UNIVERSIDADE DE LISBOA

FACULDADE DE MOTRICIDADE HUMANA

ASSOCIATIONS BETWEEN GRIP STRENGTH, CHRONIC DISEASES, AND DEPRESSIVE SYMPTOMATOLOGY IN EUROPEAN MIDDLE-AGED AND OLDER ADULTS

DIOGO MIGUEL CARVALHO VEIGA

Orientadores: Professor Doutor Adilson Passos da Costa Marques

Professor Doutor Pedro Jorge do Amaral de Melo Teixeira

Tese especialmente elaborada para obtenção do grau de Doutor em Motricidade Humana na especialidade de Atividade Física e Saúde

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2024

É aqui que tu moras?

Aqui é a minha morada.
Mas não é aqui que eu moro.
Eu moro numa casa tão grande que não se vê
E, ao mesmo tempo, tão pequena que ocupa tudo.
Uma casa de cabelos da côr do sol quando se põe.
Uma casa onde as janelas são pestanas que se penteiam.
Uma casa onde a porta é só para mim.
Seu eu quem escolhe entrar ou sair.
A porta, que só eu vejo, tem lábios desenhados por mim.
Foram outros que construíram,
Mas fui eu que desenhei.
E eles construíram mesmo não sabendo que o desenho era meu.
Lábios quentes como final de tarde no verão.
Lábios frios como quem chama mantas e carinho no Inverno.
Lábios das 4 estações do ano mais as que quisermos,
Que eu desmancho essa organização.
A minha casa tem paredes.
As paredes não dizem onde é o quê.
Deixam isso à minha escolha, mas garantem abrigo.
São feitas de um material só ao alcance de uma mulher.
Material esse que a linguagem desconhece.
Não quero dar-lhe forma.
Paredes que se sentem mas são impossíveis de comunicar.
Uma casa para mim.
Ao contrário.
Os outros não entendem a tipologia porque usam a lógica.
Usassem os sentidos.
A minha casa também tem jardim.
Não se conhece o inicio nem o fim.
Rimou com propósito.
Porque a minha casa diz que eu sou poeta.
Não percebe ela que é a mais distinta de todas as odes.

Com Amor Seguimos Adiante
CASA

ACKNOWLEDGEMENTS

Esta tese é mais um passo importante na minha carreira académica, mas gostaria de deixar registado que é o término de um processo extenso que considero ter começado em 2018, com a inscrição no Mestrado em Exercício e Saúde. A todos aqueles que, como eu, têm filhos e despesas fixas, desejo que tenham neste trabalho mais uma humilde fonte de inspiração para provar que é possível.

Como tudo na minha vida, todo este trabalho jamais teria sido possível sem algumas pessoas que, de forma direta ou indireta, deliberada ou inconsciente, tiveram uma influência pessoal e/ou profissional preponderante para a realização do mesmo.

Professor Doutor Adilson Marques. Formalmente, o meu orientador. Na vida, o Adilson. Um amigo que o acaso me deu. Fonte de abrigo e cuidado, teve sempre a disponibilidade que pedi ao universo que um orientador tivesse. Num rácio perfeito entre compaixão e pragmatismo, foram inúmeras as vezes em que se preocupou com o meu tempo, a minha saúde física e/ou mental, os meus recursos e as minhas possibilidades, algumas vezes até mais do que eu próprio. Não tenho palavras para te agradecer todo este trajecto.

Professor Doutor Pedro Teixeira. O meu co-orientador. O Pedro. Falar do Pedro obriga-me a recuar no tempo e lembrar que, após um ano de doutoramento em outra especialidade, não consegui mais calar a minha intuição e pedi, “de joelhos”, que me deixasse trabalhar com ele. Não sabia bem o conteúdo nem a forma, mas algo dentro de mim me dizia que esta era a pessoa com quem eu iria querer trabalhar e aprender. Não me enganei. Mais uma vez, com pouco mais do que vontade para oferecer, o Pedro acolheu-me de braços abertos. Recordo um e-mail que enviou à Prof. Dra. Fátima Batista, aquando da minha oficialização de mudanaça de especialidade, a referir que eu estaria “(...) à sua responsabilidade”. Tudo o que veio a partir daí, em todas as dimensões da minha vida, deu origem a uma nova versão de mim e da minha vida. Obrigado Pedro.

Miguel Peralta. Mas que tremenda surpresa. Um homem à imagem do meu orientador. Dono de uma empatia e altruísmo dignos de registo. Incansável a forma como se mostrou sempre disponível para me ajudar. Numa área onde tantas vezes as pessoas parecem confundir-se com a sua carreira e esquecerem que são pessoas, é deveras inspirador o desapego com que partilhou muito do seu conhecimento comigo ao longo da elaboração desta tese.

Jorge Encantado. Laura Carvalho. Cristiani Sequeira. Helena Miranda. Pedro Rodrigues. Lúcia Paço. Os meus amigos durante a elaboração desta tese. A família que eu escolhi. Obrigado pelas viagens, pelas músicas, pelas conversas. Obrigado por me fazerem ver a arte que mora em mim. Pelo amor incondicional. Pelo não julgamento. Pelos abraços. Obrigado, sobretudo, por me fazerem sentir que dançar é por dentro.

Fátima Carvalho. Mãe. Obrigado por, apesar de tudo, nunca me teres fechado as portas. Obrigado pela avó. Desculpa qualquer coisa menos boa pelo caminho e obrigado por tantas e tantas vezes manifestares o orgulho que tens em mim.

Álvaro Veiga. Pai. Onde quer que estejas, desejo-te orgulhoso por isto, mas sobretudo pela pessoa que me tornei.

Miguel Veiga. Maria Veiga. Manuel Veiga. Meus filhos. Desejo que este trabalho vos possa inspirar a seguirem a vossa intuição. A não seguirem guiões. A terem o discernimento e liderança pessoal de dizer "não", mesmo quando todos disserem "sim". O pai ama-vos perdidamente e, enquanto tiver ar nos pulmões, estará aqui sempre para vos receber em amor.

Telma Marques. De longe, o melhor que me aconteceu durante a elaboração deste trabalho. A minha casa. A pessoa onde rio, brinco, choro, emociono-me, converso, aprendo e amo. A pessoa que me faz sentir que há espaço no mundo para tudo o que eu sou e sinto. A alma que me ensinou que o amor é sempre a resposta. O espírito que me guia na sua intuição ancestral de mulher. O coração que tocou o meu para nunca mais o largar. Dedicar-te os dias que me faltam. Assim é. Assim será.

A quem está para chegar. Vai ser incrível.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS I

TABLE OF CONTENTS III

INDEX OF TABLES VI

INDEX OF FIGURES VII

ABBREVIATIONS VIII

INTRODUCTION 1

STRUCTURE OF THE THESIS 2
LIST OF PUBLICATIONS AND MANUSCRIPTS 3
Study I *3*
Study II (Annex 4) *3*
Study III (Annex 5) *3*

LITERATURE REVIEW 4

DEPRESSION 4
CHRONIC DISEASES AND DEPRESSION 8
Cancer *9*
Cardiovascular diseases *10*
Diabetes Mellitus *12*
GRIP STRENGTH AND DEPRESSION 14

CONCEPTUAL MODEL 18

METHODOLOGY 20

HYPOTHESIS, RESEARCH QUESTIONS AND AIMS 20
Hypothesis *20*
Research questions *20*
General aim *21*
Specific aims *21*
RESEARCH DESIGN 22
DATA SOURCE 22
DATA COLLECTION 23
SAMPLE 24
Inclusion criteria *25*
Exclusion criteria *25*
ETHICS 25

Informed consent and voluntary participation *26*
MEASURES 26
Outcome variable *26*
Exposure variables *27*
Moderator *27*
Co-variables *28*
STATISTICAL ANALYSIS 28

RESULTS 30

STUDY I. MODERATING EFFECT OF GRIP STRENGTH IN THE ASSOCIATION BETWEEN CANCER AND DEPRESSIVE SYMPTOMATOLOGY 30
Abstract *30*
Introduction *31*
Methods *33*
Results *36*
Discussion *38*
Conclusion *41*
STUDY II. MODERATING EFFECT OF MUSCULAR STRENGTH IN THE ASSOCIATION BETWEEN CARDIOVASCULAR EVENTS AND DEPRESSIVE SYMPTOMS IN MIDDLE-AGED AND OLDER ADULTS - A CROSS SECTIONAL STUDY 43
Abstract *43*
Introduction *44*
Methods *46*
Results *49*
Discussion *52*
Conclusion *55*
STUDY III. MODERATING EFFECT OF GRIP STRENGTH IN THE ASSOCIATION BETWEEN DIABETES MELLITUS AND DEPRESSIVE SYMPTOMATOLOGY 56
Abstract *56*
Introduction *57*
Methods *59*
Results *61*
Discussion *63*
Conclusion *67*

DISCUSSION 68

STRENGTHS AND LIMITATIONS 75
PERSPECTIVES AND FUTURE RESEARCH 77

CONCLUSION 80

REFERENCES **81**

APPENDICES **110**

APPENDIX 1. SHARE ETHICS APPROVALS 110
APPENDIX 2. EURO-D SCALE. 111
APPENDIX 3. COPY OF THE PUBLISHED VERSION OF STUDY II. 113
APPENDIX 4. COPY OF THE PUBLISHED VERSION OF STUDY III. 122

INDEX OF TABLES

STUDY I. MODERATING EFFECT OF GRIP STRENGTH IN THE ASSOCIATION BETWEEN CANCER AND DEPRESSIVE SYMPTOMATOLOGY

Table 1. Sample characteristics for the total sample and by sex *37*

Table 2. Pearson correlation between grip strength and depressive symptomatology *37*

Table 3. Comparison of depressive symptomatology according to the presence or absence of cancer. *38*

Table 4. Moderation analysis of grip strength for the relationship between cancer and depressive symptomatology stratified by sex *38*

STUDY II. MODERATING EFFECT OF MUSCULAR STRENGTH IN THE ASSOCIATION BETWEEN CARDIOVASCULAR EVENTS AND DEPRESSIVE SYMPTOMS IN MIDDLE-AGED AND OLDER ADULTS – A CROSS SECTIONAL STUDY

Table 1. Sample characteristics for the total sample and by sex *50*

Table 2. Comparison of depressive symptoms according to the history of cardiovascular events (myocardial infarction and/or stroke) *51*

Table 3. Moderation analysis of grip strength for the relationship between cardiovascular events and depressive symptoms stratified by sex. *51*

STUDY III. MODERATING EFFECT OF GRIP STRENGTH IN THE ASSOCIATION BETWEEN DIABETES MELLITUS AND DEPRESSIVE SYMPTOMATOLOGY

Table 1. Sample characteristics for the total sample and by sex *61*

Table 2. Pearson correlation between grip strength and depressive symptomatology *62*

Table 3. Comparison of depressive symptomatology according to the presence or absence of diabetes *62*

