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The relationship between dietary patterns and depressive symptoms in older adults

Vztah mezi stravovacími vzorci a depresivními symptomy u starších dospělých

Diploma thesis

Supervisor: prof. Hynek Pikhart, Ph.D.

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Prohlášení

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The relationship between dietary patterns and depressive symptoms in older adults

Abstract

Background: Late-life depression is a prevalent mental illness that occurs among adults aged 65 years and older that is becoming more significant with the on-going aging of population worldwide. It is a multietiological disease that appears to be more likely to be modified by lifestyle factors, including nutrition, than depression in younger age.

Aims: The aim of this diploma thesis was to summarize a wide array of risk factors for late-life depression, introduce the proposed pathways for the effect of a healthy diet on late-life depression, and longitudinally assess the relationship between depressive symptoms and adherence to a healthy dietary pattern.

Methods: Longitudinal data from 4117 Czech participants of the Health, Alcohol and Psychosocial factors In Eastern Europe study were used. Data on depressive symptoms were collected using the CES-D scale at six time points, nutritional data come from a food frequency questionnaire collected at baseline. Growth curve modelling was used for the main analysis, and subsequently for a sex-stratified analysis.

Results: The results showed an inverse association between the intensity of depressive symptoms and adherence to a healthy diet. CES-D score was lower at baseline and in all subsequent waves in respondents with high HDI. Furthermore, the relationship differed between sexes, with a significant inverse association in women but not in men.

Conclusion: This thesis enhances our understanding of nutritional psychiatry in a commonly overlooked population of older adults from the Central and Eastern European region, and further underscores the need for more research.

Key words: late-life depression, LLD, healthy dietary patterns, HDI, HAPIEE

Vztah mezi stravovacími vzorci a depresivními symptomy u starších dospělých

Abstrakt

Úvod: Deprese pozdního věku je častá duševní porucha u osob starších 65 let a nabývá na důležitosti v důsledku progresivního stárnutí populace celosvětově. Je to multietiologické onemocnění, které může být více modifikované environmentálními faktory, včetně výživy, než deprese v nižším věku.

Cíle: Cílem této diplomové práce bylo sumarizovat široké spektrum rizikových faktorů deprese pozdního věku, představit předpokládané mechanismy efektu zdravého stravování na depresi pozdního věku a longitudinálně posoudit vztah mezi depresivními symptomy a adherencí ke zdravému výživovému vzorci.

Metody: V této práci byla použita longitudinální data od 4117 českých participantů studie Health, Alcohol and Psychosocial factors In Eastern Europe. Depresivní symptomy byly měřeny pomocí CES-D škály v šesti časových bodech, nutriční data pochází z frekvenčního dotazníku sbíraného na počátku studie. Metoda modelování růstových křivek byla použita pro hlavní analýzu a následně pro analýzu stratifikovanou podle pohlaví.

Výsledky: Výsledky ukázaly inverzní asociaci mezi intenzitou depresivních symptomů a adherencí ke zdravému výživovému vzorci. CES-D skóre bylo nižší na počátku studie a ve všech následujících vlnách u respondentů s vysokým HDI. Vztah se dále lišil podle pohlaví, u žen byla tato asociace statisticky významná, u mužů nikoliv.

Závěr: Tato práce obohacuje naše porozumění nutriční psychiatrii v často přehlížené populaci starších dospělých z regionu střední a východní Evropy, a dále zdůrazňuje potřebu dalšího výzkumu.

Klíčová slova: deprese pozdního věku, zdravé stravovací vzorce, HDI, HAPIEE

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List of abbreviations

ALA	Alpha-linolenic acid
BDI	Beck Depression Inventory
CEE	Central and Eastern Europe
CES-D	The Center for Epidemiologic Studies Depression Scale
DALYs	Disability-adjusted life years
DHA	Docosahexaenoic acid
EEDS	Eastern European Diet Score
EPA	Eicosapentaenoic acid
FFQ	Food frequency questionnaire
GBD	Global Burden of Disease
GDS-15	Geriatric depression scale
HAPIEE	Health, Alcohol and Psychosocial Factors in Eastern Europe
HDI	Healthy Diet Indicator
LLD	Late life depression
LRT	Likelihood ratio test
MD	Mediterranean diet
MDD	Major depressive disorder
MUFA	Monounsaturated fatty acids
PHQ	Patient Health Questionnaire
PUFA	Polyunsaturated fatty acids
QoL	Quality of Life
SES	Socioeconomic status
WHO	World Health Organization

Chapter 1

Introduction

1.1 Importance of the topic

Depression is a prevalent mental health condition with a significant impact on society across the globe. It is one of the leading causes of morbidity and mortality worldwide and is predicted to become the leading cause by 2030 (1). Depression among adults aged 65 years or older, known as late-life depression, has become an important public health concern with the ongoing aging of the world population. In 2015, the older population aged 65 and older was estimated to be 8.5 percent, or 617.1 million worldwide. This number is projected to nearly double by the year 2050, in 2050, there will be approximately 1.6 billion older adults worldwide, representing 16.7 percent of the total world population of 9.4 billion (2), making late-life depression a non-negligible problem (3).

Late-life depression is a multietiological disorder with multiple modifiable and non-modifiable risk factors, however, in comparison with depression in younger adults, it is more likely to be modified by environmental factors (4). Furthermore, late-life depression is often comorbid with physical illnesses and other psychiatric disorders which can further decrease quality of life and lead to increased mortality and worse outcomes of treatment (5). According to a systematic review and meta-analysis from 2019, prospective cohort studies suggest that late-life depression is associated with 34% higher risk of all-cause mortality, and 31% higher risk of cardiovascular mortality (6), posing further evidence of importance of the topic. Last but not least, it is associated with a significant increase in medical costs (7).

Older adult population is a vulnerable group for several reasons. Firstly, while core features of depression such as persistent feelings of sadness and loss of interest are present in all age groups, there are some differences in late-life depression (3). Late-life depression is more likely to present with more somatic symptoms than depression in younger age, and these symptoms are commonly considered to be a normal part of the aging process or preexisting physical disorders, patients are therefore less likely to recognize their issues as part of depression, and do not seek out professional help as often (8). Furthermore, medical comorbidity is a common problem in older age, posing a significant risk of developing subsequent depression (3). Proportionately, people over age 65 commit suicide more often than people in other age groups, and are more likely to be successful (9).

As with many disorders, especially mental disorders, there are pronounced socioeconomic differences. As in all other age groups, the risk of late-life depression among women is approximately twice as high as in men. Low educational attainment, low income, and financial issues have also been linked to a higher risk of developing late-life depression. Social and psychological risk factors are just as important (3).

Late-life depression is more prevalent in Eastern European older adults, reporting up to three times higher prevalence than their North–Western counterparts (10). This is in line with the East–West health gap in Europe that has persisted to this day (11).

Looking at nutrition in regard to reducing or at least alleviating the impact of mental disorders is not a new initiative as food is an unavoidable part of daily life for each and every individual. Diet is a modifiable risk factor and although making long term changes to daily nutrition can be a difficult task (12), especially in older adults, it remains an attractive research target. Current research suggests that more than individual micronutrients or foods, the overall dietary pattern might rather play a role in the occurrence and severity of depression (13). It is important to note that the effect is most likely bi-directional.

There are several proposed pathways for the relationship between dietary patterns and depressive symptoms that commonly overlap and act synergistically. Chronic low-grade inflammation, oxidative stress, and decreased neurogenesis are all factors that play a role in major depressive disorder, and may be partially reversed by good diet quality. Healthy dietary patterns tend to be high in antioxidants and flavonoids, compounds that might have additive effect on attenuating chronic low-grade inflammation (14).

1.2 Aims and objectives

The overall aim of this study is to investigate the possible relationship between dietary patterns and late-life depression in older adults across six time points in respondents that have participated in the Czech arm of the Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE) study. This association is assessed while other characteristics, such as sociodemographic variables, health, and social factors, are accounted for. These relationships are then studied for men and women separately, as previous literature described in next chapters suggests that there may be sex-differences in these associations. Thus, the overall aim of the project is:

1. To investigate how socioeconomic factors may influence the association between depressive symptoms and dietary patterns.

Research objectives and hypotheses were constructed according to existing? research.

The objectives are:

1. To explore the association between depressive symptoms and dietary patterns in a Czech cohort of adults aged 45-70 years old over the span of 19 years.

2. To determine whether marital status, economic activity, education, smoking, and self-rated health may account, at least partially, for the association between depressive symptoms and dietary patterns in older adults.

3. To assess whether there is variation in the association between depressive symptoms and dietary patterns according to sex of study participants.

Based on existing literature, reviewed in Chapter 2, the hypotheses are:

1. There will be a higher level of depressive symptoms in people with low adherence to a healthy diet.
2. The association between adherence to a healthy diet and depressive symptoms will be partly reduced when accounting for social and demographic factors.
3. The effect of dietary patterns on depressive symptoms will be larger in women than in men.

Chapter 2.

Health in the region of Central and Eastern Europe

While Northern European countries and Great Britain undertook a positive epidemiological transformation after World War II, the transformation was significantly delayed in Central and Eastern Europe (CEE), and the health gap persists to this day (15). The gap nearly closed after World War II but between mid-1960s and 1990, the health status of adults in CEE stagnated or deteriorated. On the other hand, it steadily improved in the West (16). In CEE, the rates of communicable diseases declined while non-communicable diseases, mostly cardiovascular diseases and cancers, grew more prevalent (15). This can be partially attributed to health determinants, including harmful tobacco use and binge-drinking (16). The harmful effect of smoking was largely unknown in the Soviet Union until the 1980s due to censorship of scientific studies about tobacco from the United Kingdom and United States (17). Not only that, healthy diet and dietary habits were also neglected. Meat and dairy were some of the cheapest food groups, therefore contributing to a high intake of saturated animal fats, a known risk factor for cardiovascular disease. The out-of-season supply of fresh fruit and vegetables was also poor, inhabitants therefore relied on traditional preserved foods that add large quantities of salt into the daily intake (16). In 1990s, the life expectancy at birth was on average 7 years shorter for males and 5 years shorter for females in Central and Eastern Europe compared to Western Europe (18). Furthermore, in 2015, male and female life expectancy at birth in CEE was 8.4 and 4.8 years lower, respectively, than in Western Europe (19), suggesting that the difference for females remained stable, meanwhile it increased in males. The health gap discrepancies are noticeable across many conditions. Throughout the past two decades, the total cancer mortality rates have declined across Europe, however, the gap between CEE and Western Europe has relatively increased, and had the gap been closed, 18% cancer deaths would have been avoided in Eastern Europe in

2016 (20). Moreover, the burden of cardiovascular disease is up to threefold in the East. The identified risk factors responsible for the statistics are alcohol and smoking (19). While nutrition has been researched as well, the evidence is weaker due to its complicated nature. It is speculated that the main negative contribution of diet stems from inadequate fruit intake and high animal fat consumption (16,21,22). Crucially, there are certainly other factors at play, however, a pressing issue is the lack of social inequalities in health and health behaviors research done in CEE and the former Soviet Union. That is partly due to issues concerning data availability, partly due to a lack of funding (23).

The East–West health gap extends to late-life depression as well. Some of the risk factors that play a role in the discrepancy include poverty, health problems, widowhood, and more (24). Furthermore, while the sex gap in depression is well-documented with women having a higher risk of depression than men in all age groups (3), the effect of sex is commonly overlooked in the limited amount of research that has been done on the topic of late-life depression in the East and West (24). This proposes another important limitation since these problems tend to be more prevalent in women, and especially in women of Eastern Europe that have notably higher life expectancy than their male counterparts (25). A 2017 cross-sectional study done on representative data from 10 European countries reported that the prevalence of late life depression in CEE is up to three times higher than in North–Western countries (26). For women, the rates were 25-41% in Eastern Europe versus 14-25% in the West, for men 14-21% compared to 7-10%. The difference is the most evident among the oldest age category, accompanied by a steep age-related increase in depression rates in the East. On the other hand, the prevalence of late life depression in the West is very similar to the rates among younger adults (10). This notable difference can probably be attributed to poorer health, worse socioeconomic resources, and high rates of bereavement amongst Eastern Europeans (25). Interestingly, cultural norms might be a part of the effect, as sample "average" older Eastern Europeans seem to be less depressed than sample "average" Westerners (10). Alternatively, there might be unknown sociocultural risk factors that were not included in these works (10,26) Nonetheless, these numbers are alarming, and further highlight the importance of taking cultural differences into account.

