos, M., & Santana, M. L. P. (2017). Overweight and Obesity Associated with Higher Depression Prevalence in Adults: A Systematic Review and Meta-Analysis. *Journal of the American College of Nutrition*, *36*(3), 223–233. https://doi.org/10.1080/07315724.2016.1261053

Peterson, K. L., Jacobs, J. P., Allender, S., Alston, L. V., & Nichols, M. (2016). Characterising the extent of misreporting of high blood pressure, high cholesterol, and diabetes using the Australian Health Survey. *BMC Public Health*, *16*(1), 695. https://doi.org/10.1186/s12889-016-3389-y

Pugh, K. G., & Lipsitz, L. A. (2002). The microvascular frontal-subcortical syndrome of aging. *Neurobiology of Aging*, *23*(3), 421–431. https://doi.org/10.1016/S0197-4580(01)00319-0

Pulska, T. (2001). *Mortality of the depressed elderly*. Oulun yliopisto.

Rantanen, A. T., Kallio, M. M., Korkeila, J. J. A., Kautiainen, H., & Korhonen, P. E. (2020). Relationship of non-melancholic and melancholic depressive symptoms with all-cause mortality: A prospective study in a primary care population. *Journal of Psychosomatic Research*, *133*, 110107. https://doi.org/10.1016/j.jpsychores.2020.110107

Rapoport, M., Chetrit, A., Cantrell, D., Novikov, I., Roth, J., & Dankner, R. (2021). Years of potential life lost in pre-diabetes and diabetes mellitus: Data from a 40-year follow-up of the Israel study on Glucose intolerance, Obesity and

Hypertension. *BMJ Open Diabetes Research & Care*, *9*(1), e001981. https://doi.org/10.1136/bmjdrc-2020-001981

Reaven, G. M. (1997). Banting Lecture 1988. Role of insulin resistance in human disease. 1988. *Nutrition (Burbank, Los Angeles County, Calif.)*, *13*(1), 65; discussion 64, 66. https://doi.org/10.1016/s0899-9007(96)00380-2

Rehunen, S. K. J., Kautiainen, H., Korhonen, P. E., & Eriksson, J. G. (2021). A high lean body mass is not protecting from type 2 diabetes in the presence of a high body fat mass. *Diabetes & Metabolism*, *47*(6), 101219. https://doi.org/10.1016/j.diabet.2020.101219

Roberts, A. L., Kubzansky, L. D., Malspeis, S., Feldman, C. H., & Costenbader, K. H. (2018). Association of Depression With Risk of Incident Systemic Lupus Erythematosus in Women Assessed Across 2 Decades. *JAMA Psychiatry*, *75*(12), 1225. https://doi.org/10.1001/jamapsychiatry.2018.2462

Rooke, S., & Thorsteinsson, E. (2008). Examining the temporal relationship between depression and obesity: Meta-analyses of prospective research. *Health Psychology Review*, *2*(1), 94–109. https://doi.org/10.1080/17437190802295689

Roy, T., & Lloyd, C. E. (2012). Epidemiology of depression and diabetes: A systematic review. *Journal of Affective Disorders*, *142 Suppl*, S8-21. https://doi.org/10.1016/S0165-0327(12)70004-6

Ruderman, N. B., Williamson, J. R., & Brownlee, M. (1992). Glucose and diabetic vascular disease [1]. *The FASEB Journal*, *6*(11), 2905–2914. https://doi.org/10.1096/fasebj.6.11.1644256

Rumpf, H.-J., Meyer, C., Hapke, U., & John, U. (2001). Screening for mental health: Validity of the MHI-5 using DSM-IV Axis I psychiatric disorders as gold standard. *Psychiatry Research*, *105*(3), 243–253. https://doi.org/10.1016/S0165-1781(01)00329-8

Saint Onge, J. M., Krueger, P. M., & Rogers, R. G. (2014). The Relationship Between Major Depression and Nonsuicide Mortality for U.S. Adults: The Importance of Health Behaviors. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *69*(4), 622–632. https://doi.org/10.1093/geronb/gbu009