Table 4. Moderation analysis of grip strength for the relationship between diabetes and depressive symptomatology stratified by sex *63*

INDEX OF FIGURES

Figure 1. A conceptual diagram of the relationship between chronic diseases (X) and depression (Y) moderated by muscle strength (W) *19*

STUDY I. MODERATING EFFECT OF GRIP STRENGTH IN THE ASSOCIATION BETWEEN CANCER AND DEPRESSIVE SYMPTOMATOLOGY

Figure 1. A conceptual diagram of the relationship between cancer (X) and depressive symptomatology (Y) moderated by grip strength (W) *36*

STUDY III. MODERATING EFFECT OF GRIP STRENGTH IN THE ASSOCIATION BETWEEN DIABETES MELLITUS AND DEPRESSIVE SYMPTOMATOLOGY

Figure 1. A conceptual diagram of the relationship between diabetes (X) and depressive symptomatology (Y) moderated by grip strength (W) *61*

ABBREVIATIONS

APA	American Psychological Association
CVD	Cardiovascular Disease
CVE	Cardiovascular Event
DM	Diabetes Mellitus
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
Euro-D	European Depression Scale
GS	Grip Strength
SHARE	Survey of Health, Ageing and Retirement in Europe
SPSS	Statistical Package for the Social Sciences

INTRODUCTION

Recently, there is an increased focus on the intricate connection between mental and physical health (Singh, 2022). A deeper understanding of the mechanisms underlying this relationship is necessary in light of the rising prevalence of chronic diseases worldwide and the pervasive impacts of depression on both mental and physical health (Herrera et al., 2021; Wainberg, 2017). The association is based on the premise that overall wellness comprises both physical and mental health and that one dimension cannot be seen independently of the other. Indeed, conditions affecting one's physical health can impact one's mental health and vice versa (Ohrnberger, 2017). Common biological mechanisms that highlight this connection have also been revealed by recent research, such as disruptions in nervous, endocrine, or immune systems will likely affect both physical and mental well-being (Tizenberg, 2021). Physical and mental health integration is further supported by the influence of lifestyle variables on total wellness. Regular exercise, a healthy diet, and good sleep quality not only promote physical health and are essential for good mental health (Mahindru, 2023).

In recent years, grip strength (GS) - an objective indicator of muscle strength - has attracted some attention because of its links to general health, especially in older individuals. In addition, several studies show a strong correlation between GS and physical health in older adults, with lower GS consistently linked to functional limitations, mobility issues, and an increased risk of falls (Bohannon, 2019; Liu, 2022; Wiśniowska-Szurlej, 2019). Evidence also suggests that higher GS is associated with lower rates of anxiety and depression in this population (Jiang, 2022; Kwak, 2022).

In this thesis, the potential moderating role that GS may have in the complex relation between depression and chronic diseases is examined. A detailed analysis of the literature and three original cross-sectional studies aim to elucidate the moderating impact

of GS. This work attempted to draw attention to the importance of a patient-centred, holistic approach to well-being and shed light on a specific theoretical framework and its practical implications for healthcare interventions. New insights could change how integrated healthcare practices are thought about and impact upcoming actions.

Structure of the thesis

The 7 chapters of the current thesis describe the research's background, methods, findings, and conclusions. Three studies (original investigations) were conducted and are also included in the thesis.

The chapter “Literature review” reflects on the associations between depression, chronic diseases (cancer, cardiovascular disease (CVD) and diabetes mellitus (DM)), and muscular strength, represented by GS. The chapter “Conceptual model” is provided to communicate the main concepts and the organizational framework of this thesis.

An overview of the methodology, including hypothesis, research questions, general and specific aims, study design, data source and collection, sample, inclusion and exclusion criteria, ethical issues, measures and statistical analysis, are provided in “Methodology”.

Three original studies - two published and one pending publication in international peer-reviewed journals - are included in the chapter “Results”.

The chapters “Discussion” and “Conclusions” explore the findings of the three investigations, their strengths and limitations, the implications of the thesis’ investigation for future research, and the main conclusions.

List of publications and manuscripts

The research included in this thesis, published or pending publication in international peer-reviewed journals, was organized according to the objectives discussed later in this chapter. These include the following studies:

Study I

Veiga, D., Peralta, M., Carvalho, L., Encantado, J., Gouveia, E. R., Teixeira, P. J., Marques, A. (2023). Moderating effect of grip strength in the association between cancer and depressive symptomatology (under review).

Study II (Annex 4)

Veiga, D., Peralta, M., Gouveia, É. R., Nascimento, M. d. M., Carvalho, L., Encantado, J., & Marques, A. (2024). Moderating effect of muscular strength in the association between cardiovascular events and depressive symptoms in middle-aged and older adults – A cross sectional study. *Geriatrics*, *9*(2), 36. https://www.mdpi.com/2308-3417/9/2/36

Study III (Annex 5)

Veiga, D., Peralta, M., Gouveia, É. R., Carvalho, L., Encantado, J., Teixeira, P. J., & Marques, A. (2024). Moderating effect of grip strength in the association between diabetes mellitus and depressive symptomatology. *Sports*, *12*(1), 3. https://www.mdpi.com/2075-4663/12/1/3

LITERATURE REVIEW

Depression

One of the most common mental diseases affecting adults is depression, which can afflict people of all ages, both sexes and from various social and educational backgrounds. Up to 10% of adults will experience depression at some point in their lives. Over 264 million people worldwide are thought to be affected by the illness (World Health Organization, 2022).

Depressive symptoms are associated with decreased general health and life satisfaction. Individuals' happiness and life satisfaction are reduced, affecting society's general well-being and collective pleasure (Seo, 2018). Depression is a major cause of disability, increasing the risk of premature death and placing a significant burden on healthcare systems (Proudman, 2021). Because it involves a wide range of issues and goes beyond financial aspects, the exact cost of depression can be difficult to determine (Guan, 2022). The immediate expenses to employers and the wider economic ramifications for society are included in the economic impact. The price of antidepressant drugs, therapy sessions, and doctor visits can all be included in the cost of healthcare (Lamoureux-Lamarche, 2022). A person's capacity to work can also be severely impacted by depression, which increases the risk of absenteeism, lower productivity, and even job loss (de Oliveira, 2023). The aetiology of depression is multifaceted, involving intricate social, psychological, and biological dynamics. Its impacts can be severe and recurrent, impairing an individual's capacity to operate and lead a fulfilling life (World Health Organization, 2022).

Even though depression is common, regional differences in its frequency can be substantial. Due to aspects like cultural variations, access to mental health care, and economic inequities, some nations and areas report greater rates of depression (Knifton,

2020). The prevalence estimates of depression seem to vary between 5.5% and 14.6% in high-income countries and 5.9% and 11.1% in low- and middle-income countries (Arvind et al., 2019). Accurately identifying and treating depression may be difficult in many low- and middle-income countries because mental health resources are scarce and mental health problems are stigmatized (Naslund, 2021). In general, diagnosed rates of depression may be greater in high-income nations due to higher reporting rates, improved access to healthcare and higher awareness (Kessler, 2013).

Worldwide epidemiological surveys regularly show that women experience depression at a higher rate than men do (Albert, 2015). According to the World Health Organization, 4% of men and 6% of women suffer from depression globally (World Health Organization, 2022). On average, women are twice as likely as males to suffer from depression (Zhao, 2020). The disparity in depression rates across genders typically starts in youth and persists throughout adulthood (Salk, 2017). Some of the reasons for this gender-related disparity may be that women are generally more likely to have repetitive negative thoughts (Lilly, 2023), have more fluctuations in hormone levels (especially those related to the menstrual cycle, pregnancy, and menopause) (Santoro, 2017), may be more likely to experience certain interpersonal stressors (men may face different pressures related to work or societal expectations) (Meiser, 2019), and present higher prevalence rates of comorbid mental health conditions (such as eating disorders or anxiety) (Garcia, 2020).

Variables like life transitions, societal pressures, and physical health may also cause age-related differences in the symptoms and prevalence. People in their middle years, frequently between the ages of 50 and 60, may go through what is known as a midlife crisis. Depression around this time may be associated with health issues, ageing, employment changes, and life assessments (Infurna, 2020). Depression in older persons

can be difficult to detect since it might be confused with other medical disorders or just plain ageing. The following are risk factors for depression in older adults: social isolation, chronic sickness, loss of loved ones, and loneliness (Wu, 2020). One subtype of depression that affects people 65 years of age and older is known as "late-life depression." It often involves physical symptoms and may be related to medical comorbidities (Avasthi, 2018).

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association & Association, 2013), the diagnosis of depression requires five (or more) symptoms to be present during the same two-week period, and this must represent a change from previous functioning. Also, at least one of the symptoms must be either (1) depressed mood or (2) loss of interest or pleasure. The following symptoms are:

- Depressed mood most of the day, nearly every day.
- Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly daily.
- Insomnia or hypersomnia nearly every day.
- Psychomotor agitation or retardation nearly every day.
- Fatigue or loss of energy nearly every day.
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day.
- Diminished ability to think or concentrate, or indecisiveness, nearly every day.

- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

This diagnosis must also guarantee that these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning; the depressive episode is not attributable to the physiological effects of a substance or another medical condition; the occurrence of the depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders; there has never been a manic episode or a hypomanic episode.

Standardized surveys or questionnaires that are intended to gauge the existence and intensity of depressed symptoms are commonly used in the assessment of depression. The most commonly used are the Beck Depression Inventory (21 items, each representing a specific symptom of depression) (Richter, 1998), Patient Health Questionnaire-9 (is commonly used in primary care settings) (Sun, 2020), Hamilton Rating Scale for Depression (includes 21 items, and the clinician rates the patient based on their observations and the patient's self-report) (Olden, 2009); Center for Epidemiologic Studies Depression Scale (a self-report 20 items scale designed to measure depressive symptoms in the general population) (Cosco, 2017); Quick Inventory of Depressive Symptomatology (It includes 16 items, and clinicians rate the patient based on their observations and the patient's self-report) (Liu, 2021) and Euro-D scale (a self-report questionnaire that aims to measure the presence and severity of depressive symptoms, specifically designed for use in European populations and validated across various European countries) (Prince, 1999b).

Chronic diseases and depression

Depression usually co-occurs with other diseases. Moreover, depression and chronic diseases frequently coexist and can have intricate relationships. For example, depression is more common in people who have long-term conditions such as DM, heart disease, and cancer (Birk, 2019). Managing a chronic disease can be stressful and emotionally taxing, which can hasten the onset of depressive symptoms. Also, the biochemistry and physiology of the body can be impacted by chronic diseases, which can, therefore, have an impact on mood and raise the risk of depression (Herrera, 2021). Furthermore, managing the discomfort, uncertainty, and physical restrictions that frequently accompany chronic diseases can result in depressive symptoms, including melancholy, hopelessness, and helplessness (Ma, 2021). Chronic diseases can also result in social isolation, which can increase feelings of loneliness and sadness (Iovino, 2023). Additionally, several drugs used to treat chronic diseases may have side effects that aggravate or precipitate depressive symptoms (Celano, 2011).