Late-life depression

Depression is a widespread mental health disorder characterized by low mood, markedly diminished interest or pleasure in activities, appetite and sleep changes, fatigue or low energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think or concentrate, and recurrent thoughts of death (27). For a formal diagnosis, five or more of these symptoms have to have been present nearly every day during a 2-week period, and represent a change from previous functioning (8). Depression is commonly comorbid with other mental disorders and presents a risk of developing another mental health disorder later in life (28). A Dutch longitudinal aging study showed high prevalence of this kind of comorbidity. 47.5% of patients aged 55-85 with major depressive disorder (MDD) also met anxiety disorder criteria, and 26.1% of patients with anxiety disorders met MDD criteria (29). Moreover, there is significant comorbidity between chronic physical conditions and depression. Furthermore, patients with chronic diseases are significantly more likely to suffer from depression than healthy people. When comorbid with physical disorders, such as cancer, stroke, acute coronary syndrome, and more, depression is associated with decreased quality of life (QoL), worse physical disorder outcomes, greater disability, and increased mortality (5). Costs to the health care system are also significant since comorbid mental health issues interact with and exacerbate physical illness. After controlling for severity of physical illness, comorbid mental health disorders were associated with a 45% increase in medical costs to the National Health Service in England (30).

2.1 Prevalence

There are currently over 1 billion people over the age of 60, and according to the World Health Organization (WHO), there will be up to 1.4 billion older adults by 2030 (1). The estimated prevalence of depression is 5% in the adult population and 5.7% in the population of adults older than 60 years (31), however, some works show very different results. For example, a 2022 systematic review and meta-analysis showed that up to 28.4% of adults older than 60 years screened positive for pre-clinical depressive symptoms (32). Another

systematic review and meta-analysis from the same year using major depressive symptoms as cut-off reported that the global prevalence of major depression in the elderly was 13.3%. The European population had the second highest prevalence, 12.9% (33). Rates of subthreshold depression, such as minor depression and subsyndromal depression in older adults tend to be higher, ranging from 10% to 50% (3). The exact prevalence of depression among older adults is unknown, though it does not diminish its importance.

One of the ways of conveying why depression is a relevant issue in the current world is through an indicator called disability-adjusted life years (DALYs). It is calculated by adding the adjusted number of years living with disability and the number of years of life lost due to premature mortality (34). It is used by the Global Burden of Disease, Injuries, and Risk Factors Study (GBD) that is conducted in an international effort to quantify health loss stemming from injuries, risk factors, and various diseases, including mental health disorders such as MDD (35). The newest estimates from GBD project from 2019 showed that mental health disorders remain in the top ten leading causes of disease burden worldwide (36). The prevalence and DALYs rates of depression were the highest in the 60-64 years age group (37). Depressive disorders were the 13th leading cause of DALYs. In comparison with data from 1990, the age-standardized prevalence of depressive disorders per 100 000 people nearly hasn't changed, reaching values 3486.2 and 3440.1 for 1990 and 2019, respectively, but the number of DALYs grew by 55.1%, and it is expected to keep growing along with the constant growth of population. Analysis also showed a statistically significant difference between sexes, the age-standardized prevalence per 100 000 people being 2717.3 for men and 4158.4 for women (36). This difference highlights the need for effective interventions that are currently severely insufficient.

2.2 Differences between late-life depression and early-life depression

Older adults, traditionally defined as persons over the age 65, are a very vulnerable group when it comes to mental health. Older people commonly attribute depressive symptoms to the ageing process or to physical disorders, making them less likely to seek treatment, and suffer in silence (8). It is believed that late-life depression (LLD), defined as depression occurring

after age 60-65 for the first time (38) should be considered a geriatric syndrome with multiple etiologies that require a combination of treatments, and not a categorical disorder (6). Manifestation of late-life depression may differ from the typical picture of depression in younger adults, presenting with somatization, such as headache, musculoskeletal pain, hypochondriasis, psychomotor retardation or agitation, psychosis, and neurocognitive symptoms (3,8). As previously mentioned, older adults have a high burden of medical comorbidities accumulated with age, ranging from cardiovascular disease and cancer to respiratory diseases and other conditions. These also pose a significant risk of subsequent depression. Due to pre-existing illnesses, older adults are more likely to be exposed to polypharmacy (3), a concurrent use of five or more medications, which is associated with an increased risk of depression. However, just like many relationships described in this thesis, it is a bidirectional relationship. While depression can be a result of physical illnesses, depression also commonly leads to worsening of lifestyle and poor physical health that can in turn increase the burden of disease (39). While on the subject of medication, aging affects treatment effectiveness and treatment adherence as it causes changes in pharmacokinetics, pharmacodynamics, and drug-drug reactions (3). Furthermore, research suggests that the risk of polypharmacy and the rate of chronic somatic diseases is significantly higher in patients with late-life depression, and the higher use of drugs remains after controlling for the rate of chronic somatic diseases (40,41).

Late life depression is accompanied by neuropsychological deficits in areas such as psychomotor speed, executive functioning, learning, and memory. Along with that, these deficits are predictors of poor prognosis for progressing dementia (42). Early-onset depression and late-onset depression differ not only in presentation, but their risk factors are also distinctive. While patients with early-onset depression are more likely to have a family history of depression, suggesting an influence of genetics, late-onset depression is more likely a mix of various risk factors, cerebrovascular disease, and cognitive impairment (43).

In severe cases, depression may lead to suicide, a rare but definitive solution. One in eight people who successfully commit suicide is aged 65 years or over. While suicide attempts are more frequent in adolescents (44), the highest suicide rate is among men aged over 75 years

(9). Older adults-specific risk factors for suicide are older age, male sex, bereavement, social isolation, a history of attempted suicide and evidence of planning suicide, chronic pain or illness or disability, drug or alcohol use, and sleep disorders (8). It is important for general practitioners to recognize signs of late-life depression as they tend to be in contact with older adults more. However, preventing the development of depression might be more effective in suicide prevention than simply improving of detection and treatment of depression (9), as even after proper treatment and symptom resolution, neuropsychological deficits may persist (42). Nonetheless, offering help and treatment to already affected patients in need might lead to fewer suicides, and is a valid target to hit.

2.3 Formal diagnosis of depression versus depressive symptoms

As previously mentioned, there is a gap between depressed patients and patients that receive a formal diagnosis. Not all patients seek help, and primary care physicians often do not recognize patients' emotional distress as depression. Some of the barriers to a formal diagnosis include lack of knowledge, cultural stigmatization, lack of skills to articulate emotions, assuming that physicians are not interested or skilled in treating depression, and more (45). Furthermore, the diagnostic criteria may underestimate MDD in older adults, tending to focus on dysphoria, a symptom that is less common in older adults. On the contrary, some criteria overlap with manifestations of bereavement and physical illness (43). When controlling for effects of gender, education, physical illness, and bereavement, the frequency of depressive symptoms actually decreases with age (46), however, physical illness and bereavement can be causes of depression, not only confounders. That is why, even though the numbers decrease, LLD shouldn't be overlooked (43). It might explain why one fourth of MDD patients remains undiagnosed and fewer than half of the diagnosed ones ever receive treatment (45). That is where questionnaires focusing on depressive symptoms may be beneficial and help recognize suffering older adults without a formal diagnosis. There are several instruments to investigate depressive symptoms such as CESD, GDS-15, PHQ-9, BDI, and more (8).

One of these scales is The Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report scale that measures the current severity of depressive symptoms in the general population. It was developed from items included in previous depression scales (47). It has a high internal consistency and adequate test-retest repeatability, and focuses on depressed mood which is the affective component of depressive symptoms. It presents a set of 20 questions phrased both positively and negatively, demanding that the respondent focuses on their answers (48). While the official 20 items scale is convenient to use, elderly respondents may find the questions emotionally stressful, burdensome, or confusing (49). It has been suggested that the 20 items could be halved without appreciable loss of reliability and validity (49,50), so several shorter forms have been constructed, such as the Boston form, the Iowa form, and CES-D-10 (51). CES-D-10, a 10-item version of the 20 item CES-D scale, is commonly used as a screening instrument for identifying MDD in older adults (49).

Another scale for depression is the Geriatric depression scale (GDS-15), a short form scale specifically focusing on geriatric patients (52). It limits somatic criteria, and is well-validated in older adults, however, it is not suitable for patients with cognitive impairment (8). It is effective for dichotomous classification of depressed and non-depressed respondents, but it also has potential for classifying the intensity of depressive symptoms (53), though it is not utilized often.

The Patient Health Questionnaire (PHQ), more specifically the P-item version PHQ-9, is another used screening tool for depressive symptoms and depression severity (54). It is based on the Diagnostic and Statistical Manual of Mental Disorders IV criteria, and is validated for primary care adults aged 60 plus in the United States and Netherlands (8).

Last but not least, the Beck depression inventory (BDI) scale is a popular self-reported depression screening tool with 21 items focused on attitudes and symptoms often present in depressed psychiatric patients (55). It is however not recommended for assessing older people as it mainly focuses on somatic symptoms (8).

The issue of thresholds and cut-offs that determine the difference between a full-blown MDD/LLD, and depressive symptoms is complex. While research shows that there is a significant decrease in health across the spectrum of subthreshold depression (56), with current scales and measurements used in epidemiology, it is hard to analyze, and therefore we currently have to rely on the available definition of depression. However, recognizing subthreshold depression is just as important, as it may predict development of major depression later in life. Furthermore, subthreshold depression is also more prevalent in older adults, and is correlated with declining cognition (3), which is another risk factor for developing LLD (43). The suggested continuum of depressive symptom severity is: depressive symptoms, minor depression, dysthymia, and major depressive disorder. Results show that each level leads to a significant decrement in health, and does not qualitatively differ from regular depressive episodes (56).

2.4 Risk factors for late-life depression

The main risk factors for late-life depression include comorbid physical conditions, cognitive and functional impairment, a history of depression in younger age, lifestyle risk factors, economic change, retirement, loss of social status, social isolation, difficult social or financial situation, and frequent losses, grief, and mourning (8,57).

LLD is a disease of multifactorial etiology with a wide array of risk factors. Commonly, there are residual symptoms and dysfunction even after the administration of proper treatment, which only emphasizes the importance of prevention. The five pillars of risk and protective factors are demographic, sociodemographic, psychosocial, lifestyle/behavioral, and health/medical (38). In comparison with depression in younger adults, late-life depression is more likely to be modified by environmental factors (4).

2.4.1. Demographic risk factors

Compared to men, women have a higher risk of depression across all age groups, and the risk of both incident and recurrent depression is approximately 1.5 times higher in older women than in older men (3). Prospective studies tend to attribute this to typical psychological and social risk factors more common in women, such as prior anxiety, lower self-esteem and self-confidence, lack of power, ruminative coping style, and childhood sexual abuse (58–60). On the other hand, men tend to underreport the severity of depressive symptoms, generally report fewer mental health symptoms, and avoid or distract themselves in reaction to depressed feelings (61). So while there is a psychological and social basis for higher prevalence of depression in women, it is also important to keep in mind the discrepancy in reporting mental health issues.