Salaycik, K. J., Kelly-Hayes, M., Beiser, A., Nguyen, A.-H., Brady, S. M., Kase, C. S., & Wolf, P. A. (2007). Depressive Symptoms and Risk of Stroke: The Framingham Study. *Stroke*, *38*(1), 16–21. https://doi.org/10.1161/01.STR.0000251695.39877.ca

Schmidt, A., Clynes, R., Moser, B., Yan, S., Ramasamy, R., & Herold, K. (2007). Receptor for AGE (RAGE): Weaving Tangled Webs Within the Inflammatory Response. *Current Molecular Medicine*, *7*(8), 743–751. https://doi.org/10.2174/156652407783220714

Schulz, R., Drayer, R. A., & Rollman, B. L. (2002). Depression as a risk factor for non-suicide mortality in the elderly. *Biological Psychiatry*, *52*(3), 205–225. https://doi.org/10.1016/S0006-3223(02)01423-3

Segers, P., Rietzschel, E. R., De Buyzere, M. L., Vermeersch, S. J., De Bacquer, D., Van Bortel, L. M., De Backer, G., Gillebert, T. C., & Verdonck, P. R. (2007). Noninvasive (Input) Impedance, Pulse Wave Velocity, and Wave Reflection in Healthy Middle-Aged Men and Women. *Hypertension*, *49*(6), 1248–1255. https://doi.org/10.1161/HYPERTENSIONAHA.106.085480

Sell, D. R., & Monnier, V. M. (2012). Molecular basis of arterial stiffening: Role of glycation - a mini-review. *Gerontology*, *58*(3), 227–237. https://doi.org/10.1159/000334668

Seppälä, J., Koponen, H., Kautiainen, H., Eriksson, J. G., Kampman, O., Männistö, S., Mäntyselkä, P., Oksa, H., Ovaskainen, Y., Viikki, M., & Vanhala, M. (2012). Association between folate intake and melancholic depressive symptoms. A Finnish population-based study. *Journal of Affective Disorders*, *138*(3), 473–478. https://doi.org/10.1016/j.jad.2012.01.007

Seppälä, J., Koponen, H., Vanhala, M., Kautiainen, H., järvenpää, J., Eriksson, J., Kampman, O., Oksa, H., Ovaskainen, Y., & Viikki, M. (2010). Beck Depression Inventory (BDI) as ascreening tool for depression. A population-based Finnish cross-sectional study. *Psychiatria Fennica*, *41*, 42–52.

Seppälä, J., Vanhala, M., Kautiainen, H., Eriksson, J., Kampman, O., Mäntyselkä, P., Oksa, H., Ovaskainen, Y., Viikki, M., & Koponen, H. (2012). Prevalence of metabolic syndrome in subjects with melancholic and non-melancholic depressive symptoms. A Finnish population-based study. *Journal of Affective Disorders*, *136*(3), 543–549. https://doi.org/10.1016/j.jad.2011.10.032

Sgoifo, A., Carnevali, L., Pico Alfonso, M. de los A., & Amore, M. (2015). Autonomic dysfunction and heart rate variability in depression. *Stress*, *18*(3), 343–352. https://doi.org/10.3109/10253890.2015.1045868

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59 Suppl 20*, 22-33;quiz 34-57.

Slavich, G. M., & Irwin, M. R. (2014). From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. *Psychological Bulletin*, *140*(3), 774–815. https://doi.org/10.1037/a0035302

Smithson, S., & Pignone, M. P. (2017). Screening Adults for Depression in Primary Care. *Medical Clinics of North America*, *101*(4), 807–821. https://doi.org/10.1016/j.mcna.2017.03.010

Spauwen, P. J. J., van Eupen, M. G. A., Köhler, S., Stehouwer, C. D. A., Verhey, F. R. J., van der Kallen, C. J. H., Sep, S. J. S., Koster, A., Schaper, N. C., Dagnelie, P. C., Schalkwijk, C. G., Schram, M. T., & van Boxtel, M. P. J. (2015). Associations of Advanced Glycation End-Products With Cognitive Functions in Individuals With and Without Type 2 Diabetes: The Maastricht Study. *The Journal of Clinical Endocrinology & Metabolism*, *100*(3), 951–960. https://doi.org/10.1210/jc.2014-2754