In addition, there are risk factors that are similar for depression and chronic diseases, such as smoking, poor diet, insufficient exercise, and unhealthy lifestyle choices. These factors can raise the chance of developing either condition and lead to a vicious cycle in which depression deteriorates the prognosis of chronic diseases while also making it more difficult for depressed people to follow treatment plans, adopt healthy lifestyles, or seek medical attention when necessary, all of which can have a detrimental effect on their general health (Ng, 2020).

Globally, cancer, CVD, and DM rank among the top causes of morbidity and mortality among all chronic diseases (Bray, 2021; Kocarnik, 2022; Roth, 2020). These chronic diseases have multiple contributing variables, including environmental, lifestyle, and psychological factors (Hu, 2014). Due to these diseases' complexity, there are many

chances to investigate how they interact with mental health, enabling a more in-depth analysis.

Cancer

Almost any tissue or organ in the body can acquire cancer (the body's aberrant cells growing and spreading out of control), and tumours may arise from it (Hausman, 2019). There are numerous types of cancer, and each is distinguished by unique characteristics, such as the site of the tumour's genesis and the behaviour of the cancer cells (Upadhyay, 2021). Mutations in the DNA of healthy cells are the fundamental process by which cancer develops. They can result in losing control over cell division and proliferation (Alhmoud, 2020). Numerous reasons, such as genetic predisposition, exposure to some drugs, infections, and other environmental variables, might result in these mutations (Hausman, 2019).

Cancer is a major worldwide health concern that has become more common. Worldwide, an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and almost 10.0 million cancer deaths (9.9 million excluding nonmelanoma skin cancer) occurred in 2020. (Sung, 2021). Age is a common factor in cancer prevalence, which tends to rise with increasing age (Johnstone, 2022). Furthermore, there may be a gender bias in some cancer forms, with prostate cancer being more common in men and breast cancer in women (Rivera-Izquierdo, 2023). Depending on the type of cancer, there might be significant differences in the risk factors and therapies, as well as the precise origin of the disease. Cancer is a complicated, multidimensional disease that presents a big obstacle for medical research and patient care. Regular cancer screenings, alterations to lifestyle, and public health campaigns are essential in mitigating the effects of cancer on both individuals and communities (Jefford, 2022).

Cancer is a disease known to co-exist with depression (Wang, 2020). These two health problems are distinct but frequently related to one another. Depending on the kind, stage, and course of treatment of the disease, the prevalence of depression in cancer patients can vary. However, there appears to be a strong correlation. Usually, estimates fall between 25% and 30% (Caruso, 2017). The precise association between depression and cancer risk is unclear. It may be somewhat higher among those who have experienced depression in the past (Jefford, 2022). A cancer diagnosis can significantly affect a person's mental health. Feelings of doubt, worry, anxiety, and melancholy may result from it. Many people deal with the psychological and physical effects of cancer by developing a type of situational depression (Niedzwiedz, 2019).

However, depression remains an underrecognized comorbidity in cancer patients that involves unique symptomatology and a strong biological aetiology, being markedly different from depression in physically healthy individuals (Smith, 2015). Adressing depression is crucial for cancer patients' general health and healing. In addition to enhancing mental health and general quality of life, treating depression in cancer patients can potentially increase how well they respond to cancer treatment (Niedzwiedz, 2019). Medication (antidepressants), psychotherapy (such as cognitive-behavioural therapy or counselling), and support from friends and family can be used as forms of treatment. Interventions involving physical activity are also utilized to address the psychological and physical components of cancer (Gerber, 2019).

Cardiovascular diseases

A collection of medical diseases that impact the cardiovascular system, particularly the heart and blood vessels, are called CVDs. These ailments cover a wide range of diseases, such as valve diseases, arrhythmias, heart failure, stroke, hypertension, and coronary artery disease. Heart and blood artery abnormalities, both structural and

functional, are hallmarks of CVDs. These abnormalities can result in diminished oxygen and nutrition delivery to tissues, poor blood flow, and various clinical symptoms. Processes, including atherosclerosis, endothelial dysfunction, inflammation, oxidative stress, and genetic predisposition, are among the fundamental mechanisms of CVDs (Flora, 2019).

CVDs are a major cause of illness and mortality worldwide, making them a serious public health problem. CVDs are the leading cause of death in many nations, accounting for a sizable portion of mortality rates (Roth, 2020). Globally, there are differences in the prevalence of CVDs due to various factors, such as location, socioeconomic status, and lifestyle choices (Schultz, 2018). Depending on local, state, and federal factors, CVD prevalence rates might vary from 100 to 300 cases per 100,000 people annually. Age-related increases in the prevalence of CVDs are common, and an increase in the overall burden of CVD is anticipated as populations age (Rodgers, 2019).

Depression is also common in people with CVD. In patients with CVD, depression is estimated to be one in five (Blatch, 2023), and nearly 45% of patients with CVD seem to struggle with major depressive symptoms (Rafiei, 2023). Furthermore, having comorbid depression is independently linked to a worse prognosis for people with CVD (Hare, 2023). Previous studies have indicated a reciprocal relationship between depression and CVD, with a considerable rate of co-morbidity between the two diseases. Not only does depression raise the chance of CVD, but those who already have been diagnosed with CVD are more likely to have depression in the future. (Halaris, 2017; Harshfield, 2020; Rajan, 2020).

Though there is a complex relationship between depression and CVD, the precise causes of this correlation are not fully known (Dhar, 2016). Psychologically, people with depression are more inclined to partake in risky habits that raise their chance of CVD,

like smoking, binge drinking, eating poorly, and not exercising (Jao, 2019). Physiologically, depression leads to several alterations that might impair cardiovascular health, including inflammation, elevated levels of stress hormones (such as cortisol), and disruptions in the autonomic nerve system (Yaribeygi, 2017). Additionally, various risk factors, both modifiable (e.g., smoking, poor diet, physical inactivity) and non-modifiable (e.g., genetics, age, gender), influence an individual's susceptibility to CVD (Hajar, 2017). Depression and CVD share common risk factors, such as obesity, hypertension, and DM, and share common pathogenic mechanisms (Shiga, 2023). These risk factors can further intertwine the two conditions. Several investigations have suggested that muscle dysfunction is a plausible mechanism for these associations, as it predisposes to the development of CVD (Ozemek, 2018).

Medical therapies and public health campaigns are crucial to addressing the high prevalence of CVD. Strategies include early identification and management of risk factors, improvements in medical treatments and therapies, and lifestyle changes to lower risk factors (e.g., quitting smoking, improving diet, and encouraging physical activity) (Rippe, 2019).

Diabetes Mellitus

Dysregulation of glucose (sugar) metabolism is the hallmark of DM, a chronic metabolic disease. Insulin function impairment and/or inadequate insulin production are the main causes of this syndrome. The hormone insulin, which is essential for controlling blood sugar levels, is secreted by the pancreas, and insulin function impairment and/or inadequate insulin production are the main causes of DM (Cloete, 2022).

There are two main types of DM. Type 1 DM is an autoimmune disease where the immune system unintentionally attacks and kills the pancreatic beta cells that produce insulin. Because of this, the body is unable to manufacture insulin, and those who have

type 1 DM need to take insulin for the rest of their lives. Type 2 DM is caused by insulin resistance. The body's cells not responding to insulin as well as relative insulin deficiency, or the pancreas not producing enough insulin to offset the resistance, are the two main characteristics of this type of DM. It is frequently linked to lifestyle choices, including obesity and sedentary behaviour.

Hyperglycemia, a condition caused by increased blood glucose levels in both forms of DM, can have several negative effects on the heart, blood vessels, neurons, eyes, kidneys, and other organ systems if left unchecked (Galicia-Garcia, 2020). To maintain glycemic control and avoid complications, DM care usually entails medication, dietary and physical activity modifications, and routine blood sugar monitoring (Shrivastav, 2018).

Globally, an estimated 422 million individuals have DM, and it is predicted that the prevalence of DM will increase by 25% over the next ten years, making it a growing public health concern (Saeedi, 2019).

Depression is more common in people with DM compared to the general population (Wirkner, 2022). DM and depression rank among the leading causes of disease burden worldwide and are present in the top 10 causes of disability-adjusted life years worldwide (Habib, 2022). The onset of depressive symptoms may be facilitated by the strain of treating a chronic disease such as DM. The ongoing need for self-care and the worry of complications from DM can be emotionally draining once that it can be emotionally and psychologically taxing to manage DM daily, cope with its complications, and acknowledge that the disease is chronic (Mukherjee, 2019).

Depression and DM are closely linked, and there is a bidirectional relationship between these two conditions (Alzoubi, 2018). Just as depression increases the risk of developing DM, having DM can increase the risk of developing depression. DM increases

the risk of depression by 15– 28% (Chireh, 2019), and, on the other hand, depression was confirmed as a risk factor for DM (34% and 60% risk increase) (Kozela, 2023). Even when other known DM risk factors are considered, such as a poor diet, family history, inflammation, the use of some antidepressants, and a sedentary lifestyle, the elevated risk for DM associated with depression persists (Hunter, 2018).

Both depression and DM have shared biological mechanisms. Both diseases are associated with faulty modulation of neurotransmitters in the brain, insulin resistance, and chronic inflammation. DM patients may experience impaired blood sugar regulation as a result of depression. Numerous studies have also demonstrated that DM and depression both negatively impact the quality of life, with the consequences being much greater when they coexist (Zurita-Cruz, 2018).

Individuals with depression may find it more difficult to follow their DM treatment regimen, which calls for taking prescription drugs, checking blood sugar levels, and leading a healthy lifestyle (Owens-Gary, 2019).

Grip strength and depression

The physical and mental health benefits of physical activity and fitness are well-established (Marques, 2018). Physical activity provides various benefits, including preventing chronic diseases, lowering the risk of depression, increasing physical strength, and reducing mental stress (Mahindru, 2023). Physical activity can have a significant impact on depression, both in terms of prevention and as a part of a treatment plan (Cuijpers, 2019).

It has been demonstrated that physical activity causes the production of endorphins, which are naturally occurring mood enhancers that can lessen stress, anxiety, and depressive symptoms and promote happiness and overall well-being (Basso, 2017).

As a vital component of a healthy lifestyle that can help protect against a variety of mental health disorders (e.g., lower the risk of developing depression), regular physical activity can also lower the body's production of stress hormones (like cortisol), improve sleep quality and regulate sleep patterns, improve cognitive function (Alnawwar, 2023). Although physical activity cannot take the place of professional mental health treatment, it can be a beneficial supplement to other forms of therapy. For many depressed people, the best outcomes come from combining psychotherapy or medication with regular physical activity (Xie, 2021).