Retirement is an important turning point in the life of an individual, but it is also a significant social stressor that can considerably affect well-being, both positively and negatively. For some workers with a background of stressful jobs, it may promote well-being, possibly due to a reduction of work stress, and positive lifestyle changes (62). On the other hand, for some, losing their occupational attachments, social network, and a part of their identity, may be dejecting (63). The adjustment from a relatively busy lifestyle to a relatively inactive one can prove to be a challenge, one that may trigger the development of mental health issues, such as LLD (64). The effects may also differ between countries. A 2018 review found that in developed countries, such as the United States, Canada, Australia, and European countries, the effect of retirement is predominantly positive, stating a decrease of stress levels, depressive symptoms, fatigue, and distress. On the other hand, developed Asian countries like Japan and Singapore showed a negative impact of retirement (65). Another variable is whether the retirement is voluntary, associated with economic security such as savings and pension-like benefits, involuntary, forced into retirement by health reasons or reorganization, or regulatory, after reaching the country-specific retirement age (62). A 2022 meta-analysis of longitudinal studies focused on the bidirectional relationship between involuntary retirement and depression, and showed that involuntary retirement led to an increased risk of depression. On the other hand, depression can also lead to involuntary retirement by affecting

physical and social abilities of an individual (66). In general, research is fairly inconsistent about the consequences of retirement on depression and depressive symptoms (67,68).

Marital status is commonly seen as a protective factor for LLD, and is associated with fewer depressive symptoms. It is based on the assumption that married people face fewer stressful experiences than unmarried and single people, however, the protective effect only plays a role when the marriage is good (69). On the contrary, conflict with a partner seems to be related to LDD both in men and women (70). Research shows very conflicting results on this topic. A 2011 meta-analysis showed robust findings that never married people had a significantly higher risk of depression than their married counterparts, albeit their risk was lower than the risk of widowed people (71). On the other hand, different studies present a lack of association between marital status and depressive symptoms, claiming that having a spouse can be substituted by having a confidant (69). Widowhood is often related with higher depressive symptoms, but singlehood may not be (72). Spousal bereavement is an emotionally stressful turning point in one's life that can negatively impact other aspects of life, such as loss of social networks or financial insecurity (73). Furthermore, older adults tend to have fewer close social relationships than younger persons do, therefore a loss of a loved one might make them particularly vulnerable to experiencing loneliness and isolation, known risk factors for LLD (Chapter 2.4.3)(74). A Dutch longitudinal study reported a 2-fold increased risk of LLD associated with spousal loss (75), meanwhile a Costa Rican longitudinal study reported a 2.5% mean increase in likelihood of LLD following spousal bereavement (76).

2.4.2 Socioeconomic risk factors

One of socioeconomic risk factors that is consistent among LLD studies is low educational attainment. Adults with less than high school level of education have significantly higher odds of developing LLD than adults with higher education (77–81). The underlying mechanism is unknown, but it is thought to be related to lower self-efficacy and cognitive functions in people with lower educational attainment (77).

While there is evidence for lower socioeconomic status (SES) leading to a higher risk of LLD (82–84), the mechanisms are once again unknown. Lower income may be associated with higher presence of financial stress and lack of resources for receiving appropriate treatment, worse psychosocial and physical work environment, and more (85). Debt is another stressor associated with LDD (82). Income is also tightly tied together with other SES risk factors (85).

Poor childhood SES is a reliable predictor for the development of depression across all age groups, probably via poorer cognitive development and emotional issues of children from such households (86). A 2019 Spanish study reported that bad and very bad childhood financial situation is associated with LLD, even after adjusting for other demographic factors. This effect was only mediated by higher educational attainment (87).

2.4.3 Psychosocial risk factors

Loneliness, a subjective feeling of social isolation, is a globally well-known problem in older adults that has only been enhanced by the lockdowns and social distancing due to the COVID-19 pandemic, especially in older adults living alone. Loneliness has many possible causes, such as loss of a spouse, nursing home admission, and loss of functional abilities. It is related to increased morbidity and mortality, cognitive decline, and poor self-rated health, and is strongly associated with late life depression as a stressor (88,89). Furthermore, social isolation tends to be associated with less desirable health behaviors, such as smoking, inconsistent moderate to vigorous physical activity, being obese or overweight, and consuming less than five fruit and vegetable servings per day (90). Pooled estimate of loneliness prevalence amongst older adults in high income countries is 28.5%. The prevalence appears to be higher in Mediterranean countries and Eastern Europe (91). Loneliness has been shown to be an independent risk factor for depressive symptoms, and plays a further negative role in pre-existing depression. Longitudinally, loneliness also appears to impede LLD remission (88). Social relations are interlaced with loneliness. Social relations play a crucial role in developing LLD. Social support, quality of relations, and

presence of confidants are consistently found to be protective factors for mental health in old age, and are significantly associated with decreased risk of depression (69).

Closely related to loneliness is social isolation. While there is no one definition of social isolation, it is described as a state with limited contact with family members, friends, or neighbors (92). Socially isolated older adults are a concern in countries with aging populations. WHO estimates that 1 in 4 older adults experience social isolation (93). Social isolation is therefore an important target for prevention of not only depression, but also physical illnesses in older adults. Social isolation may be caused by decline in health and events such as relocation or spousal bereavement (92). Loss of a loved one is an established risk factor for developing depressive symptomatology. Widows and widowers may face financial issues, new household management tasks, and modifications of social circles. It may cause psychological distress, depression (94), or bereavement related depression, a condition with strong similarities to regular MDD (95). Spousal bereavement elevates depressive symptoms, mostly loneliness, sadness, and loss of appetite. The mechanism seems to work via loneliness, which in turn exacerbates other depressive symptoms (89). Findings on bereavement are mostly consistent, agreeing that loss of a loved one leads to a significant increase in risk of LLD (75,76,96).

2.4.4 Lifestyle risk factors

Nutrition is a daily part of one's life, therefore it has been extensively researched in relation to late life depression as one of modifiable risk factors. Recent studies have been inclined to research dietary patterns over singular nutrients, as the overall dietary pattern possibly plays a bigger role due to the synergistic effect of the components (97). However, there are some individual nutrients linked to vascular health that might play a role. Unlike in early-life depression, neurological and other biological factors seem to be more prominent in LLD. Vascular risk factors such as hypertension, atherosclerosis, stroke, diabetes, and more are more common in older depressed adults than in their younger counterparts (98). Furthermore, depressed persons are at a higher risk of heart disease and diabetes, while simultaneously, these diseases increase the risk of depression (99,100). This is the basis for vascular

depression hypothesis, which assumes that vascular diseases may precipitate, predispose or perpetuate LLD (101). Nutrients that are thought to have positive impact on vascular risk factors directly affect brain health through myelin synthesis, membrane fluidity, and neurotransmitter metabolism. The candidate nutrients are folate, vitamin B_{12}, and omega-3 fatty acids (98).

Folate, also known as vitamin B_9, is an essential nutrient present in both in animal and plant foods. High concentrations can be found in liver, sunflower and flax seeds, beans, green leafy greens, and wholewheat grain products. Folate is also present in peanuts, oranges, bananas, tomatoes, and more (102). A steady consumption is required as the human body has few stores (98). Folate is crucial for the synthesis of neurotransmitters, phospholipids, S-adenosyl methionine, and for the conversion of homocysteine to methionine (103). Natural folate consumption seems to be more beneficial than supplementing folic acid which must first undergo additional reduction before it crosses the blood-brain barrier. However, it is also possible that consuming naturally present folate may be associated with other beneficial nutrients present in foods rich in folate (98). Several meta-analyses report that low folate status and lower dietary folate intake are associated with depression (104,105), however, it is difficult to discuss whether the relationship is causal since the main body of evidence comes from weaker, cross-sectional studies. The population reference intake is 330 µg of dietary folate a day for healthy adult population (106).

Vitamin B_{12}, cobalamin, is a water-soluble vitamin exclusively present in animal foods, such as meat, liver, fish, dairy, and eggs (102). The liver stores about a 5-7 years supply, long-time vegans might therefore be at a risk of deficiency sufficient supplementation (98). Older adults are another vulnerable group. Cobalamin absorption is a complex process involving the stomach, pancreas, and small intestine. Any mild dysfunction impairs the absorption and may potentially lead to a deficiency. The efficiency of this process also tends to decrease with age (107). Vitamin B_{12} is important for folate metabolism, serotonin and myelin sheath synthesis, and acts as a coenzyme (98). It is also crucial for the reduction of homocysteine. Accumulated homocysteine may become neurotoxic and thus increase the risk of subsequently developing depression (108). Research suggests that higher intake of dietary

cobalamin intake is associated with a lower risk of developing depression (108,109). Vitamin B_{12} deficiency is linked with permanent neurological damage, it is therefore crucial to keep the body stores saturated (98). The adequate intake of cobalamin is 4 μg a day for healthy adults (110).

Omega-3 fatty acids are polyunsaturated fatty acids (PUFA). The base molecule is alpha-linolenic acid (ALA) that is then metabolized into other products, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The conversion is inefficient in humans, it is therefore recommended to consume EPA and/or DHA itself. The main food source of EPA and DHA is fatty, cold-water fish. Plant sources, such as flaxseeds and nuts, especially walnuts, contain ALA (102). Omega-3 fatty acids influence membrane fluidity, serotonin metabolism, protect cells from oxidative stress, decrease triglycerides, inflammation, blood pressure, and platelet aggregation (98). While consumption of omega-3 fatty acids is important, the ratio between pro-inflammatory omega-6 fatty acids and anti-inflammatory omega-3 fatty acids is not dismissible either. The ideal ratio is around 2:1, however, with the shift to more Western dietary habits, it is closer to 15-20:1 in present day population. The inflammatory properties of omega-6 fatty acids are thought to be involved in the pathogenesis of depression (111). There is some evidence that omega-3 fatty acids show therapeutic effect on the improvement of depression, however, it is debated whether the contribution stems from EPA, DHA, or both (112,113). Another study observed lower omega-3 levels in patient with on-going depressive episode which suggests that lower omega-3 levels may be an underlying predisposition but a consequence of depression (114). There is no recommended daily intake value but The European Food Safety Authority claims that 2-4 g of EPA and DHA a day are needed to achieve positive health effects in healthy adults (115). Supplementation might be all the more important in areas that consume less fish, such as countries of Central and Eastern Europe (116).

It is important to remember that depression is commonly associated with changes in appetite that might also influence nutrient levels during depressive episodes, only further showing the bi-directionality of nutritional psychiatry (27,98).

Dietary patterns, the main focus of this work, are further discussed in chapter 3.

Physical activity is a recognized tool for managing depression, and is a significant factor in lowering the risk of developing LLD (38,117,118) and reducing the severity of depressive symptoms (119,120). Exercise is generally well-tolerated when tailored to the individual fitness level, improves sleep quality and appetite, and increases physical fitness. It is not yet understood whether physical activity alleviates mainly somatic symptoms, or can also impact other core depressive symptoms such as mood, and what the underlying mechanisms are. On a biological level, it is speculated that the positive effect of exercise may stem from modulating neurotransmission, directly improving psychomotor retardation, or indirectly via improving cognitive functioning (121). Furthermore, there is limited evidence suggesting that exercise may be beneficial for battling lingering cognitive impairment of LLD that often remains even after traditional treatment improves other depressive symptoms (122). Older adults are advised to engage in at least 150 minutes of moderate intensity activity in a week or 75 minutes of vigorous intensity activity. On top of that, it is recommended to be physically active in some way every single day (123).

Research on the relationship between obesity and late life depression is scarce. The consensus is that it is a bidirectional relationship, with depression increasing the risk of obesity while simultaneously, obesity being an etiological factor that may lead to developing depression in late life (124). However, findings on the impact of obesity on LLD have been mixed, with either moderate, or non-significant results after adjusting (38,125,126). Interesting could be sarcopenic obesity, a condition characterized by coexisting sarcopenia and obesity that is clinically relevant in older adults, and has seemingly more negative impact on health than regular obesity. One small study didn't confirm the inherent effect of sarcopenic obesity on developing LLD, but predicted nonremission at 2-year follow-up. Metabolic dysregulation and physical frailty are present in sarcopenic obesity, and closely contribute to a chronic course of LLD, the results are therefore in line with previous findings (127). Still, the relationship between obesity and LLD deserves more spotlight as the prevalence of obesity keeps growing both in developed and developing countries, and is projected to rise to 33% by 2023 (128).