Stein, M. B. (2005). Sweating away the blues. *American Journal of Preventive Medicine*, *28*(1), 140–141. https://doi.org/10.1016/j.amepre.2004.09.024

Stephan, A. H., Barres, B. A., & Stevens, B. (2012). The Complement System: An Unexpected Role in Synaptic Pruning During Development and Disease. *Annual Review of Neuroscience*, *35*(1), 369–389. https://doi.org/10.1146/annurev-neuro-061010-113810

Sullivan, M. D., O'Connor, P., Feeney, P., Hire, D., Simmons, D. L., Raisch, D. W., Fine, L. J., Narayan, K. M. V., Ali, M. K., & Katon, W. J. (2012). Depression Predicts All-Cause Mortality: Epidemiological evaluation from the ACCORD HRQL substudy. *Diabetes Care*, *35*(8), 1708–1715. https://doi.org/10.2337/dc11-1791

Sullivan, P. F., Prescott, C., & Kendler, K. (2002). The subtypes of major depression in a twin registry. *Journal of Affective Disorders*, *68*(2–3), 273–284. https://doi.org/10.1016/S0165-0327(00)00364-5

Talbot, F., & Nouwen, A. (2000). A review of the relationship between depression and diabetes in adults: Is there a link? *Diabetes Care*, *23*(10), 1556–1562. https://doi.org/10.2337/diacare.23.10.1556

Tamada, Y., Inoue, T., Sekine, A., Toda, H., Takeshima, M., Sasaki, M., Shindome, K., Morita, W., Kuyama, N., & Ohmae, S. (2021). Identifying Subjective Symptoms Associated with Psychomotor Disturbance in Melancholia: A Multiple Regression Analysis Study. *Neuropsychiatric Disease and Treatment*, *Volume 17*, 1105–1114. https://doi.org/10.2147/NDT.S300233

Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Molecular Psychiatry*, *18*(9), 963–974. https://doi.org/10.1038/mp.2013.20

THL. (n.d.). *THL Kansallinen koodistopalvelin*. THL Tautiluokitus ICD-10. https://koodistopalvelu.kanta.fi/codeserver/pages/classification-view-page.xhtml?classificationKey=23&versionKey=58

Thomas, O., Cain, J., Nasralla, M., & Jackson, A. (2019). Aortic Pulsatility Propagates Intracranially and Correlates with Dilated Perivascular Spaces and Small Vessel Compliance. *Journal of Stroke and Cerebrovascular Diseases*, *28*(5), 1252–1260. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.01.020

Tiemeier, H., Breteler, M. M. B., Van Popele, N. M., Hofman, A., & Witteman, J. C. M. (2003). Late-Life Depression is Associated with Arterial Stiffness: A Population-Based Study. *Journal of the American Geriatrics Society*, *51*(8), 1105–1110. https://doi.org/10.1046/j.1532-5415.2003.51359.x

Tucker, J. M., Welk, G. J., & Beyler, N. K. (2011). Physical Activity in U.S. Adults. *American Journal of Preventive Medicine*, *40*(4), 454–461. https://doi.org/10.1016/j.amepre.2010.12.016

Turecki, G., & Meaney, M. J. (2016). Effects of the Social Environment and Stress on Glucocorticoid Receptor Gene Methylation: A Systematic Review. *Biological Psychiatry*, *79*(2), 87–96. https://doi.org/10.1016/j.biopsych.2014.11.022

Van Bortel, L. M., Laurent, S., Boutouyrie, P., Chowienczyk, P., Cruickshank, J. K., De Backer, T., Filipovsky, J., Huybrechts, S., Mattace-Raso, F. U. S., Protogerou, A. D., Schillaci, G., Segers, P., Vermeersch, S., & Weber, T. (2012). Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *Journal of Hypertension*, *30*(3), 445–448. https://doi.org/10.1097/HJH.0b013e32834fa8b0

van Dooren, F. E. P., Pouwer, F., Schalkwijk, C. G., Sep, S. J. S., Stehouwer, C. D. A., Henry, R. M. A., Dagnelie, P. C., Schaper, N. C., van der Kallen, C. J. H., Koster, A., Denollet, J., Verhey, F. R. J., & Schram, M. T. (2017). Advanced Glycation End Product (AGE) Accumulation in the Skin is Associated with Depression: The Maastricht Study: Research Article: Advanced Glycation End Products and Depression. *Depression and Anxiety*, *34*(1), 59–67. https://doi.org/10.1002/da.22527