From all the health-related components of physical fitness (Caspersen, 1985), muscle strength, in particular, influences many physiological and metabolic processes in the body and is essential for general health and wellbeing (Weakley, 2023). It makes a substantial contribution to metabolic regulation once it has been connected to enhancements in lipid profiles (Teixeira, 2020), insulin sensitivity (Iaccarino, 2021), and glucose metabolism (Consitt, 2019), all of which lower the incidence of type 2 DM and CVD (Shiroma, 2017).

Muscle strength significantly impacts quality of life, functional independence and has metabolic benefits (Hortobágyi, 2023). Sustaining sufficient muscle strength is essential for everyday tasks like walking, lifting, and stair climbing, which are vital for preserving autonomy and movement, particularly as people age (Larsson, 2019). It enhances general well-being and longevity (Suchomel, 2018).

Muscle strength is also beneficial for reducing depressive symptoms (da Costa, 2022). Research has linked poorer mental health in older adults with weaker muscles and depression, and cognitive function appears to be negatively correlated with muscle strength in this population (Shin, 2022), highlighting the importance of physical health and exercise in preventing depression. Strength training (training to increase muscle

strength) releases endorphins, naturally occurring mood enhancers (Jiang, 2023). It also enhances body image (regular strength trainers frequently see improvements in their physical appearance and body composition) (SantaBarbara, 2017), improves functional abilities in daily life (Olsen, 2019), and helps depressed people manage their daily responsibilities (Gordon, 2018).

GS, the force the hand muscles generate when gripping an object, correlates with muscular fitness (Chan, 2022). GS is a measure of overall body strength and a maximum hand static force measure commonly used to capture muscular strength and monitor the health status in the general population, especially in older age (Bae, 2019). While GS itself is not a direct treatment or preventive measure for depression, it has been considered a legitimate and trustworthy measure of overall muscle strength and the state of one’s physical and mental health (Oh, 2023). Although GS seems to have a protective effect on depression (Lee, 2018), some studies have shown otherwise (Stessman, 2017). Weaker GS has been connected to physical diseases and disorders such as chronic pain, CVD, or chronic sickness that may cause or be linked to depression. It is a powerful predictor of CVD (Leong, 2015), metabolic syndrome (Lopez-Jaramillo, 2014), neurological disorders (Mehta, 2002), and future disability (McGrath, 2018). Among middle-aged and older adults, GS may mediate the relationship between depression and the estimated 10-year risk of CVD (Lee, 2022). Also, among people with DM, strength training may not only help alleviate depressive symptoms (Kandola, 2019) but also assist in achieving glycaemic control (Arsh, 2023). Regular strength training helps regulate normal glucose uptake into peripheral tissues. It increases insulin receptors and insulin sensitivity, thus contributing to blood glucose control (Kim, 2018). Strength training is also associated with reduced incidence of some types of cancer (Nascimento, 2021).

However, large transnational studies assessing the association of GS to depression in middle-aged and older adults are still scarce (Ribeiro, 2020). The possible moderating effect of GS in the relationship between chronic diseases and depression is unknown.

CONCEPTUAL MODEL

The conceptual model representing the possible moderating role of muscle strength (W) in the relationship between chronic diseases (X) and depression (Y) is presented in Figure 1.

There is an association between chronic diseases (cancer, CVD and DM) and depression (Hunter et al., 2018; Mössinger, 2023; Warriach, 2022). This association can be attributed to several interrelated variables. In terms of physiological mechanisms, this link may be explained by the fact that cancer, CVD and DM trigger inflammatory processes (releasing pro-inflammatory mediators like cytokines and affecting neurobiological pathways linked to mood regulation) (Furman, 2019), causing neurotransmitter dysregulation (disrupt neurotransmitter homeostasis in the brain) (Al-Sayyar, 2023) and are also responsible for hormone disruptions (mood-regulating pathways can be affected by changes in hormone levels and contribute to the onset of depression) (Fu, 2020).

In parallel, there is an association between muscle strength and depression. Muscle strength seems to have a protective effect on depression (Bao, 2022). Higher levels of muscle strength have been linked to higher serotonin levels (Kavanagh, 2019) and endorphins in the brain (Mikkelsen, 2017), and lower cortisol (Katsuhara, 2022) and inflammatory markers (Tuttle, 2020).

This conceptual model suggests that muscle strength, measured by GS, can impact the strength of the relationship between chronic diseases (namely cancer, CVD and DM) and depression. In contrast to those with lower muscle strength, measured by GS, it is plausible that people with higher muscle strength are expected to encounter a less prominent association between chronic diseases and depression. Put differently, muscle

strength is thought to attenuate or buffer the effects of depressive symptomatology on long-term diseases like cancer, CVD and DM.

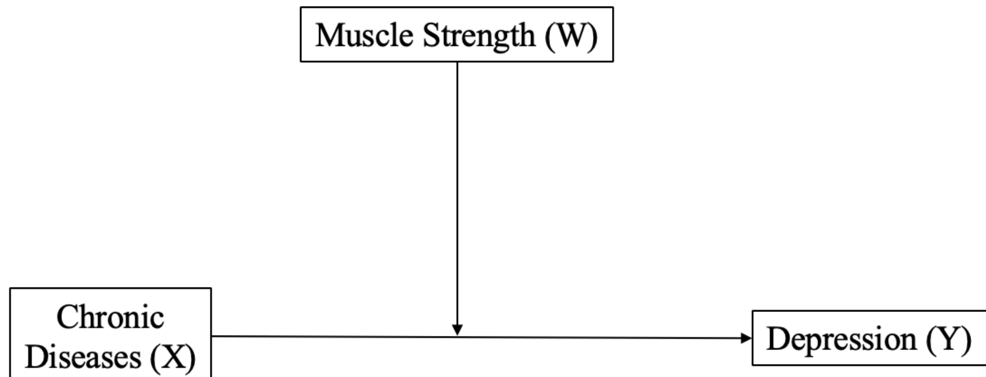


Figure 1. A conceptual diagram of the relationship between chronic diseases (X) and depression (Y) moderated by muscle strength (W).

METHODOLOGY

Hypothesis, research questions and aims

Hypothesis

Muscle strength has been suggested as a useful biomarker for evaluating an individual's physiological resistance and is a proxy measure of total muscular strength (Naimo, 2021). Higher GS has been linked in studies to a lower incidence of chronic diseases like DM (Boonpor, 2021), cancer (Parra-Soto, 2022), and CVDs (Peralta, 2023). The beneficial effects of muscle strength on metabolic health (Kim, 2020), inflammatory control (Chupel, 2017), and general physical health (Hillsdon, 2018) may be the underlying mechanisms. Consequently, it is conceivable that those with greater muscle strength would have a more robust physiological health, which could lessen the influence of depressive symptomatology on the onset or course of chronic diseases.

Given this and according to the theoretical interpretation of the conceptual model (see Figure 1), the following hypothesis was established: muscle strength weakens the link between depressive symptomatology and chronic diseases (cancer, CVD and DM) among European middle-aged and older adults of both sexes.

Research questions

There is a complex and reciprocal interaction between depression and chronic diseases, with one disorder impacting and aggravating the other (Herrera, 2021). As a proxy for overall muscle health, muscle strength may be a protective factor by improving an individual's capacity to participate in physical activities and uphold a healthier lifestyle (Langhammer, 2018). Increased muscle strength makes regular physical activity easier, which has been repeatedly linked to a lower risk of chronic diseases and better mental health (Rippe, 2018). Stronger muscle strength may protect against the negative

associations between chronic diseases and depressive symptomatology, promoting a more robust and flexible physiological response.

To address the established hypothesis, the following research question was formulated: Among European middle-aged and older adults of both sexes, does muscle strength have a moderating role in the relationship between depressive symptoms and chronic diseases such as cancer, CVD and DM?

General aim

There is strong evidence that there is a reciprocal association between depressive symptoms and chronic diseases, indicating that those who have chronic diseases are more likely to experience depression and vice-versa (Ma, 2021). To further improve our awareness of potential protective factors that may lessen the negative effects of chronic diseases on mental health, this project aimed to analyse how GS moderates the relationship between chronic diseases (cancer, CVD and DM) and depressive symptoms among European middle-aged and older adults. Examining how muscle strength affects this relationship may reveal how physical resilience functions as a buffer, reducing the psychological toll that chronic diseases take on a person.

Specific aims

The specific aims of this research were the following:

- To quantify the prevalence of depressive symptoms among middle-aged and older adults from 28 European countries and Israel, stratified by sex and according to the presence or absence of cancer, CVD and DM.
- To characterize the moderating role of muscle strength in the relationship between depressive symptoms and cancer, CVD and DM, stratified by sex.

Research design

The proposed aims were accomplished by employing a multi-country observational study using data from the Survey of Health, Ageing and Retirement in Europe (SHARE) project.

Data source

SHARE started in 2002, and since 2011, it has served as the first-ever European Research Infrastructure Consortium. It was developed as a longitudinal survey by and for academics from various disciplines in response to the European Commission's keen interest in acquiring scientific evidence on population ageing in its member states. The result is to provide high-quality micro-level panel data on economic, social, and health aspects that accompany and impact ageing processes at the individual and societal levels. While multidisciplinary and longitudinal, SHARE was created as a transnational project to allow researchers to examine how various European welfare state regimes moderate and mediate outcomes and implications of population ageing. The scientific community receives free access to data on adults 50 and older gathered every two years in 28 European countries and Israel. For its data, SHARE has an open-access policy (http://www.share-project.org). More information about the SHARE project can be found elsewhere (Borsch-Supan, 2013; de Luca, 2005; Klevmarken, 2005).

SHARE applies a concept of ex-ante harmonisation: one common generic questionnaire is automatically processed in a computer-assisted personal interviewing tool after being translated into the national languages (in certain countries, more than one language). Although each participating planned its translation effort, the central coordinator started several initiatives to help the various translation processes. First, instructions on hiring translators, testing translators, organising the translation, and

reviewing and assessing the translation were sent to SHARE countries. Second, the project coordinator hired a survey translation specialist to help SHARE participants with questions. Third, the project coordinator hired an expert to examine the initial SHARE translation document sample. An outside team of translators, each working in their primary language of expertise, provided comments to SHARE countries.

Centrally, the SHARE project is coordinated by professor Axel Börsch-Supan and at the responsibility of Max-Planck Institute for Social Law and Social Policy, which is part of the Munich Center for the Economics of Aging.

SHARE receives funding from the European Commission, the American National Institute on Aging and national sources, the German Federal Ministry of Education and Research and the Deutsche Forschungsgemeinschaft.

Data collection

The interviewers conduct in-person interviews using a laptop with the computer-assisted personal interviewing instrument installed (de Luca, 2005). For SHARE, in-person interviews are essential since they enable the administration of physical examinations. It is only feasible for a respondent to be aided by a so-called "proxy respondent" to complete the interview if their physical and/or cognitive disabilities make it impossible for them to do so themselves. Proxy interviews are permitted when a person has hearing loss, speech difficulties, Alzheimer's disease, or other circumstances that make it impossible to focus for the duration of the interview.