Alcohol and alcohol dependence are tightly interlaced with both early-life and late-life depression. While adults under 30 years of age are most likely to engage in risky alcohol use patterns, adults over 60 years have the highest probability of daily alcohol consumption (129). Alcohol dependence in combination with depression increases the risk of worse mental and physical health outcomes among older adults (130). Alcohol is notable for interfering with the metabolism of psychoactive drugs such as antidepressants and benzodiazepines and may lead to adverse reactions (131). Furthermore, patients with alcohol dependence are at a higher risk of suffering from treatment-resistant depression (132). Depression and alcohol dependence are the most common co-occurring disorders in older adults. In an American national survey, 13.3% of 65+ years old adults with lifetime MDD also met criteria for alcohol use disorder. On the other hand, only 4.5% of respondents with lifetime alcohol use disorder did not have a history of depression. Older adults struggling with alcohol abuse also had a three-fold chance of MDD than those not (133). There are several hypotheses about why these conditions are often comorbid. Some of the leading ones are shared genetic and environmental risk factors and causal processes like the self-medication theory (134). Concurrent alcohol abuse may further exacerbate the symptoms of depression in some patients (132). Furthermore, comorbidity of LLD and alcohol dependence is associated with greater risk of suicide than either of the disorders existing separately, their relationship additive or synergistic in effect (130). A combination of psychotherapy and pharmacotherapy is recommended for treatment of alcohol-related treatment-resistant depression (130,132).

Closely related to drinking problems is cigarette smoking. It may occur in tandem or individually. The relationship between smoking and depression once again appears to be bidirectional. The exact mechanism is not clear, however, there are several hypotheses. First, tobacco and alcohol are psychoactive substances that can change neural activity and improve the mood, which led to creating a self-medication theory, a theory that depressed individuals may use these substances to try to alleviate depressive symptoms themselves (135,136). Another one proposes that alcohol and tobacco use produces change in neurotransmitter activity, and makes individuals more vulnerable to developing depression (137,138). Among older adults, patients with higher depressive symptoms appear to be less likely to cease smoking (139,140). Last but not least, smoking cigarettes is associated with microvascular

dysfunction, which is linked to depression, and more specifically treatment-resistant depression (141). Concurrent drinking problems seem to further lower the likelihood of smoking cessation in depressed older individuals (140). Another study reported that smoking prospectively predicted future depression onset and vice versa, and the same bidirectional link between smoking and future heavy drinking among middle-aged and older adults (142). This might be particularly relevant due to the East–West health gap that has been explained previously.

2.4.5 Medical risk factors

Older persons are particularly susceptible to experiencing pain due to a higher prevalence of polypharmacy and comorbid diseases. Furthermore, their rates of surgery and hospitalization are also higher than in other age groups (143). The reported prevalence of chronic pain in older age has a broad range, between 27% and 86% in different studies (144). Despite some existing evidence of bidirectionality, the general consensus is that chronic pain is more likely to lead to the development of depression and intensifying depressive symptoms in previously diagnosed patients than vice versa (132). Chronic pain negatively impacts quality of life, affecting various areas of life, from mood disturbances to impaired function, and decreased quality of sleep (143). Poor sleep is integrated in both depressive symptoms scales and a formal diagnosis, as it is tightly interlaced with depression (27,48). The sociology perspective suggests that stress, such as stress caused by persistent pain, may influence mental well-being by depleting psychological resources, and lead to a decreased sense of control over what happens in one's life (145). Negative effect of pain on LLD has been reported time and time again (38,146,147).

There is a high burden of chronic medical comorbidities among older adults, such as cardiovascular disease, respiratory disease, diabetes, blood pressure problems, dyslipidemia, and cancer. These conditions are significantly associated with increased risk of subsequent LLD (3). The relationship between medical comorbidity and LLD appears to be a dose-response one, meaning that a linear increase in comorbidities is related to an increasing risk of developing LLD (38,75,80,81). From a clinical point of view, comorbidity may prevent

patients from a formal depression diagnosis with depressive symptoms commonly attributed to the physical illness (148).

Depression is commonly accompanied by sleep disturbance or insomnia, so much so that sleep changes are included in the criteria for a formal MDD diagnosis (27). Sleep disturbances include difficulty falling or remaining asleep and waking up early (149). A meta-analysis of longitudinal data showed that non-depressed subjects with insomnia are twice as likely to develop MDD, compared to subjects with no sleep difficulties. In the same analysis, incidence of depression was significantly higher in the group with baseline insomnia (150). Since sleep disturbance is a common residual symptom of treated depression, it is speculated that sleep problems may be an early manifestation of depression, or that they are a part of the causal pathway that unravels a depressive episode (149).

Last but not least, depression is an inflammatory disease associated both with chronic low-grade inflammation and acute inflammatory response (151), while simultaneously, higher levels of inflammation seem to increase the risk of de novo depression (152). A longitudinal study of older adults with a 21-year follow-up found that repeated chronic elevation of inflammatory markers led to greater depressive symptoms than in individuals without. Furthermore, it was also significantly associated with an elevated risk of developing depressive symptoms during later life, even after adjusting for demographic and other health risk factors (153). Collectively, research suggests that inflammation may have a causal relationship with depression (154,155).

Chapter 3

Dietary patterns

3.1 Introduction

Food is an essential part of life. There are countless ways of eating healthy, different between continents and regions. This is reflected in nutritional research as well. Trying to separate and quantify specific effects of nutrients or food groups on health outcomes is difficult due to the highly intercorrelated nature of dietary exposures, therefore research prioritizes analyzing dietary patterns as they tend to consider the complexity of overall diet better (156). Generally, studies divide dietary patterns into two main subgroups, healthy dietary patterns and unhealthy dietary patterns. Healthy dietary patterns are often referred to as prudent, other names for unhealthy dietary patterns include Western, high fat, and traditional (157).

There are many reasons why dietary patterns should be studied within the scope of late-life depression. As previously mentioned, late-onset depression seems to be more likely to be modified by environmental factors, including diet (97). Furthermore, dietary patterns are a modifiable risk factor (3), making them an attractive research question. However, the field of nutritional psychiatry commonly focuses on the younger adult population, and the available research on dietary patterns and late-life depression is insufficient.

3.2 Proposed pathways

The field of nutritional psychiatry proposes diet quality to be one of modifiable risk factors for mental illnesses. There are several proposed pathways for this relationship, ones that commonly overlap and act in synergy, enhancing the impact.

Firstly, it is chronic low-grade inflammation, characterized by elevated inflammatory markers such as interleukin-6, C-reactive protein, and tumor necrosis factor α (14). This kind of inflammation may have multiple causes, from poor diet, psychological stress, and lack of sleep, to smoking and obesity (151). The association runs on several levels. Patients with physical illnesses associated with chronic inflammation are commonly depressed (158). Not only that, proinflammatory cytokines can induce sickness-like behaviors, symptoms that mirror those present in depressive states, such as sleep issues, reduced motivation or ability to experience pleasure, and fatigue (159). Moreover, some antidepressants significantly decrease the production of proinflammatory cytokines (151), and anti-inflammatory medication has an antidepressant effect on depressed individuals (160).Collectively, research suggests that inflammation may have a causal relationship with depression (154,155). Furthermore, there is some evidence that unhealthy/Western dietary patterns are linked with chronic low-grade inflammation, while a priori healthy dietary patterns are associated with lower chronic inflammation (161,162). This proposes a possible underlying connection between dietary patterns and depressive symptoms.

Another one is the impact of oxidative stress with robust evidence for being a cause of MDD. The human brain is a vulnerable organ as it requires plenty of oxygen and contains a higher oxidizable lipid concentration. Due to the high oxygen consumption, it may lead to generating more reactive oxygen species that exhaust antioxidative defenses, damage cells, and trigger the release of proinflammatory molecules that were previously mentioned. Oxidative stress is responsible for altering brain structure, the same functional perturbations found in patients with MDD (163). Reportedly, patients with MDD show lower levels of antioxidants that help balance out oxidative stress in comparison with healthy controls (164). Since fruit and vegetables are rich in antioxidants and flavonoids, and have a beneficial effect

on inflammatory markers and oxidative stress (165), it is another studied direction of nutritional psychiatry (14).

Neurogenesis within the hippocampus is the process of forming new neurons, and plays a role in memory, learning, and regulating the mood. It can be stimulated by physical activity and enriched activity, while psychological stress, oxidative stress, aging, and chronic low-grade inflammation are associated with a decline in neurogenesis. In adults with MDD, the hippocampal volume is reduced (166). On top of possessing antioxidant and anti-inflammatory capacity, nutrients such as omega-3 fatty acids, polyphenols, l-theanine, and vitamin E can also stimulate neurogenesis, proposing another nutritional psychiatry hypothesis to test (14).

3.3 Healthy and unhealthy dietary patterns

Healthy dietary patterns share common elements, such as higher fruits, vegetables and nuts intake, lower intake of pro-inflammatory food items such as processed meats and trans fats, and a moderate alcohol consumption (167). On the other hand, unhealthy dietary patterns are characterized by high consumption of red and processed meats, refined grains, sweet, high fat dairy products, butter, potatoes, and low intakes of fruits and vegetables (157). There is some evidence for healthy dietary patterns reducing the risk of depression (167–169). On the other hand, unhealthy dietary patterns seem to be associated with an increased risk of depression (4,169), however, the evidence is more conflicting in this case (170). While these results are mostly positive, it is important to note that dietary change is not easy to establish, nor to retain long term, and is even more difficult in older adults (168). There is a dire need for prospective studies on the topic as most available research is done on cross-sectional data.

One healthy dietary pattern that is recognized for its role in the prevention of chronic diseases is the Mediterranean dietary pattern (171,172). The original definition of the Mediterranean diet (MD) is based on the observed diet in olive-growing areas of Crete, Greece, and Southern Italy in the late 1950s and early 1960s. It is a mostly unprocessed diet characterized

by high intake of plant foods, such as fruit, vegetables, breads and other forms of cereals, potatoes, legumes, nuts, and seeds. Monounsaturated fatty acids (MUFA) from olive oil are the main source of fat. Total energy from fat ranges from 25 to 35%, What makes MD special is the 15–20% of all fat coming from MUFA. Other food groups, such as dairy, fish, poultry, eggs, wine, and red meat are consumed in low to moderate amounts. As a lifestyle, it also includes regular physical activity (173,174). MD is a traditional anti-inflammatory diet that has been shown to prevent or lower the burden of cardiovascular disease, various cancers, depression, diabetes, erectile dysfunction, and cognitive decline, and reduce total mortality (171,172). It is speculated that its positive effect on health outcomes stems from the high concentration of B-vitamins, and antioxidants, and a beneficial fat intake composition. In a large biracial cohort of older people, closer adherence to MD was associated with decreased likelihood of developing depressive symptoms (175). The same outcome was reported in a multi-national sample of Mediterranean older adults (176). Another cohort of middle-aged Swedish women had the same results (177), and so did a large cohort of healthy Spanish adults (13). While these results are positive, it is important to note a big limitation, and that is that the definition of MD often differs between studies, with different cut-off values and different amounts of foods from particular food groups recommended (178).

However, MD is a quite region-specific diet, and may be harder to promote in the Central and Eastern European region as it vastly differs from traditional regional diets. That is important to consider because dietary patterns also constitute a large part of ethnic identity (179), and are not universally applicable to every individual. Furthermore, many people, especially older ones, tend to prefer traditional flavors over marketed health foods that do not correspond with their ethnic background and upbringing (19).