van Gool, C. H., Kempen, G. I. J. M., Bosma, H., van Boxtel, M. P. J., Jolles, J., & van Eijk, J. T. M. (2007). Associations Between Lifestyle and Depressed Mood: Longitudinal Results From the Maastricht Aging Study. *American Journal of Public Health*, *97*(5), 887–894. https://doi.org/10.2105/AJPH.2004.053199

van Sloten, T. T., Mitchell, G. F., Sigurdsson, S., van Buchem, M. A., Jonsson, P. V., Garcia, M. E., Harris, T. B., Henry, R. M. A., Levey, A. S., Stehouwer, C. D. A., Gudnason, V., & Launer, L. J. (2016). Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: Cross-sectional findings from the AGES-Reykjavik Study. *Journal of Psychiatry and Neuroscience*, *41*(3), 162–168. https://doi.org/10.1503/jpn.140334

van Sloten, T. T., Protogerou, A. D., Henry, R. M. A., Schram, M. T., Launer, L. J., & Stehouwer, C. D. A. (2015). Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, *53*, 121–130. https://doi.org/10.1016/j.neubiorev.2015.03.011

van Sloten, T. T., Schram, M. T., Adriaanse, M. C., Dekker, J. M., Nijpels, G., Teerlink, T., Scheffer, P. G., Pouwer, F., Schalkwijk, C. G., Stehouwer, C. D.

A., & Henry, R. M. A. (2014). Endothelial dysfunction is associated with a greater depressive symptom score in a general elderly population: The Hoorn Study. *Psychological Medicine*, *44*(7), 1403–1416. https://doi.org/10.1017/S0033291713002043

van Waateringe, R. P., Slagter, S. N., van der Klauw, M. M., van Vliet-Ostaptchouk, J. V., Graaff, R., Paterson, A. D., Lutgers, H. L., & Wolffenbuttel, B. H. R. (2016). Lifestyle and clinical determinants of skin autofluorescence in a population-based cohort study. *European Journal of Clinical Investigation*, *46*(5), 481–490. https://doi.org/10.1111/eci.12627

Vanhala, M., Jokelainen, J., Keinänen-Kiukaanniemi, S., Kumpusalo, E., & Koponen, H. (2009). Depressive symptoms predispose females to metabolic syndrome: A 7-year follow-up study. *Acta Psychiatrica Scandinavica*, *119*(2), 137–142. https://doi.org/10.1111/j.1600-0447.2008.01283.x

Vasegh, S., & Baradaran, N. (2014). Using the Persian-Language Version of the Beck Depression Inventory–II (BDI-II-Persian) for the Screening of Depression in Students. *Journal of Nervous & Mental Disease*, *202*(10), 738–744. https://doi.org/10.1097/NMD.0000000000000183

Vieira, E. R., Brown, E., & Raue, P. (2014). Depression in Older Adults: Screening and Referral. *Journal of Geriatric Physical Therapy*, *37*(1), 24–30. https://doi.org/10.1519/JPT.0b013e31828df26f

von Zimmermann, C., Winkelmann, M., Richter-Schmidinger, T., Mühle, C., Kornhuber, J., & Lenz, B. (2020). Physical Activity and Body Composition Are Associated With Severity and Risk of Depression, and Serum Lipids. *Frontiers in Psychiatry*, *11*, 494. https://doi.org/10.3389/fpsyt.2020.00494

Ware, J. J., & Sherbourne, C. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.*, *30*(6), 372–383.