In October 2019, fieldwork for the eighth SHARE wave started. The COVID 19 epidemic, which began in 2020, expanded throughout Europe and significantly impacted practically every aspect of daily life, including survey research. Due to stringent epidemiological control requirements in the 29 participating nations, SHARE, like other

surveys, was forced to halt routine in-person interviews in March 2020. This was especially important because SHARE focuses on those over 50, including extremely old responders and people living in nursing homes and retirement communities who are most at risk of contracting an infection. In response, SHARE adopted telephone interviews and created the unique "SHARE Corona" survey, successfully carried out between April and August 2020 in all 29 countries.

The data is organized into 25 modules, comprising about 1000 questions, with a complex structure. Certain factors are readily available for SHARE users to ensure quick and simple entry into international data and great comfort when working with the data (additional generated variables like indices and scales like the EURO-D scale on depression and GS).

Sample

All individuals aged 50 and over at the time of sampling (i.e., in 2019/2020 for Wave 8) who have their primary residence in the particular SHARE country make up the target population for SHARE. As a result, the SHARE target population could also be described in terms of households, i.e., all households with at least one member of the SHARE target population. SHARE includes residents of nursing homes and residential care whenever they are included in the sampling frame from which the baseline/refreshment samples are obtained, in contrast to many other research.

The SHARE wave 8 (2019/2020) data was utilized. There were 23698 women and 18003 men in all, with a mean age of 70.65 (9.1) and participated from 29 different countries (Austria, Germany, Sweden, the Netherlands, Spain, Italy, France, Denmark, Greece, Switzerland, Belgium, Israel, the Czech Republic, Poland, Ireland, Luxembourg, Hungary, Portugal, Slovenia, Estonia, Croatia, Lithuania, Bulgaria, Cyprus, Finland, Latvia, Malta, Romania, and Slovakia).

Inclusion criteria

The inclusion criteria were the following:

1. Middle-aged and older adults from European countries and Israel, aged 50 and over;
2. Presenting valid information on GS collected in 2019/2020 (SHARE wave 8).

Exclusion criteria

People were excluded if they could not be located due to errors in the sampling frame (such as a non-existent address or a vacant house) or if they had moved to an unknown address. Other exclusion criteria include being incarcerated, hospitalized, or out of the country for the entirety of the survey period. Regardless of their age, spouses and partners of adults 50 and older are included in the target group because the household level is crucial for many of the SHARE data's collected factors.

Ethics

The SHARE data collection procedures are subject to continuous ethics review (Appendix 1). The Ethics Committee of the University of Mannheim, and the Ethics Council of the Max Planck Society for the Advancement of Science approved the SHARE protocol and verify the procedures to protect confidentiality and data privacy (http://www.share-project.org/ organisation/dates-facts.html).

SHARE's activities related to human subjects research are guided by international research ethics principles such as the Respect Code of Practice for Socio-Economic Research (professional and ethical guidelines for conducting socio-economic research) and the Declaration of Helsinki.

Informed consent and voluntary participation

In all of the SHARE countries, potential respondents received an invitation letter containing information on the SHARE project and the data confidentiality and protection rules the project adopted. Verbal informed consent was sought and recorded by the interviewers before the interview, and any physical health measures (e.g., GS) were conducted. On the completion of the interview, respondents were asked to grant permission to be re-contacted for future waves of survey (Borsch-Supan, 2013).

Measures

Outcome variable

Depressive symptoms served as the outcome measure. The 12-item EURO-D scale (Appendix 2) was employed to rate depressive symptoms. The EURO-D scale was initially created to create a scale for assessing common depressive symptoms from a variety of late-life depression instruments used in various European nations. The EURO-D scale offers sufficient psychometric qualities for detecting differences between men and women and assessing depression symptoms in old age (Tomas, 2022). The EURO-D scale was developed by merging items from these scales: GMS, SHORT-CARE, ZSDS and the CPRS (Courtin, 2015) and the scale's validity and justification are covered elsewhere (Prince, 1999b).

The scale consists of the following items: depression, pessimism, suicidality, guilt, sleep, interest, irritability, appetite, fatigue, concentration (on reading or entertainment), enjoyment, and tearfulness. These items are structured to provide a comprehensive assessment of depressive symptoms. Scores range from 0 to 12, with higher numbers denoting more severe depressive symptoms.

SHARE provides the EURO-D variable and the EURO-D caseness variable as generated variables. EURO-D variable is generated as a composite index of sixteen items. The information in *mh005_/mh006_*, *mh008_/mh009_*, *mh011_/mh012_* and *mh014_/mh015_* is combined when generating the EURO-D variable so that the list of 16 items is reduced to 12 final items. The maximum score a respondent can get is 12 "very depressed", and the minimum score is 0 "not depressed". EURO-D caseness variable is the attainment of a scale score where 4 or higher is categorized as a "case of depression" and a scale score below 4 as "not depressed" (Gallagher, 2013; Prince, 1999b).

Exposure variables

The exposure measures were cancer, CVD (cardiovascular event such as stroke and/or myocardial infraction) and DM. The participants had to answer the question: "*Has a doctor ever told you that you had/ Do you currently have any of the conditions on this card? (With this, we mean that a doctor has told you that you have this condition and that you are either currently being treated for or bothered by this condition)".*

Moderator

The moderator in use was GS. A dynamometer (Smedley, S Dynamometer, TTM, Tokyo, 100 kg) was measured twice on each hand, alternating between the left and right hands (Roberts, 2011). The dynamometer's inner lever was adjusted to the hand. While standing or sitting, participants kept their upper arm close to their bodies with the elbow at a 90-degree angle, the wrist in neutral, and the elbow snugly against them. Participants fully supported the dynamometer for 5 seconds. Participants have the chance to practice before the test. One the one hand, it was accepted that measurements with a difference of less than 20 kg were valid. The maximum value of the GS readings for both hands, independently of each hand, was contained in the GS variable.

Co-variables

Covariates included sex, age, physical activity and country in study I. In study II covariates also included hypertension. Sex and age were the only covariates included in study III. All covariates were self-reported. Physical activity was measured as ‘‘frequency of moderate physical activity’’ (e.g., gardening, cleaning the car, going for a walk) and ‘‘frequency of vigorous physical activity’’ (e.g., sports, heavy housework, a job involving physical labour). The response alternatives for both moderate and vigorous activity were: (1) more than once a week, (2) once a week, (3) up to three times a month, and (4) hardly ever or never. The last two response options were grouped into one category called less than once a week.

Statistical analysis

Descriptive statistics (mean, standard deviation, and frequency) were calculated for all variables. The depressive symptomatology of men and women according to the diagnosis (cancer, CVD and DM), as well as the association between GS and depressive symptomatology, were compared using an independent sample t-test and a Pearson correlation analysis, respectively. Using the suggestions for moderation made by Baron and Kenny (Baron, 1986), a moderated analysis of GS (moderator, W) on the connection between cancer, CVD or DM (categorical, X) and depressive symptoms (continuous, Y) was conducted. The moderation analysis was carried out using Andrew Hayes' PROCESS macro-3.5. In the context of moderation analysis using the PROCESS macro, moderation refers to the influence of an external variable (moderator) on the strength or direction of the relationship between an independent and dependent variable. The Johnson-Neyman method was used to evaluate statistically significant interactions and find regions of significance. This process was also used to determine a threshold of

statistical significance. Data analysis was performed using IBM SPSS Statistics version 28 (SPSS Inc., an IBM Company, Chicago, Illinois, USA). For all tests, the statistical significance was set at $p<0.05$.

RESULTS

Study I. Moderating effect of grip strength in the association between cancer and depressive symptomatology

Abstract

Background: Depression, as one of the leading causes of disease burden, frequently co-occurs with other diseases. Cancer seems to be strongly associated with depression more than any other disease. As an outcome of physical fitness, grip strength seems to have a protective effect on depression. This study aimed to analyse how grip strength moderates the relationship between cancer and depressive symptomatology among older European adults. *Methods:* Cross-sectional data from wave 8 (2019/2020), including 41666 participants (17986 men) of the population-based Survey of Health, Aging, and Retirement in Europe, were analysed. Grip strength, used as the moderator, was measured twice on each hand using a dynamometer. The EURO-D 12-item scale was used to measure depressive symptomatology. *Results:* Grip strength had a significant effect as a moderator in the association between cancer and depressive symptoms (male: B= -0.025, 95% CI = -0.04, -0.01; female: B = -0.02, 95% CI = -0.04, 0.00). Also, the grip strength moderation values are below 55.3kg for males and 39.4kg for females. *Conclusions:* Muscular fitness, as measured by grip strength, moderated the relationship between cancer and depressive symptomatology. This supports the theory that recovery programs could include physical activity, namely muscle-strengthening exercises, to prevent depression.

Keywords: depression; elderly; fitness; handgrip; moderation; preventive medicine.

Introduction

Adults of all ages, both sexes and from various educational and socioeconomic backgrounds are susceptible to depression, which is one of the most common mental diseases (Marques, 2020). Depression is associated with heightened comorbidity (Vancampfort, 2016), increased health costs (Chisholm, 2016), poor adherence to medical treatment (Saz, 2001), risk of suicide (Ferrari, 2013), and premature mortality (Walker, 2015). The causes of depression are multifaceted and involve intricate social, psychological, and biological dynamics (World Health Organization, 2022).

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association & Association, 2013), the diagnosis of depression requires five (or more) symptoms to be present during the same two-week period, and this must represent a change from previous functioning. Also, at least one of the symptoms must be either (1) depressed mood or (2) loss of interest or pleasure. The following symptoms are depressed mood most of the day, nearly every day; markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day; significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day; insomnia or hypersomnia nearly every day; psychomotor agitation or retardation nearly every day; fatigue or loss of energy nearly every day; feelings of worthlessness or excessive or inappropriate guilt nearly every day; diminished ability to think or concentrate, or indecisiveness, nearly every day; recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Depression frequently co-occurs with other diseases (Tong, 2021). In this context, cancer is a disease known to co-exist with depression (Wang, 2020). The unchecked

development and spread of aberrant cells is the hallmark of cancer. Via the lymphatic and circulatory systems, these cells can travel to other areas of the body and invade, destroying nearby healthy tissues (Brown, 2023). Cancer is one of the major global causes of illness and mortality and in the upcoming decades, ageing, changing lifestyles, and population increase are all predicted to have a major impact on the worldwide cancer burden (Xie, 2023).

Although the relationship between cancer and depression may vary (depending on the course, stage, and prognosis of the disease), cancer seems to be strongly associated with depression (Caruso, 2017). However, depression remains an underrecognized comorbidity in cancer patients that involves unique symptomatology and a strong biological aetiology, being markedly different from depression in healthy individuals (Smith, 2015).