3.4 Dietary scores

Human diet is a complex exposure that is most commonly studied using predefined dietary scores that present valuable tools to assess nutritional intake and habits on individual and population level (180). Dietary scores provide a more comprehensive view of food and nutrient intake, and therefore may offer better predictive insights into disease risk than

individual foods and nutrients. Moreover, dietary scores can be used to assess the adherence to a dietary pattern or dietary guidelines (181).

There are three main ways of studying an individual's overall diet. The first approach, the a priori method, is using a score or index of diet quality based on existing knowledge of what belongs in a healthy diet, and is defined by the researcher. The second method, also called a posteriori, is conducting principal component analysis or cluster analysis on available dietary data. In cluster analysis, population subgroups are formed by grouping individuals based on their dietary habits together. On the other hand, in principal component analysis, the scales are determined by examining the underlying relationships between different food groups. These patterns are not replicable in other populations and may not reflect what a healthy diet is (167,182). The third method is still in an exploration phase, however, it combines biological pathways and available dietary data through reduced rank regression or decision tree analysis (182).

3.4.1 Eastern European diet score

A more relevant dietary pattern for assessing the diet quality of older adults in Central and Eastern Europe may be the Eastern European Diet Score (EEDS). It is based on eating habits of rural communities in the 1950s and early 1960s across the CEE region and identifies nine food groups. The way of eating has dramatically changed with the influx of modern methods and a shift from self-sufficiency to shop-dependance. The nine food groups are: a) bread and grain products, (b) potatoes, (c) legumes, (d) storable vegetables, (d) preserved fruits and vegetables, (e) dairy products and eggs, (f) poultry, (g) processed meat products and (h) cooking lard. The score ranges from 0 to 18 points, 0–6 is considered low, 7–10 as moderate, and 11–18 as high adherence to the traditional Eastern Europe diet. The only study that has used EEDS found a significantly higher risk from all-causes and cardiovascular diseases in individuals who closely adhered to traditional Eastern European diet. When individual food groups were analyzed, vegetable intake and preserved fruit seemed to lower the all-cause, cancer, and cardiovascular deaths, while lard consumption had a positive link (19). This study did not focus on depression; therefore, it could be an interesting research target.

3.4.2 Healthy diet indicator

Another specialized diet score is the healthy diet indicator (HDI). It is originally based on the 1990 WHO dietary recommendations for prevention of noncommunicable diseases, and later modified to reflect the 2003 version of guidelines (Table 1.)(183,184). The score can be dichotomous or continuous. The dichotomous version was used in the original study, for each food group a respondent consumed within the recommended range was awarded 1, otherwise it was coded as 0. The score was the sum of all the results. For most included countries, the cut-off values were divided into thirds, <2 classified as low adherence to the WHO recommendations, 2 as medium, and >2 as high. After adjusting, the study showed that the high HDI group had a 13% lower risk of all-cause mortality than the lowest group (183). Another study that investigated the effect of dichotomous HDI on mortality in elderly population found a significantly lower risk of all-cause mortality in subjects adhering to the WHO guidelines (185). The continuous version of the score was used in an older adult CEE population to reflect that nutritional factors do not have strict cut-off points. It found a statistically significant inverse association with cardiovascular disease and coronary heart disease mortality, however, not with all-cause mortality (180). HDI hasn't been researched in relation to depression and depressive symptoms despite also falling into the category of chronic diseases.

Components of the HDI scores (180)	**Recommendations**
SFAs, energy %	0-10
n3-PUFAs, energy %	1-2
n6-PUFAs, energy %	5-8
Trans fatty acids, energy %	<1
Mono- and disaccharides, energy %	0-10
Protein, energy %	10-15
Cholesterol, mg/day	0-300
Fruits/vegetables, g/day	>400
Non-starch polysaccharides	>20

Table 1 HDI score composition

3.5 Social inequalities and differences in dietary patterns

Socioeconomic status is a variable that cannot be overlooked in the research of dietary patterns as it is a crucial determinant of health. There is a lack of studies on this topic, however, the general consensus is that in high-income countries, high SES tends to be associated with a healthier diet, and it is used as a reasoning to explain social differences in health status. These individuals may be more inclined to choose healthy foods such as whole grains, fish, lean meats, low-fat dairy products, fruit, and vegetables. On the other hand, individuals with a low SES commonly consume less fiber and more fat in their overall diet (186,187). In low-income countries, nutrition transition is a common trend following socioeconomic development. It is a shift from traditional diets rich in fiber and grains to diets higher in fat and sugar that usually starts in urban areas and affects high SES individuals first (188). However, that may reverse as the transition progresses, as individuals with low SES tend to adopt less healthy dietary patterns, and the burden of obesity shifts more towards this group than to the high SES group (189). It is important to note that consuming an unhealthy/Western diet in people with lower SES is not just a matter of insufficient knowledge about what constitutes a healthy diet, it is complicated by other SES factors, such as other necessary expenses being perceived as more important than diet changes, perceived high cost of "healthy" foods combined with their quicker perishability, and insufficient access to transportation. Feelings of guilt, social isolation, and disrupted relationships due to the challenge of trying to meet daily financial requirements also negatively affect food choices (190).

It is likely that sex plays a role in the relationship between dietary patterns and depressive symptoms, it is however often not considered in research. A 2013 study analyzing adherence to healthy dietary guidelines and future depressive symptoms showed that adherence to healthy dietary recommendations reduced the likelihood of developing depressive symptoms later in life in women but not in men even after adjusting for other covariates. It is unclear whether that is due to differences between sex, a low sensitivity of used depressive score

scale to male depression, or an outsider factor (191). Nevertheless, it is an interesting question for future research.

3.6 Summary and research gaps

One of the main limitations of studying dietary patterns is the lack of standardization between dietary pattern scores that are in use. Nearly every study constructs its own score with different scoring criteria and a wide range of cut-off values despite using guidelines of the same diet, such as the Mediterranean diet. A 2014 meta-analysis compared data from 26 cohort studies that used a variation of Mediterranean diet score and noted poor correlation between most indices, suggesting that the used definition of MD varies between these studies (178). Generally, these diet scores lack empirical testing, and cannot be used to compare results between studies. It is a significant limitation in the world of nutritional epidemiology.

This research contributes evidence for a geographic area that is continuously understudied in terms of nutritional psychiatry and depression. It uses healthy diet indicator, a dietary score that has been used in previous works, and focuses on a vulnerable age group.

Chapter 4

Data and methods

This chapter introduces the HAPIEE study, the dataset used for the analysis, and a detailed description of conducted analyses.

4.1 The HAPIEE study

The Health, Alcohol and Psychosocial Factors in Eastern Europe (HAPIEE) study is a large, prospective cohort study that aims to investigate the effect of various risk factors on non-communicable diseases in CEE and the former Soviet Union. It consists of four urban cohorts in Czechia, Russia, Poland, and Lithuania. The Czech cohort is located in seven midsize centers (Havířov/Karviná, Hradec Králové, Jihlava, Kroměříž, Liberec, and Ústí nad Labem), Russian in Novosibirsk, Polish in Krakow, and Lithuanian in Kaunas (192).

For this work, only the Czech arm of the study is included in analyses.

The baseline sample consists of random samples of men and women between the ages 45-69, stratified by 5-year age groups and gender. In total, 8856 people participated in the Czech cohort at baseline. The subjects completed the questionnaire upon a visit at home, and subsequently attended a short examination at the clinic. The response rate was 55% (192).

The baseline data collection happened between the years 2002 and 2005. A complete response includes a structured questionnaire, examination at the clinic, and a fasted sample of venous blood. The areas covered in the questionnaire were health, lifestyle, food frequency in the last 3 months, socioeconomic circumstances, psychosocial factors, quality of life, and work environment. The questions were double translated for accuracy (192).

All participants signed an informed consent form and the study was approved by ethical committees at University College London, UK, and ethical committees at the participating centers.

To this day, there have been several phases of the Czech arm of the HAPIEE study. As previously mentioned, the baseline data was collected from 2002 to 2005. In 2006–2008, respondents from the first wave were asked to update their health data and share more information related to healthy aging and economic situation. After that, a postal questionnaire was sent out once approximately every two years. It was sent out in the years 2006, 2009–2010, 2012, 2013–2014, 2015–2016, 2017–2018, and 2020–2021. Currently, there is a reexamination ongoing 20 years after baseline collection. It aims to investigate changes in risk factors and their effect on health and the process of aging. The complete data is predicted to be collected by autumn 2024 (193).

The physical examination collected measurements of height, weight, trunk length, waist and hip circumference, blood pressure, lung function and cognitive function (192).

The blood test measured total cholesterol, HDL cholesterol, and triglycerides. A random subset of respondents had a detailed analysis of folate, vitamin B12, homocysteine, glycated hemoglobin, vitamin C, alpha-tocopherol, beta-carotene, retinol and C-reactive protein levels done (192).

4.2 Analytic sample

For the practical part of this thesis, only certain respondents entered the analysis. Four exclusion criteria were applied. From the original 8856 respondents of the Czech leg of the HAPIEE study, respondents with missing depressive symptoms data from the first wave were excluded. To calculate the score, 9 or 10 out of 10 questions had to be answered. This reduced our sample down to 8203 respondents. Furthermore, patients without sufficient FFQ data were excluded as HDI was selected as the main exposure. This resulted in a sample of 7502 participants. Thirdly, respondents have had to provide complete DS data in at least two waves. The sample size was further reduced to 4209 respondents. Last but not least, respondents with missing answers in one or more covariates were excluded, leaving us with a final sample of 4117 participants for complete analysis. Since longitudinal analysis requires a long format of data, the total number of observations was 24702. The long format assigns six rows for six possible time points for each respondent; however, the 0-4 rows may be empty depending on how many DS responses the respondent provided. For example, if a respondent provided three time points, three rows of DS contain the corresponding CES-D score, and three rows are empty. A flow chart illustrating the selection of the final analytical sample was obtained is provided in Figure 1.

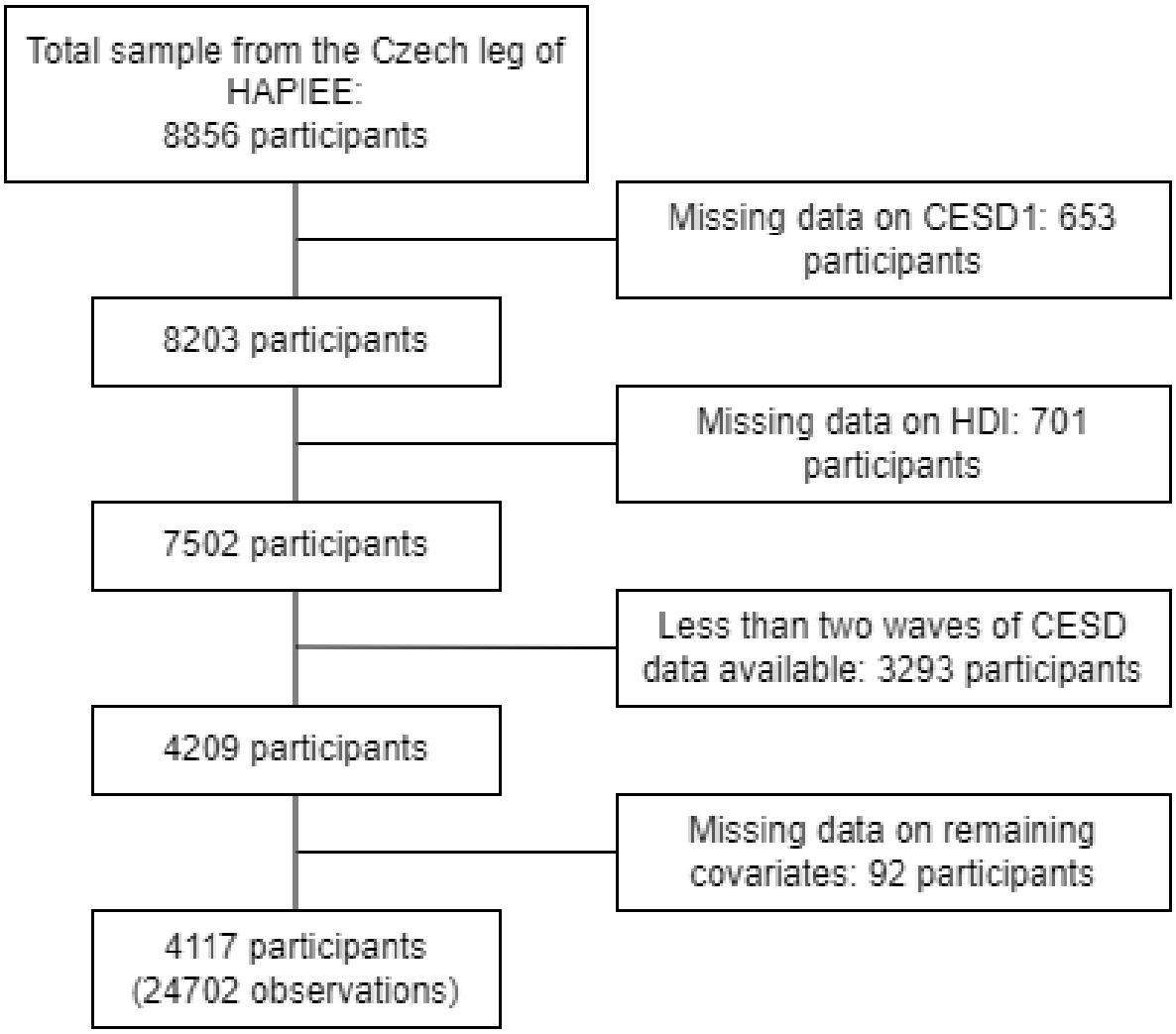

Figure 1 Flow chart outlining selection of participants into the analytical sample