WHO. (2017a, January 3). *Depression and Other Common Mental Disorders*. World Health Organization. https://www.who.int/publications/i/item/depression-global-health-estimates

WHO. (2017b, December 12). *Mental health of older adults*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults

WHO. (2020, January 30). *Depression*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/depression

WHO. (2021a, June 9). *Obesity and Overweight*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

WHO. (2021b, September 13). *Depression*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/depression

WHO. (2022a, May 9). *Alcohol*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/alcohol

WHO. (2022b, May 24). *Tobacco*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/tobacco

Wild, B., Herzog, W., Lechner, S., Niehoff, D., Brenner, H., Müller, H., Rothenbacher, D., Stegmaier, C., & Raum, E. (2012). Gender specific temporal and cross-sectional associations between BMI-class and symptoms of depression in the elderly. *Journal of Psychosomatic Research*, *72*(5), 376–382. https://doi.org/10.1016/j.jpsychores.2012.01.019

Wiltink, J., Michal, M., Wild, P. S., Zwiener, I., Blettner, M., Münzel, T., Schulz, A., Kirschner, Y., & Beutel, M. E. (2013). Associations between depression and different measures of obesity (BMI, WC, WHtR, WHR). *BMC Psychiatry*, *13*(1), 223. https://doi.org/10.1186/1471-244X-13-223

Working group set up by the Finnish Medical Society Duodecim and the Finnish Cardiac Society. (2022, June 29). *Depression*. Current Care Guidlines. https://www.kaypahoito.fi/hoi50023

Wu, Y., Kralj, C., Acosta, D., Guerra, M., Huang, Y., Jotheeswaran, A. T., Jimenez-Velazquez, I. Z., Liu, Z., Llibre Rodriguez, J. J., Salas, A., Sosa, A. L., Alkholy, R., Prince, M., & Prina, A. M. (2020). The association between, depression, anxiety, and mortality in older people across eight low- and middle-income countries: Results from the 10/66 cohort study. *International Journal of Geriatric Psychiatry*, *35*(1), 29–36. https://doi.org/10.1002/gps.5211

Yamagishi, S. (2011). Role of advanced glycation end products (AGEs) and receptor for AGEs (RAGE) in vascular damage in diabetes. *Experimental Gerontology*, *46*(4), 217–224. https://doi.org/10.1016/j.exger.2010.11.007

Zanoli, L., Briet, M., Empana, J. P., Cunha, P. G., Mäki-Petäjä, K. M., Protogerou, A. D., Tedgui, A., Touyz, R. M., Schiffrin, E. L., Spronck, B., Bouchard, P., Vlachopoulos, C., Bruno, R. M., & Boutouyrie, P. (2020). Vascular consequences of inflammation: A position statement from the ESH Working Group on Vascular Structure and Function and the ARTERY Society. *Journal of Hypertension*, *38*(9), 1682–1698. https://doi.org/10.1097/HJH.0000000000002508

Zanoli, L., Cannavò, M., Rastelli, S., Di Pino, L., Monte, I., Di Gangi, M., Boutouyrie, P., Inserra, G., Laurent, S., & Castellino, P. (2012). Arterial stiffness is increased in patients with inflammatory bowel disease. *Journal of Hypertension*, *30*(9), 1775–1781. https://doi.org/10.1097/HJH.0b013e3283568abd

Zanoli, L., Lentini, P., Boutouyrie, P., Fatuzzo, P., Granata, A., Corrao, S., Gaudio, A., Inserra, G., Rapisarda, F., Rastelli, S., Laurent, S., Malatino, L. S., & Castellino, P. (2018). Pulse wave velocity differs between ulcerative colitis and chronic kidney disease. *European Journal of Internal Medicine*, *47*, 36–42. https://doi.org/10.1016/j.ejim.2017.08.020

Zanoli, L., Tuttolomondo, A., Inserra, G., Cappello, M., Granata, A., Malatino, L., & Castellino, P. (2020). Anxiety, depression, chronic inflammation and aortic stiffness in Crohn's disease: The brain--gut--vascular axis. *Journal of Hypertension*, *38*(10), 2008–2017. https://doi.org/10.1097/HJH.0000000000002517

Zhu, K., Allen, K., Mountain, J., Lye, S., Pennell, C., & Walsh, J. P. (2017). Depressive symptoms, body composition and bone mass in young adults: A prospective cohort study. *International Journal of Obesity*, *41*(4), 576–581. https://doi.org/10.1038/ijo.2016.214

Zich, J. M., Attkisson, C. C., & Greenfield, T. K. (1990). Screening for Depression in Primary Care Clinics: The CES-D and the BDI. *The International Journal of Psychiatry in Medicine*, *20*(3), 259–277. https://doi.org/10.2190/LYKR-7VHP-YJEM-MKM2