The health benefits of physical activity and fitness are well-established (Marques, 2018). Grip strength (GS) is a maximum hand static force measure commonly used to capture muscular strength (one of the key components of physical fitness) and monitor the health status in the general population, especially in older age (Bae, 2019). It is a powerful predictor of cardiovascular disease (Leong, 2015), metabolic syndrome (Lopez-Jaramillo, 2014), neurological disorders (Shaughnessy, 2020), and future disability (McGrath, 2018). Nevertheless, there are still few large multinational studies evaluating the interaction between GS and depression in middle-aged and older adults (Marconcin, 2020), and it is unclear if GS may have a moderating role in the relationship between depression and cancer. We hypothesised that GS could moderate depressive symptomatology even in the presence of cancer because depression and GS are negatively correlated, and cancer survivors frequently experience depressive symptoms (X. M.

Zhang, 2022). Thus, this study aimed to analyse how GS moderates the relationship between cancer and depressive symptoms among European middle-aged and older adults.

Methods

Participants and Procedures

This study was based on data from wave 8 (2019/2020) of the population-based Survey of Health, Aging, and Retirement in Europe (SHARE). The SHARE methodology has been previously described (Borsch-Supan, 2013). Every two years, since 2002, SHARE gathers data on people in many European nations as well as Israel who are 50 years of age or older. The SHARE data collection procedures are subject to continuous ethics review. For more details please see: https: //share-eric.eu/fileadmin/user_upload/Ethics_Documentation/SHARE_ethics_approvals.pdf (accessed on 21 January 2023). The protocols to ensure data privacy and confidentiality were verified by the Ethics Council of the Max-Planck Society for the Advancement of Science and the University of Mannheim, who accepted the SHARE protocol. Written informed permission was acquired from every study participant.

The final sample comprised 41666 participants (17986 men, 23680 women), mean age of 70.65 (9.1) years old, from 29 countries (Austria, Germany, Sweden, Netherlands, Spain, Italy, France, Denmark, Greece, Switzerland, Belgium, Israel, Czech Republic, Poland, Ireland, Luxembourg, Hungary, Portugal, Slovenia, Estonia, Croatia, Lithuania, Bulgaria, Cyprus, Finland, Latvia, Malta, Romania, and Slovakia). SHARE data collection is based on computer-assisted personal interviewing (CAPI). The interviewers conducted face-to-face interviews using a laptop on which the CAPI instrument was installed. The data are freely accessible. The data can be accessed through the SHARE project website - https://share-eric.eu/ (accessed on 21 January 2023).

Measures

Depressive symptomatology was used as the outcome measure. The EURO-D 12-item scale was used to measure depressive symptomatology. Score range between zero to 12, with higher scores indicative of higher depressive symptoms. A cut-off point of ≥4 points diagnoses a clinically significant depression (Gallagher, 2013; Prince, 1999b). The scale description and validation are described elsewhere (Prince, 1999b).

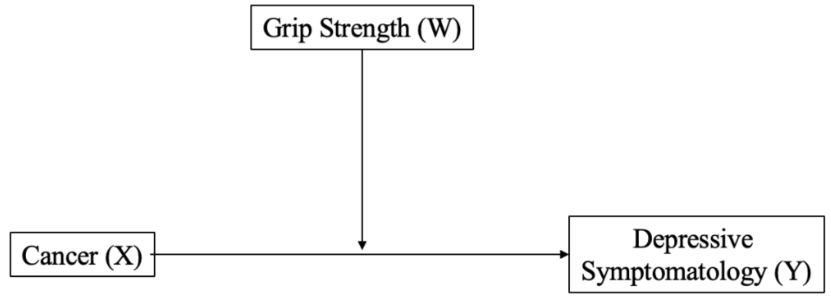
The exposure measure was previously diagnosed with cancer. Participants were asked to report the presence or absence of cancer previously diagnosed by a medical doctor. The participants had to answer the question: "*Has a doctor ever told you that you had/ Do you currently have any of the conditions on this card? (With this, we mean that a doctor has told you that you have this condition and that you are either currently being treated for or bothered by this condition)"*.

GS was used as the moderator. It was measured twice on each hand using a dynamometer (Smedley, S Dynamometer, TTM, Tokyo, 100 kg) (Roberts, 2011). Participants were standing or sitting, with the elbow at a 90° angle, the wrist in a neutral position, keeping the upper arm tight against the trunk, and the inner lever of the dynamometer adjusted to the hand. Participants squeezed the dynamometer with their hands as hard as possible and sustained it for 5 seconds. Before the assessment, participants had the opportunity to train. Values were recorded twice for each hand, alternating left and right. GS variable contained the maximum value of the GS measurement of both hands. Valid measurements were values of two in one hand that differed by less than 20 kg. GS measurements with values equal to 0 kg or higher than 100 kg were excluded, as well as if GS was only measured once in one hand.

Statistical Analysis

Descriptive statistics were calculated for all variables (means, standard deviation, and frequencies) for the entire sample and stratified by sex. The comparison of depressive symptomatology between men and women according to cancer diagnosis was tested by independent sample t-test. The correlation between GS and depressive symptomatology was assessed by a Pearson correlation analysis (Janosky, 1991). Moderation analysis of GS (moderator, W) on the relationship between cancer (categorical, X) and depressive symptomatology (continuous, Y) was based on the moderation paths proposed by Baron and Kenny (Baron, 1986), as shown in Figure 1. Andrew Hayes' PROCESS macro-3.5 was used for the moderation analysis stratified by sex. For this simple moderation model, the process macro automatically centres the variables, computes the interaction term, runs the regression model with the interaction term, and then tests the simple slopes. The Johnson-Neyman approach was applied to test statistically significant interactions and identify regions of significance. This procedure was also used to obtain a threshold of statistical significance. Analysis was stratified by sex. Covariates included sex, physical activity, age, and country, which were self-reported. Physical activity was measured as ''frequency of moderate physical activity'' (e.g., gardening, cleaning the car, going for a walk) and ''frequency of vigorous physical activity'' (e.g., sports, heavy housework, a job involving physical labour). The response alternatives for both moderate and vigorous activity were: (1) more than once a week, (2) once a week, (3) up to three times a month, and (4) hardly ever or never. The last two response options were grouped into one category called less than once a week. Data analysis was performed using IBM SPSS Statistics version 28 (SPSS Inc., an IBM Company, Chicago, Illinois, U.S.A.). For all tests, the statistical significance was set at $p<0.05$.

Figure 1. A conceptual diagram of the relationship between cancer (X) and depressive symptomatology (Y) moderated by grip strength (W).



Results

Descriptive analysis of the total sample and according to sex are presented in Table 1. A greater percentage of women (30.5%) reported depressive symptoms than men (18.3%). On the other hand, more men (5.7%) reported being diagnosed with cancer than women (4.6%).

Table 1. Sample characteristics for the total sample and by sex.

	Mean (SD) or *n* (%)			
	Total (*n*=41666)	Male (*n*=17986)	Female (*n*=23680)	p-value
Age (years)	70.65 (9.14)	71.12 (8.77)	70.29 (9.40)	<.000
Grip strength (kg)	32.04 (11.18)	40.68 (9.93)	25.47 (6.72)	<.000
EURO-D score	2.32 (2.16)	1.90 (1.95)	2.63 (2.25)	<.000
EURO-D ≥ 4				<.000
Yes [*n* (%)]	10523 (25.3)	3295 (18.3)	7228 (30.5)	
No [*n* (%)]	31143 (74.7)	14691 (81.7)	16452 (69.5)	
MPA [*n* (%)]				<.000
< 1x/week	7696 (18.5)	3166 (17.6)	4530 (19.1)	
1/week	6215 (14.9)	2695 (15.0)	3520 (14.9)	
> 1/week	27755 (66.6)	12125 (67.4)	15630 (66.0)	
VPA [*n* (%)]				<.000
< 1x/week	21788 (52.3)	8719 (48.5)	13069 (55.2)	
1/week	6326 (15.2)	2699 (14.5, 15.0)	3627 (15.3)	
> 1/week	13552 (32.5)	6568 (36.5)	6984 (29.5)	
Cancer				<.001
Yes [*n* (%)]	2117 (5.1)	1032 (5.7)	1085 (4.6)	
No [*n* (%)]	39549 (94.9)	16954 (94.3)	22595 (95.4)	

Abbreviations: SD, standart deviation.

Table 2 presents the correlation between grip strength and depressive symptoms. Grip strength was significantly and negatively related to depressive symptoms for the total sample (r = -0.254, p<0.001), for men (r = -0.193, p<0.001) and women (r = -0.210, p<0.001).

Table 2. Pearson correlation between grip strength and depressive symptomatology.

	Depressive symptoms (EURO-D 12 score)					
	Total sample		Male		Female	
	r	p-value	r	p-value	r	p-value
Grip Strength	-0.254	<0.001	-0.193	<0.001	-0.210	<0.001

Table 3 compares depressive symptoms between participants diagnosed and not diagnosed with cancer in the total sample and according to sex. The mean depressive

symptomatology was higher in participants diagnosed with cancer, regardless of sex (men: 2.66 vs 1.86, p<0.001; women: 3.39 vs 2.59, p<0.001).

Table 3. Comparison of depressive symptomatology according to the presence or absence of cancer.

	Depressive symptoms (EURO-D 12 score)					
	Total		Male		Female	
	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value
With Cancer	3.03 (2.31)	<0.001	2.66 (2.2)	<0.001	3.39 (2.24)	<0.001
Without Cancer	2.28 (2.14)		1.86 (1.9)		2.59 (2.40)	

Table 4 shows the moderation effect of GS (W) on the relationship between cancer (X) and depressive symptomatology (Y) for males and females. GS was a significant moderator in the association between cancer and depressive symptoms (male: B= -0.025, 95% CI = -0.04, -0.01; female: B = -0.02, 95% CI = -0.04, 0.00). Also, according to the Johnson-Neyman test, the GS moderation values in the significance region were below 55.3kg for males and 39.4kg for females.

Table 4. Moderation analysis of grip strength for the relationship between cancer and depressive symptomatology stratified by sex.

	Depressive symptoms (EURO-D 12 score)					
	Total sample		Male		Female	
	B	95% CI	B	95% CI	B	95% CI
Cancer (X)	1.09	0.81, 1.37	1.65	1.13, 2.17	1.17	0.66, 1.68
Grip Strength (W)	-0.04	-0.04, -0.04	-0.02	-0.03, -0.02	-0.05	-0.06, -0.05
Cancer*Grip Strength	-0.01	-0.02, -0.01	-0.03	-0.04, -0.01	-0.02	-0.04, 0.00

Abbreviations: CI, confidence interval.

Discussion

This study aimed to analyse how GS moderates the relationship between cancer and depressive symptomatology in european middle-aged and older adults. Findings

showed that GS was significantly associated with fewer depressive symptoms in middle-aged and older people and that both men and women with cancer had more depressive symptoms. Furthermore, when facing a cancer diagnosis, GS was a moderator of depressive symptomatology, attenuating its association with cancer.

This study indicates that depression affects women more frequently than it does men. This result seems to be in line with the results of other studies (Albert, 2015; Shi, 2021). These differences in depression rates between genders are probably due to a confluence of biological (hormonal fluctuations) (J. Zhang, 2023), psychological (socialization and coping mechanisms) (Chen, 2019), and genetic (genetic susceptibility and family history) (Kang, 2020) factors.