4.3 Variables

Since depression and depressive symptoms are complex states with many modifiable and non-modifiable risk factors, it only makes sense for various variables to take a part in the analysis. For this thesis, sociodemographic, health, and social factors were used.

4.3.1 Outcome: Depressive symptoms (CESD)

The outcome variable depressive symptoms is a continuous latent variable calculated from a battery of 10 statements regarding the respondent's feelings within the last week. The validity of the short 10 item version has been investigated previously, is good, and has reliability and validity comparable to the original CES-D (49,50). The questions were directly taken from CES-D-10 (51) and were as follows:

1. I was bothered by things that usually don't bother me.
2. I had trouble keeping my mind on what I was doing.
3. I felt depressed.
4. I felt that everything I did was an effort.
5. I felt hopeful about the future.
6. I felt fearful.
7. My sleep was restless.
8. I was happy.
9. I felt lonely.
10. I could not get going.

The full CES-D-10 and CES-D batteries of questions can be found in the Appendices section (Appendix A, Appendix B).

The rating was 0= less than 1 day, 1= 1-2 days, 2= 3-4 days, 3= 5-7 days. Questions 5 and 8 are reversely scored, and the total depressive symptoms score is a sum of all 10 items. A maximum of one item is allowed to be missing. The cut-off score for considering an older adult respondent depressed is 10 (194). The variable was kept continuous for the sake of

analysis and is available in six data points. Since longitudinal analysis requires data in the long format, these six depressive symptoms variables were merged into one long variable CES-D, therefore each respondent occupies two to six rows in the long form dataset.

4.3.2 Main exposure: HDI

The main exposure, HDI, was constructed from food frequency questionnaire (FFQ) data obtained at baseline. It assessed diet in the preceding three months using a 9-point scale with a range of choices from "never or less than once per month" to "six or more times per day". 136 dietary items were included in the Czech FFQ. It was then converted into daily food consumption, and daily intakes of 42 nutrients were calculated (19,195). Following that, a dichotomous yes=1/no=0 variable was generated for each group included in the WHO recommendations for the prevention of chronic disease depending on whether the participant has reached the recommended dietary goal. The HDI score is a sum of these seven variables, the value range is therefore 0-7 (195). The cut-off values were divided into thirds, <2 classified as low adherence to the WHO recommendations, 2 as medium, and >2 as high (183). In our analysis, it is used as a categorical variable 0= low adherence, 1= medium adherence, 2= high adherence.

4.3.3 Covariates

Several covariates which may confound or modify the association between depressive symptoms and adhering to a healthy diet were chosen based on literature research. The covariates were: age, sex, marital status, economic activity, education, self-rated health, and smoking. All these variables were collected at baseline. Age was coded as a continuous measure, sex as binary (male, female). All other variables were categorical.

Marital status was based on a question: What is your marital status?" The responses were as follows: single, married, cohabiting, divorced/separated, widowed.

Question: "What is your current employment situation?" was used to define economic activity. Options employed, entrepreneur, self-employed/freelance, housewife, farmer, pensioner, still employed, pensioner, not employed, and unemployed were then recategorized as 0= employed, 1= retired, and 2= economically inactive or unemployed, following a similar approach to Milner et al. (196).

Education was defined as the highest completed level of education, and was classified according to the International Standard Classification of Education (197). For the sake of analysis, it was then recategorized into three categories, 0= low (incomplete, primary, vocational, apprenticeship), 1= medium (secondary, college), 2= high (university).

Self-rated health was measured with a question: "In the last 12 months, would you say that your health was: very good, good, average, poor, and very poor?" Even after accounting for objective health status, behavioral risk factors, and sociodemographics, self-rated health remains a strong predictor of not only mortality (198), but is also independently associated with depressive symptoms in older adults (199).

Last but not least, question: "Do you smoke cigarettes?" provided responses such as 0= yes, regularly, at least one cigarette a day, 1= yes, occasionally, less than one cigarette a day, 2= no, I smoked in the past, but I stopped, and 3= no, I have never smoked.

4.4 Applied statistical methods

Statistical analysis was done using IBM SPSS Statistics 29 and Stata SE 17 software packages.

4.4.1 Descriptive statistics

Methods of descriptive statistics were used to describe and introduce the dataset. For categorical variables entering the analysis, frequencies were calculated. These results are also presented for males and females separately (Table 2). Furthermore, the mean CESD1 score and standard deviation is reported for each category (Table 3).

4.4.2 Crude analyses

The association between depressive symptoms and covariates at baseline was examined in a crude unadjusted analysis. One-way ANOVA was conducted for each covariate with three or more categories. Normality and homogeneity of variances were tested with Kolmogorov-Smirnoff test and Levene's test. For variables violating the ANOVA assumptions, the robust Brown-Forsythe test was used. For dichotomous covariates, the association was tested by Welch's test, an unpaired t-test with unequal variances because the assumptions were violated (Table 3). This test was used on the basis of rejecting the null hypothesis for tests of normality for both concerned variables (sex, marital status).

4.4.3 Growth curve model

To respond to objective 1, the chosen analysis is growth curve modelling that allows us to explore the relationship between depressive symptoms and dietary patterns longitudinally. For objective 2, sociodemographic factors will be included in the multilevel model to determine the effect of socioeconomic status on the relationship. Finally, to respond to objective 3, the multilevel model is then stratified by sex to assess whether there is variation in the association between depressive symptoms and dietary patterns between males and females.

Growth curve modelling is a type of longitudinal multilevel modelling method. Unlike traditional multilevel models, the within-subject variance presents level 1 and between-subject variance is level 2 in longitudinal multilevel modelling. Growth curve modelling allows for the estimation of inter-individual variability in intra-individual patterns of change

over time. These within-person trajectories are commonly known as growth curves or latent trajectories, and might take on different characteristics that vary between persons. There are several options, such as remaining flat, systematically increasing or decreasing. They might also be linear or curvilinear in nature. Basic growth model contains both fixed and random effects that best capture the individual trajectories over time (200).

To create a growth curve model, the dataset had to be modified from wide format to long format. In the long format, each row presents a time point per participant. Variable depression is created from variables CESD1-CESD6, all other measures repeat. That means that a participant that filled out the CES-D-10 assessment in all six waves of the HAPIEE study is now represented by six rows instead of one.

For the analysis itself, firstly, a model with ID as random intercept was created, followed by a model with wave as random slope and ID as random intercept. Afterwards, a likelihood ratio test (LRT) comparing these two models showed that model 2 with random intercept and random slope was a significantly better fit ($p = <0.001$). A baseline model with depressive symptoms as an outcome, HDI, age, and wave, as fixed effects, and participant and wave as random effects was then fitted to the data.

Three more models were constructed, adding more variables as fixed effects (Table 5). That in total yielded four models:

1. Crude model adjusted for age, sex, and wave
2. Sociodemographic variables (education, marital status, economic status)
3. Health behaviors (smoking)
4. Self-rated health

In the second part of the analysis, an interaction between sex and HDI was included in the model.

Chapter 5

Analysis results

5.1 Descriptive summary

Table 2 summarizes the characteristics of the baseline sample (n = 4117). The table reports variables and categories with absolute and relative frequencies. Absolute and relative frequencies are also presented for men and women separately.

The sample includes 2314 (54.2%) women and 1803 (43.8%) men which corresponds with the fact that the proportion of women in older populations is naturally higher. The higher percentage of respondents (23.7%) falls into the 60-64 years old category, but all five categories are quite balanced, around 20% of participants in each age group. 40.6% respondents reported primary or vocational education, 42.2% secondary, and only 17.2% respondents have completed university education. The baseline analytical sample has a higher proportion of employed people (59.0%), married people or people in partnership (78.5%), and never smokers (47.3%). The majority of the sample classified their self-reported health status as good or average, with only 7.7% reporting poor or very poor health status.

14.5% of respondents reported statistically significant depressive symptoms, women nearly twice the frequency of men (18.2% versus 9.8%) which also corresponds with research. According to collected nutrition data, only 10.5% of respondents have a high adherence to the WHO healthy diet recommendations. This number also differs between sexes, reaching 7.0% for men and 13.2% for women, once again nearly twice as high.

However, with the response rate only reaching 55% and many missing values, the sample may not be representative.

Table 2 Characteristics of the baseline sample

Variable	Category	N (%)	Male	Female
Total		4117 (100)		
Sex	Male	1803 (43.8)		
	Female	2314 (56.2)		
Age	<50 years	715 (17.4)	296 (16.4)	420 (18.2)
	50-54 years	868 (21.1)	341 (18.9)	526 (22.7)
	55-59 years	855 (20.8)	396 (22.0)	460 (19.8)
	60-64 years	977 (23.7)	412 (22.9)	565 (24.4)
	65+ years	701 (17.0)	358 (19.8)	343 (14.8)
Education	Primary, vocational	1672 (40.6)	767 (42.5)	905 (39.1)
	Secondary	1738 (42.2)	632 (35.1)	1106 (47.8)
	University	707 (17.2)	404 (22.4)	303 (13.1)
Marital status	Married/partnership	3230 (78.5)	1580 (87.6)	1650 (71.3)
	Si/Div/Sep/Wid	887 (21.5)	223 (12.4)	664 (28.7)
Self-rated health	Very good or good	1906 (46.3)	826 (45.8)	1080 (46.7)
	Average	1895 (46.0)	837 (46.4)	1058 (45.7)
	Poor or very poor	316 (7.7)	140 (7.8)	176 (7.6)
Employment status	Employed	2427 (59.0)	1193 (66.2)	1234 (53.3)
	Retired	1591 (38.6)	567 (31.4)	1024 (44.3)
	Unemployed	99 (2.4)	43 (2.4)	56 (2.4)
Smoking	Regularly	834 (20.3)	412 (22.9)	422 (18.2)
	Occasionally	125 (3.0)	56 (3.1)	69 (3.0)
	Smoked in the past	1212 (29.4)	684 (37.9)	528 (22.8)
	Never smoked	1946 (47.3)	651 (36.1)	1295 (56.0)
HDI	Low	1814 (44.1)	971 (53.9)	843 (36.4)
	Medium	1872 (45.5)	706 (39.2)	1166 (50.4)
	High	431 (10.5)	126 (7.0)	305 (13.2)
Depressive symptoms	No	3519 (85.5)	1627 (90.2)	1892 (81.8)
	Yes	598 (14.5)	176 (9.8)	422 (18.2)

5.2 Crude analysis

Analysis of variance has three assumptions (201):

1. Independence of observations
2. Normality
3. Homogeneity of variances

Observations are independent. All variables entering the analysis violate normality (Kolmogorov-Smirnov test <0.001). Variables sex, age, education, marital status, self-rated health, employment status, and depressive symptoms violate assumption of homogeneity of variances (Levene statistic <0.001). For these variables, the robust Brown-Forsythe test was used. Dichotomous variables that violate the assumptions were tested with Welch's test, an unequal variance test.

Table 3 reports mean CES-D score for every category, examining the distribution of depressive symptoms according to each covariate. CES-D score was slightly higher among women, two youngest age categories, primary and vocational education attainment, single, divorced, separated, or widowed respondents, unemployed category, and occasional smokers.

Just like research suggests, the biggest difference was among categories of self-rated health.

The difference of CES-D between categories was deemed significant with one-way analysis of variance in all covariates except for smoking and HDI, suggesting that there is insufficient evidence of difference in CES-D score according to smoking frequency and adherence to a healthy diet. Overall, the descriptive analysis seems to mostly align with literature.

Table 3 Mean CESD score at baseline

Variable	Category	CES-D score (mean, SD)	One-way ANOVA
Total			
Sex	Male	4.78 (4.11)	<0.001*
	Female	5.70 (4.93)	
Age	<50 years	5.68 (4.98)	<0.001**
	50-54 years	5.70 (4.78)	
	55-59 years	5.44 (4.74)	
	60-64 years	4.76 (4.05)	
	65+ years	4.99 (4.48)	
Education	Primary, vocational	5.55 (4.81)	<0.001**
	Secondary	5.31 (4.64)	
	University	4.67 (3.95)	
Marital status	Married/partnership	5.06 (4.48)	<0.001*
	Si/Div/Sep/Wid	6.17 (4.96)	
Self-rated health	Very good or good	4.12 (3.76)	<0.001**
	Average	5.85 (4.69)	
	Poor or very poor	9.12 (5.89)	
Employment status	Still working	5.26 (4.54)	0.012
	Retired	5.25 (4.62)	
	Unemployed	6.83 (5.70)	
Smoking	Regularly	5.34 (4.63)	0.143
	Occasionally	5.90 (4.53)	
	Smoked in the past	5.08 (4.47)	
	Never smoked	5.37 (4.47)	
HDI	Low	5.39 (4.68)	0.512
	Medium	5.23 (4.56)	
	High	5.30 (4.61)	
Depressive symptoms	No	3.83 (2.67)	<0.001*
	Yes	13.93 (4.14)	

*Unpaired t-test with unequal variances

** Brown-Forsythe test

5.3 Growth curve models

Within a baseline model adjusted for age, sex, and wave as fixed effects, and participant and wave as random effects (Table 4), there is some evidence of higher HDI being associated with lower depressive symptoms, though it is not significant. The difference in CES-D scores is -0.15 (95% CI: -0.39, 0.10) for medium HDI and -0.43 (95% CI: -0.82, -0.03) for high HDI when compared with individuals with low HDI. In subsequent models, other covariates were added by predefined categories to assess whether they impacted the association between CES-D and HDI in any way (Chapter 4.4.3). The effect has remained nearly identical between models adjusting for sociodemographic factors and health behaviors.

However, a 35% reduction in the size of the effect has been assessed in a model adjusted for self-rated health, nonetheless, the value is not significant (95% CI: -0.65, 0.09). Moreover, the intra-class correlation coefficient decreased from 48% down to 44%, meaning that this combination of covariates explains 4% less of the variance between participants than the previous models. Upon consideration, multilevel models constructed for both sexes separately do not include self-rated health as a variable.

Table 4 also reports LRTs comparing each model with the previous one. Only model adjusting for health behaviors did not pose a significant improvement when compared to model adjusting for sociodemographic factors.

Table 4 Multilevel models

	Model 1 Adjusted for age, sex, and wave	**Model 2** Model 1 and sociodemographic factors	**Model 3** Model 1 and health behaviors	**Model 4** Model 1 and self-rated health
Fixed effects				
HDI				
Low	Ref.	Ref.	Ref.	Ref.
Medium	-0.15 (-0.39; 0.10)	-0.16 (-0.40; 0.08)	-0.16 (-0.40; 0.07)	-0.17 (-0.40; 0.05)
High	-0.43 (-0.82; -0.03)	-0.47 (-0.86; -0.08)	-0.48 (-0.87; -0.10)	-0.28 (-0.65; 0.09)
Random effects				
Var(wave)	0.35 (0.29; 0.41)	0.35 (0.29; 0.42)	0.35 (0.30; 0.42)	0.35 (0.30; 0.42)
Var (_cons)	10.75 (10.00; 11.56)	10.35 (9.62; 11.14)	10.35 (9.61; 11.14)	8.84 (8.17; 9.57)
Cov(wave/_cons)	-0.24 (-0.41; -0.07)	-0.28 (-0.44; -0.11)	-0.28 (-0.47; -0.11)	-0.26 (-0.43; -0.10)
Residual variance	11.15 (10.86; 11.45)	11.15 (10.86; 11.45)	11.15 (10.86; 11.44)	11.15 (10.86; 11.44)
ICC	0.49 (0.47; 0.51)	0.48 (0.46; 0.50)	0.48 (0.46; 0.50)	0.44 (0.42; 0.46)
LRT	344.25	154.87	3.55	473.18
	<0.001	<0.001	0.3148	<0.001

Furthermore, the model has been extended by assuming the change in CES-D scores between waves of the study may differ for individuals in different HDI categories. The changes in depressive symptom score over six waves of data collection are separately presented for all three categories of HDI (Figure 2). The difference between HDI categories appears to be minor but it illustrates a lower baseline CES-D score in respondents with high HDI as hypothesized as well as lower CES-D scores in all subsequent waves in respondents with high HDI.

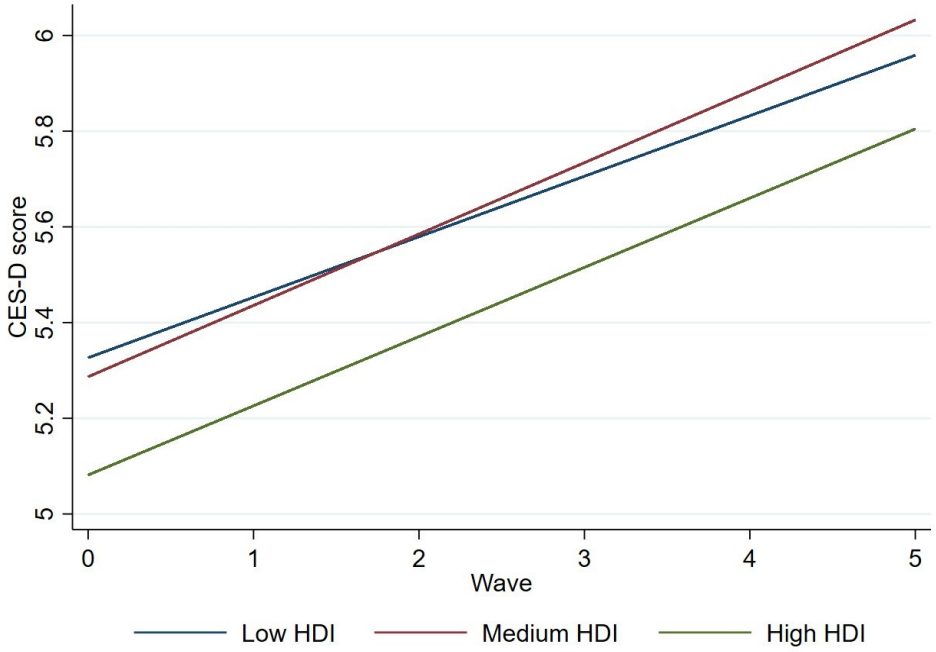

Figure 2 Changes in CESD score according to HDI

As mentioned earlier, based on existing research, an interaction between HDI and sex was added to the models. LRT test with p value of 0.001 signaled that there is evidence in the dataset to construct the multilevel models for males and females separately. While the change in CES-D score according to the HDI category was not significant, the interaction between HDI and sex was.

Therefore, the same multilevel model to test the relationship was constructed for each sex separately. Firstly, the model was constructed for male respondents only. The change in CES-D score according to HDI categories was not significant. The medium HDI adherence category showing higher CES-D score is not in line with the hypothesis, although the high HDI adherence category shows the lowest CES-D scores, as expected. The intra-class correlation coefficient indicates that 44% of the variance of CES-D scores can be attributed to differences between participants. However, 56% of the variance can be attributed to residual variance in different variables that have not been included in this study (Table 5.)

Table 5 Multilevel model for males

		Final model	P values
Fixed effects			
HDI	Low	Ref.	
	Medium	0.31 (-0.30; 0.65)	0.07
	High	-0.50 (-1.15; 0.15)	0.13
Random effects			
Var(wave)		0.32 (0.25; 0.43)	
Var (_cons)		8.16 (7.23; 9.20)	
Cov(wave/_cons)		0.08 (-0.15; 0.31)	
Residual variance		10.54 (10.12; 10.97)	
ICC		0.44 (0.40; 0.47)	

A graph illustrating the difference between CES-D score according to HDI categories for males only was constructed again for the model assuming that the slope of change between waves can differ between HDI groups. We can see that differences in slopes are minimal, and, in line with Table 5, individuals with medium adherence to healthy diet had on average CES-D score higher than those with low adherence. Those with high adherence to healthy diet had the lowest scores of CES-D across all waves of the study.

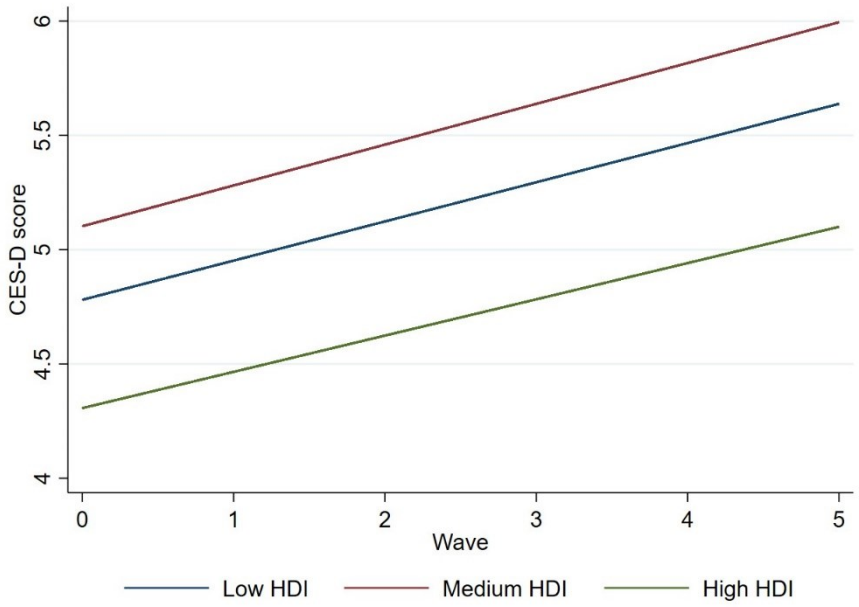

Figure 3 Changes in CESD score according to HDI in males

The last step of multilevel analysis was constructing the final model for female respondents only (Table 6). The CES-D score was significantly lower among women in both medium and high adherence to healthy diet categories, though the values did not differ much. Furthermore, the intra-class correlation coefficient indicates that 50% of the variance between CES-D scores can be attributed to differences between participants, making it the highest intra-class correlation coefficient of all models. The leftover 50% variance can be attributed to residual variance not captured by the variables included in this study.