The inverse correlation between GS and depressive symptoms presented is in line with the literature reporting that there is an association between lower GS and higher levels of depression (Marques, 2021) and that a decline in GS over time is associated with an increased risk of developing depression (Ganipineni, 2023).

Our findings reinforce that persons diagnosed with cancer present more depressive symptoms, mainly middle-aged and older. In a study with of inpatients with lung cancer in general hospitals, 43.2% of cancer patienst experienced clinically significant depressive symptoms (Gu, 2017). Also, when analysing the association between cancer and depression, Vucic et al. (Vucic, 2021) observed that a large percentage of patients had symptoms of mild (27.2%), moderate depression (22%), and major depression (18%), and the severity of depression was higher in middle-aged and older adults. Given that, it is plausible to assume that cancer is associated with depressive symptomatology (Wang et al., 2020) and that this association seems to be present regardless of the type of cancer (Aminisani, 2017; Zhang, 2021).

GS seems to play a moderating role in the emergence of depressive symptoms after a cancer diagnosis, acting as a surrogate for muscular strength. Although this effect is very small, it is significant, which allows us to deduce, as expected, that there may be many other variables influencing the relationship between cancer and depression. According to the literature, it is expected that this relationship is influenced, for example, by nutrition (Xu, 2022), smoking habits (Trudel-Fitzgerald, 2022) and also alcohol consumption (Révész, 2022). Anyway, according to the observed moderating effect, physical strength and functionality-focused therapies may be beneficial in reducing the psychological discomfort linked to cancer.

In this study, using the Johnson-Neyman test, threshold values in which GS moderates depressive symptoms in cancer are reported. Compared to people with higher GS values, those with lower GS values seem to be more affected by this moderating effect. Put differently, a subject with lower GS values who yet manages to gain more muscular strength seems to experience a stronger protective impact than a different subject who likewise gains this muscular strength but possesses higher baseline levels of strength. These results are in agreement with Wiegert et al. (Wiegert, 2022) that recently aimed to describe reference values and cut-off points for GS in adults with incurable cancer and to verify the association of reference values with prognostic. When compared to GS ≥50th percentile, patients with GS ≤10th percentile had significantly lower survival, as well as patients classified below the GS cut-off point (values ranged from 32.5 to 24.5 kg in males and 20.5 to 18.5 kg in females). These values may be used in the clinic and recovery programs as a monitoring tool to improve muscular fitness and prevent depression. Notwithstanding, future investigations are needed to understand these values' true prognostic and preventive significance.

These results imply that the correlation between GS and depression, particularly in cancer patients, is a multifaceted phenomenon with numerous linkages to physiological, psychological, and physiological aspects that make it difficult to fully understand. It is probable that physical limitations associated with reduced GS account for cancer patients' increased vulnerability to depressive symptoms. Conversely, higher GS may serve as a buffer, affecting coping strategies and resilience in the event of a cancer diagnosis.

The present study has strengths and limitations that have to be acknowledged when interpreting its findings. To the best of our knowledge, this is the first study analysing the moderating effect of GS in the association between cancer and depressive symptomatology. Also, in large sample studies, physical activity is often measured by self-reported questionnaires, which generally creates higher estimates than when derived from objective measures (Olds, 2019). A model with GS as a moderator measured by an objective physical fitness test constitutes strength in this study. On the other hand, a major limitation was the inability to consider several confounding factors, such as nutrition, cigarette smoking, alcohol use/abuse, history of depression and type of cancer. Despite the multi-national, large sample, the cross-sectional nature of the study limits the interpretation of the current findings in a cause-and-effect manner.

Conclusion

Muscular strength, as measured by GS, acts as a moderator of depressive symptomatology, attenuating its association with cancer. This supports the theory that recovery programs could include physical activity, namely muscle-strengthening exercises, to prevent depression. As a complex phenomenon, future should examine the

potential moderating influence of additional variables on these associations and should be able to consider more confounding variables.

Study II. Moderating effect of muscular strength in the association between cardiovascular events and depressive symptoms in middle-aged and older adults - a cross sectional study

Abstract

Background: Depression and cardiovascular diseases are two main health conditions contributing to the global disease burden. Several studies indicate a reciprocal association between them. It is still unclear how changes in overall muscle strength may impact this association. This study aimed to analyse how muscular strength moderates the relationship between cardiovascular events and depressive symptoms among middle-aged and older adults. *Methods:* Wave 8 of the population-based Survey of Health, Ageing, and Retirement in Europe (2019/2020) cross-sectional data, which included 41,666 participants (17,986 men) with a mean age of 70.65 (9.1) years old, was examined. Grip strength was measured twice on each hand using a dynamometer. The 12-item EURO- D scale was employed to gauge depressive symptoms. *Results:* Grip strength negatively moderates the link between cardiovascular events and depressive symptoms (male: B = −0.03, 95% CI = −0.04, −0.03; female: B = −0.06, 95% CI = −0.06, −0.05). Additionally, the grip strength moderation values in the significant zone for males and females were less than 63.2 kg and 48.3 kg, respectively. *Conclusions:* Muscular strength modifies depressive symptoms and lessens their correlation with cardiovascular diseases. Muscle-strengthening activities could be incorporated into primary and secondary preventive strategies to reduce the burden of depression in people with CVD.

Keywords: depression; elderly; grip strength; moderation; cardiovascular diseases.

Introduction

Depression and cardiovascular diseases (CVD) are two main health conditions contributing to the disease burden globally (Sultan-Taïeb, 2022). Depression can harm mental and physical health, hamper daily activities, and negatively impact the quality of life (Luo, 2018). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the diagnosis of depression requires five or more symptoms to be present within a 2-week period (Tolentino, 2018). One of the symptoms should, at least, be either a depressed mood or anhedonia. The secondary symptoms are appetite or weight changes, sleep difficulties, psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to think or concentrate, feelings of worthlessness or excessive guilt, and suicidality. Although depression is one of the top causes of disability worldwide, most who have depression still do not obtain effective treatment (Ormel, 2019). Althought there is significant variance between countries, the lifetime risk of depression is (at least) 10% (Bromet, 2011; Hasin, 2005), and in patients with CVD depression is estimated to be one in five (Blatch, 2023). According to statistical reports, nearly 45% of patients with CVD struggle with major depressive disorder (Rafiei, 2023). Furthermore, having comorbid depression is independently linked to a worse prognosis for people with CVD (Hare, 2023).

Both CVD and depression share common pathogenic mechanisms (Shiga, 2023). Increased levels of inflammatory markers (Warriach, 2022), abnormalities in sympathetic and parasympathetic activity (Pinter, 2019) and irregularities in hormone and neurotransmitter levels (such as cortisol and serotonin) (Dziurkowska, 2021) have all been linked to depression and CVD. Additionally, there is data indicating that the co-occurrence of these diseases may be influenced by similar genetic variables (Rome, 2022). Therefore, it is plausible that CVD is an important risk factor for depression. A

cardiovascular disease diagnosis or ongoing condition can result in substantial emotional anguish, worry, and depression. Furthermore, mood and mental health can be directly impacted by the physiological effects of cardiovascular disease on the brain and body as a whole (Huffman, 2013). Depression is associated with physiological changes, including increased inflammation, altered autonomic nervous system activity, and hormonal imbalances, which can contribute to the development and progression of CVD (Mattina, 2019). Prior research has demonstrated a significant rate of co-morbidity between depression and CVD, indicating a reciprocal association between the two conditions (Halaris, 2017; Harshfield, 2020; Rajan, 2020). Delivering physical exercise or physical activity may not only improve depression severity, but also directly tackle the constitutive elements of cardiovascular risk (Belvederi Murri, 2020). Several investigations have suggested that muscle strength is a plausible mechanism for these associations, as it has a protective effect to the development of CVD (Murri, 2020; Bucciarelli, 2023; Ozemek, 2018). Also, both dynapenia (muscle weakness) and depressive symptoms are common in the elderly population (Bertoni, 2018), altought women seem to live longer and with more years free of dynapenia than men (Borges, 2022). Dynapenia is often accompanied by increased inflammation and oxidative stress. Chronic inflammation and oxidative stress are common features of both depression and CVD (Gracia, 2017). Among middle-aged and older adults, grip strength (GS) may mediate the relationship between depression and the estimated 10-year risk of CVD (Lee, 2022). GS is a measure of overall body strength and it is also a maximum hand static force measure commonly used to capture muscular strength and monitor the health status in the general population, especially in older age (Bae, 2019)

As the world's population ages and life expectancy rises, it is increasingly important to consider middle-aged and older adults' health, including depression and

CVD. There is a substantial complexity in the associations between depression, GS, and CVD. Although some of these links are understood, it is still unclear how changes in GS, as a proxy for overall muscle strength, may impact the association between CVD and depression. The research question was established: among european middle-aged and older adults of both sexes, does GS have a moderating role in the relationship between depressive symptoms and CVDs? Towards the hypothesis that GS weakens the link between depressive symptoms and CVDs among European middle-aged and older adults, of both sexes, this study aimed to analyse how GS moderates the relationship between two major cardiovascular events, myocardial infarction and stroke, and depressive symptoms among middle-aged and older adults by sex.

Methods

Participants and Procedures

Data from wave 8 (2019/2020) of the population-based Survey of Health, Aging, and Retirement in Europe (SHARE) served as the foundation for this research. The SHARE methodology was previously detailed in (Borsch-Supan, 2013). It is a biennial survey that gathers data in several European nations and Israel. The target population consists of all people living in residential households who are 50 years of age or older, plus their (possibly younger) partners. Those who do not reside at the sampled address (e.g. because it was a seasonal or vacation residence), are physically or mentally unable to participate, died before the start of the field period, cannot speak the specific language of the national questionnaire, were excluded. The Ethics Council of the Max-Planck-Society for the Advancement of Science and the University of Mannheim Ethics Committee accepted the SHARE protocol. Written informed consent was obtained from all participants involved in the study.

A total of 41666 participants (17986 men and 23680 women), mean age of 70.65 (9.1) years old, from 29 different countries (Austria, Germany, Sweden, the Netherlands, Spain, Italy, France, Denmark, Greece, Switzerland, Belgium, Israel, the Czech Republic, Poland, Ireland, Luxembourg, Hungary, Portugal, Slovenia, Estonia, Croatia, Lithuania, Bulgaria, Cyprus, Finland, Latvia, Malta, Romania, and Slovakia) made up the final sample.

Measures

Depressive symptoms

Depressive symptoms, the outcome measure,. were assessed with the 12-item EURO-D scale. Scores vary from 0 to 12, with higher scores indicating more severe symptoms of depression. A cut-off ≥4 points indicates clinically significant depression (Gallagher, 2013; Prince, 1999b). The validation and explanation of the scale are covered elsewhere (Prince, 1999b).