Table 6 Multilevel model for females

		Final model	P values
Fixed effects			
HDI	Low	Ref.	
	Medium	-0.57 (-0.90; -0.24)	0.001
	High	-0.62 (-1.12; -0.13)	0.014
Random effects			
Var(wave)		0.37 (0.30; 0.46)	
Var (_cons)		11.81 (10.75;12.99)	
Cov(wave/_cons)		-0.53 (-0.77; -0.29)	
Residual variance		11.59 (11.20; 12.00)	
ICC		0.50 (0.48; 0.53)	

Figure 4 indicates that moderate or high HDI could be beneficial for lower depressive symptoms in females as the CES-D scores in these two categories are lower across all waves of the study than among those with low HDI scores.

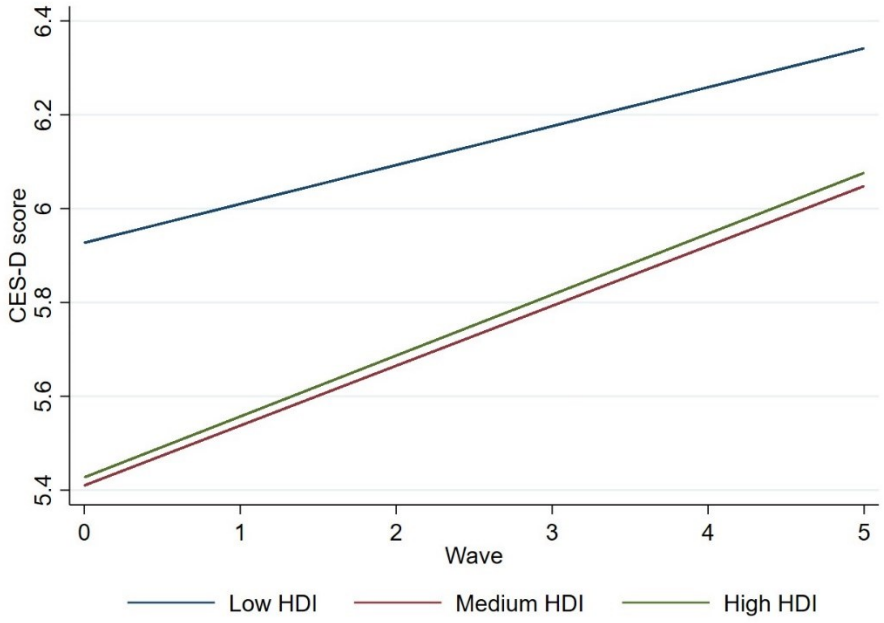

Figure 4 Changes in CESD score according to HDI in females

Chapter 6

Discussion

This chapter discusses analysis results in regard to hypotheses.

6.1 Summary of results and contextualizing the findings

Hypothesis 1: There will be a higher level of depressive symptoms in people with low adherence to a healthy diet.

The objective of hypothesis 1 was to explore the association between depressive symptoms and dietary patterns in a Czech cohort of older adults over the span of 19 years. The findings from the base growth curve model confirm this hypothesis. The analysis was adjusted for age, sex, and wave, and shows that respondents with a high adherence to a healthy diet have statistically significant lower depressive symptoms when compared to respondents with a low adherence to a healthy diet. On average, respondents with a high adherence scored 0.43 points less on the CES-D-10 scale. The results for medium adherence were not statistically significant.

While there have not been studies analyzing healthy diet indicator in itself in relation to depressive symptoms, plenty other studies have suggested that healthy dietary patterns may be associated with a reduced risk of depression and depressive symptoms, these finding are therefore aligned with the literature (167–169). Healthy dietary patterns are characterized by

common elements, such as higher fruits, vegetables and nuts intake, lower intake of pro-inflammatory food items such as processed meats and trans fats, and a moderate alcohol consumption (167). These diets tend to be higher in folate, vitamin B_{12}, and omega-3 fatty acids, all nutrients associated with vascular depression hypothesis (98), but also other antioxidants and flavonoids (167). The overall synergistic, anti-inflammatory effect of a healthy diet appears to be higher than the impact of individual nutrients (156). Since depression is an inflammatory disease (151), the positive impact of healthy diet is possibly carried out through a combination of lowering chronic low-grade inflammation and oxidative stress, and stimulating neurogenesis (14).

Hypothesis 2: The association between adherence to a healthy diet and depressive symptoms will be partly reduced when accounting for social and demographic factors.

The objective of hypothesis 2 was to determine whether marital status, economic activity, education, smoking, and self-rated health may account, at least partially, for the association between depressive symptoms and dietary patterns in older adults. This hypothesis was supported by findings from multilevel models 2 and 3. Model 2 adjusted for sociodemographic factors showed a 0.47 point decrease in depressive symptoms in respondents with high adherence to a healthy diet. Model 3 that introduced smoking as a health behavior showed a slight change, averaging a 0.48 decrease in the same respondents. The changes in respondents with a medium adherence remained non-significant. According to ICC, sociodemographic factors and smoking explained 48% of the variance between participants. Model 4 adjusting for self-rated health showed a 0.28 decrease in depressive scores in respondents with high adherence, however, the relationship was not significant. The ICC also decreased. Self-rated health appears to be a variable that could potentially explain the association between depressive symptoms and healthy diet, possibly even mediate the relationship.

Because late-life depression is a multietiological disorder, it is especially important to consider sociodemographic factors that may partially explain the relationship between healthy dietary patterns and depressive symptoms, such as in many previous works

(13,177,180). Similarly, sociodemographic factors influence adherence to a healthy dietary pattern as well. In high-income countries, high SES tends to be associated with a healthier diet, and is suggested as an explanation of social disparities in health. Individuals with high SES may be more inclined to choose healthy foods such as whole grains, fish, lean meats, low-fat dairy products, fruit, and vegetables. On the other hand, individuals with a low SES commonly consume less fiber and more fat in their overall diet (186,187).

Hypothesis 3: The effect of dietary patterns on depressive symptoms will be larger in women than in men.

The objective of hypothesis 3 was to assess whether there is variation in the association between depressive symptoms and dietary patterns according to sex. For assessment, model 3 was stratified by sex. For males, the change in depressive symptoms score was not significant. Furthermore, medium adherence to a healthy diet was associated with a higher depressive score, albeit not significantly. For females, the depressive symptoms score was significantly lower in females with both medium and high adherence to a healthy diet when compared with females with low adherence, by 0.57 and 0.62 points respectively.

This hypothesis was based on the notably higher prevalence of depression in women in all age groups, and the risk of incident and recurrent depression is approximately 1.5 times higher in older women than in older men (3). The sex-specific results are in line with available research where adherence to healthy dietary guidelines led to a decreased risk of developing depressive symptoms later on in women but the relationship was not found in men (191). With the current state of research, it is unclear whether that is due to differences between sex, a low sensitivity of used depressive score scale to male depression, (202), underestimation of dietary intake (203), or an unknown outsider factor.

6.2 Strengths and limitations

The main strength of this study is the use of a healthy dietary pattern score HDI in the context of its association with measure of depressive symptoms. HDI has been positively associated with a lower risk of all-cause mortality in elderly population, and an inverse association with cardiovascular disease and coronary heart disease mortality has also been reported (180). Using it in the context of depressive symptoms is, however, a new initiative.

Another strength is stratifying the models by sex. There are important differences between depression and depressive symptoms in men and women, and many studies do not account for that. This study shows that association between HDI and depressive symptoms differs in men and women, and that such stratification is an important aspect of the analysis.

The use of longitudinal data of an aging cohort is a strength of this study. The sample is quite large (n=4117) and provides several waves of data over the span of 19 years. Using such repeated sample in assessing the relationship between health behaviors and mental health outcomes is rare.

Lastly, the data and study focus on a Czech cohort. The research of populations in the CEE region is limited and important due to the still present East–West health gap in general health but also in mental health.

The study also has several limitations. The first set of limitations is rooted in the HAPIEE study itself. With its moderate response rate and participants coming only from urban areas, the results may not be generalizable for the entire Czech older adult population (197). Secondly, only 46% of participants entered the analysis due to missing data on depressive symptoms, healthy diet indicator, less than two valid depressive symptoms responses, and/or some of the covariates. This project used complete case analysis approach although other

methods such as multiple imputations could be possible alternatives in the future. Multiple imputations approach is beyond the scope of this MSc thesis.

Food frequency questionnaire, although a popular, inexpensive method of collecting nutritional data, has many limitations. It is a semi-quantitative method and it commonly over- or underestimates an individual's intake. There is a risk of reporting error, wrong estimation of frequency or quantity of food consumption (204). Furthermore, there might be some sex disparities. Literature suggests that women are more likely to report health-promoting behaviors and underestimate their total energy intake more than men (205,206), however, a 2021 meta-analysis showed that both men and women significantly underestimate total energy intake (203).

Regarding HDI score, some components were constructed from dietary data that has not been confirmed by other methods (180). Furthermore, seasonal variability of nutrient intake could play a role in presented HDI scores, and might differ if FFQ were collected at a different time of the year (207).

Self-reporting bias is also possible for depressive symptoms. There is a theory that men and women report depressive symptoms in accordance with stereotypes (61). Another problem is possible underreporting of depressive symptoms in general (208). Last but not least, the CES-D-10 is speculated to be less sensitive to male depression (191).

Similarly, some covariates used for adjustment, such as smoking, are also sensitive to reporting bias. Although the effect of such misreporting on the associations of interest is probably small, it should be kept in mind while interpreting the results.

Despite using longitudinal data, the study is limited in determining causality. As late-life depression is a multietiological disorder, it is highly unlikely that only nutrition might help

predict the intensity of depressive symptoms. Furthermore, the relationship between depressive symptoms and dietary patterns is thought to be bi-directional. Poor mental health may lead to unhealthy eating habits.

Conclusions

The focus of this study was to investigate and assess the relationship between adherence to a healthy diet and depressive symptoms in older adults. The first part of this study presented aims and objectives and introduced the reader to the topic of late-life depression, and summarized the wide array of risk factors. The latter part of the research was dedicated to nutritional psychiatry, dietary patterns, and proposed mechanisms of action. The practical part of the study started with a description of the HAPIEE study and the analyzed sample, variables entering the analysis, and a list of used statistical methods. The hypotheses were tested with the use of growth curve modelling and stratified by sex. Results of the analyses were then discussed in the context of hypotheses in Discussion.

The study discovered a link between the intensity of depressive symptoms and adherence to a healthy diet that was partially explained by demographic and social factors, and lifestyle and health behaviors. The relationship differed between sexes, there was a significant inverse association between depressive symptoms and higher adherence in women but not in men. The results correspond with literature and further underline the need for more nutritional psychiatry research, especially in the CEE region.

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Appendices

Appendix 1. CES-D scale

During the past week:

1.	I was bothered by things that usually don't bother me.
2.	I did not feel like eating; my appetite was poor.
3.	I felt that I could not shake off the blues even with help from my family or friends.
4.	I felt that I was just as good as other people.
5.	I had trouble keeping my mind on what I was doing.
6.	I felt depressed.
7.	I felt that everything I did was an effort.
8.	I felt hopeful about the future.
9.	I thought my life had been a failure.
10.	I felt fearful.
11.	My sleep was restless.
12.	I was happy.
13.	I talked less than usual.
14.	I felt lonely.
15.	People were unfriendly.
16.	I enjoyed life.
17.	I had crying spells.
18.	I felt sad.
19.	I felt that people dislike me.
20.	I could not get "going."

Appendix 2. CES-D-10 scale

During the past week:

1.	I was bothered by things that usually don't bother me.
2.	I had trouble keeping my mind on what I was doing.
3.	I felt depressed.
4.	I felt that everything I did was an effort.
5.	I felt hopeful about the future.
6.	I felt fearful.
7.	My sleep was restless.
8.	I was happy.
9.	I felt lonely.
10.	I could not get going.