Cardiovascular events

The exposure measure was being previously diagnosed with a cardiovascular event (stroke and/or myocardial infraction). Participants were asked to report being previously diagnosed with a cardiovascular event (stroke and/or myocardial infraction) by a medical doctor.

Grip Strength

The moderator employed was GS. Using a dynamometer, it was measured twice on each hand (Smedley, S Dynamometer, TTM, Tokyo, 100 kg), switching between the left and right hand (Roberts, 2011).Participants held their upper arm tightly against their bodies while standing or sitting, with the elbow at a 90-degree angle, the wrist in neutral, and the inner lever of the dynamometer set to the hand.After practicing, participants exerted the dynamometer's maximum pressure for 5 seconds. GS variable contained the

maximum value of the GS measurement of both hands. Values of two measures that differed by more than 20 kg were considered invalid. Measurements of GS that were equal to or more than 100 kg were excluded, as well as measurements where GS was only assessed once in one hand.

Co-variables

Covariates included sex, physical activity, hypertension, age, and country, which were self-reported. Physical activity was measured as ''frequency of moderate physical activity'' (e.g., gardening, cleaning the car, going for a walk) and ''frequency of vigorous physical activity'' (e.g., sports, heavy housework, a job involving physical labour). The response alternatives both for moderate and vigorous activity were: (1) more than once a week, (2) once a week, (3) up to three times a month, and (4) hardly ever or never. The last two response options were grouped into one category called less than once a week.

Statistical Analysis

Descriptive statistics, including mean and standard deviation for continuous variables and frequency for categorical variables, were calculated. The t-test (for continuous variables) and chi-square (for categorical variables) were used to compare participants' characteristics between sexes. An independent sample t-test and a Pearson correlation analysis were used to compare the depressive symptoms of men and women according to cardiovascular event diagnosis and to determine the relationship between GS and depressive symptoms. Based on the moderation methods suggested by Baron and Kenny (Baron, 1986), a moderated analysis of GS (moderator, W) on the connection between cardiovascular events (categorical, X) and depressive symptoms (continuous, Y) was conducted and unstandardized coefficients were presented. The moderation analysis was carried out using Andrew Hayes' PROCESS macro-3.5. The Johnson-Neyman method was used to evaluate statistically significant interactions and find regions of

significance. This process was also used to determine a threshold of statistical significance. Analysis was stratified by sex and adjusted for age. Data analysis was performed using IBM SPSS Statistics version 28 (SPSS Inc., an IBM Company, Chicago, Illinois, USA) for Apple Mac®. For all tests, the statistical significance was set at $p<0.05$.

Results

Participants characteristics

Table 1 presents the descriptive analysis. More women (30.5%) than men (18.3%) reported having depressive symptoms above cut off. In contrast, more men (18.4%) than women (12.4%) reported having a history of cardiovascular events (myocardial infarction and/or stroke). A total of 6262 men and women had at least one of the cardiovascular events (5153 myocardial infractions and 1548 strokes in total) were reported.

Table 1. Sample characteristics for the total sample and by sex.

	Mean (95% CI) or % (95% CI)			
	Total (*n*=41666)	Male (*n*=17986)	Female (*n*=23680)	p-value
Age (years)	70.65 (70.56, 70.73)	71.12 (70.99, 71.25)	70.29 (70.17, 70.41)	<.000
GS (kg)	32.04 (31.93, 32.14)	40.68 (40.54, 40.83)	25.47 (25.38, 25.55)	<.000
EURO-D score	2.32 (2.30, 2.34)	1.90 (1.87, 1.93)	2.63 (2.60, 2.66)	<.000
EURO-D ≥ 4				<.000
Yes [% (95% CI)]	25.3 (24.8, 25.7)	18.3 (17.8, 18.9)	30.5 (29.9, 31.1)	
No [% (95% CI)]	74.7 (74.3, 75.2)	81.7 (81.1, 82.2)	69.5 (68.9, 70.1)	
Hypertension				<.000
Yes [% (95% CI)]	45.1 (44.7, 45.6)	44.9 (44.1, 45.6)	45.3 (44.7, 46.0)	
No [% (95% CI)]	54.9 (54.4, 55.3)	55.1 (54.4, 55.9)	54.7 (54.0, 55.3)	
MPA				<.000
< 1x/week	18.5 (18.1, 18.8)	17.6 (17.0, 18.2)	19.1 (18.6, 19.6)	
1/week	14.9 (14.6, 15.3)	15.0 (14.5, 15.5)	14.9 (14.4, 15.3)	
> 1/week	66.6 (66.2, 67.1)	67.4 (66.7, 68.1)	66.0 (65.4, 66.6)	
VPA				<.000
< 1x/week	52.3 (51.8, 52.8)	48.5 (47.7, 49.2)	55.2 (54.6, 55.8)	
1/week	15.2 (14.8, 15.5)	15.0 (14.5, 15.5)	15.3 (14.9, 15.8)	
> 1/week	32.5 (32.1, 33.0)	36.5 (35.8, 37.2)	29.5 (28.9, 30.1)	
CVE*				<.001
Yes [% (95% CI)]	15.0 (14.7, 15.4)	18.4 (17.9, 19.0)	12.4 (12.0, 12.8)	
No [% (95% CI)]	85.0 (84.6, 85.3)	81.6 (81.0, 82.1)	87.6 (87.2, 88.0)	

Abbreviations: GS, grip strength; CVE, cardiovascular events;
*CVE is history of cardiovascular events (myocardial infarction and/or stroke)

Association between depression and cardiovascular health

The correlation analysis between GS and depressive symptoms showed that GS was significantly and negatively correlated with depressive symptoms for the total sample (r = -0.254, p<0.001), as well as for males (r = -0.193, p<0.001) and females (r = -0.210, p<0.001) separately.

Table 2 compares depressive symptoms between participants according to the history of cardiovascular events (myocardial infarction and/or stroke). Regardless of sex, participants with a cardiovascular event had higher mean depressive symptoms than participants without CVD (males: 2.53 vs 1.76, p<0.001; females: 3.55 vs 2.50, p<0.001).

Table 2. Comparison of depressive symptoms according to the history of cardiovascular events (myocardial infarction and/or stroke).

	Depressive symptoms (EURO-D 12 score)						
	Total		Male		Female		p-value
	Mean (SD)	Cohen's *d*	Mean (SD)	Cohens *d*	Mean (SD)	Cohens *d*	
CVE history	3.01 (2.39)	2.14	2.53 (2.21)	1.93	3.55 (2.47)	2.23	<.001
No CVE history	2.19 (2.09)		1.76 (1.85)		2.50 (2.19)		

Abbreviations: CVE, history of cardiovascular events (myocardial infarction and/or stroke); SD, standard deviation.

Moderating effect of grip strength

Table 3 presents the small moderating effect of GS (W) on the association between cardiovascular events (X) and depressive symptoms (Y). The link between cardiovascular events and depressive symptoms was negatively moderated by GS (male: B= -0.03, 95% CI = -0.04, -0.03; female: B= -0.06, 95% CI = -0.06, -0.05), meaning that greater GS led to a weaker association. The Johnson-Neyman test also revealed that the GS moderation values in the significant zone for males and females were less than 63.2kg and 48.3kg, respectively.

Table 3. Moderation analysis of grip strength for the relationship between cardiovascular events and depressive symptoms stratified by sex.

	Depressive symptoms (EURO-D 12 score)					
	Total sample		Male		Female	
	B	95% CI	B	95% CI	B	95% CI
CVE (X)	1.05	0.89, 1.21	1.13	0.84, 1.42	1.03	0.74, 1.33
Grip Strength (W)	-0.04	-0.04, -0.04	-0.02	-0.03, -0.02	-0.05	-0.05, -0.04
CVE*Grip Strength	-0.01	-0.02, -0.01	-0.01	-0.02, -0.01	-0.01	-0.03, -0.01

Abbreviations: CI, confidence interval; CVE, cardiovascular events

Discussion

This study aimed to analyse how GS moderates the relationship between two major cardiovascular events, myocardial infarction and stroke, and depressive symptoms among middle-aged and older adults. Results revealed that GS was positively related to lower depressive symptoms in middle-aged and older individuals. Furthermore, GS had a small moderating role in the association between CVEs and depressive symptoms in both men and women, possibly weakening its link to CVD.

Gender differences in depression have been extensively addressed over the past few decades. Our results support the evidence that women suffer more from depression than men (30.5% and 18.3%, respectively), which is in line with the majority of research that has found that women tend to experience depression twice as frequently as males do, independently of the culture (Bromet, 2011). The reasons for the disparities in depression between men and women include biological, psychological and social factors (Zhang, 2022).

Although using different methodologies, the negative correlation between GS and depression in this study matches other large-scale multinational studies carried out with older people (Oh, 2023; Wang, 2022). The association of GS with depressive symptoms seems significant and inverse in individuals with and without chronic diseases, namely, CVD (Marconcin, 2020). Findings also suggested that participants with a cardiovascular event diagnosis tend to present higher scores of depressive symptoms than those without it, both in males and females. Depression seems to be highly prevalent in cardiac patients (Karami, 2023). The fact that longer a person lives with CVD, the greater the cumulative psychological impact (Dar, 2019); the functional impairment caused by CVD can decrease the ability to engage in desired activities and lead to depression (Dhar, 2016); intensive treatments, medications, or invasive procedures used to manage severe CVD

can have physical and psychological side effects (Jain, 2017), could possibly explain how duration and intensity of CVD can affect depression and vice versa. There may be a physiological connection between CVD and depression, as prior research demonstrates the close relationship between these two clinical diseases (Okunrintemi, 2019). Although these relationships can be complex and multifaceted, several physiological mechanisms can also help explain the connections between these conditions and GS. Cardiovascular health is linked to GS through the muscle-heart axis (myokines production) (Pinckard, 2019); high GS may indicate a lower overall inflammatory and oxidative burden (contributing to better cardiovascular and mental health) (Petek, 2022); muscle strength exercises promote neuroplasticity and brain health, helping to mitigate the risk of depression by enhancing brain function and structure, as well as reducing the risk of cardiovascular diseases by improving cerebral blood flow and reducing vascular risk factors (Vecchio, 2018). Still, most underlying mechanisms underpinning the connection between these two illnesses are unknown (Shao, 2020). For instance, compared to people without CVD, CVD patients are more prone to experience depression.

GS moderated the relationship between depressive symptoms and cardiovascular events (myocardial infarction and stroke), slightly buffering this association for both males and females. According to the findings, people with cardiovascular events tend to suffer more from depression (presenting higher score values of depressive symptoms) and although the effect was small, having greater GS protected against depressive symptoms. It is important to note that, although the effect is significant, as it is small, intervention studies are needed that can analyze this moderation effect in terms of clinical practice. Nevertheless, once nearly 45% of patients with CVD present depressive symptoms (Rafiei, 2023) and it is estimated that depression is one in five in this population (Armon,

2023), improving muscule strength may be an effective non-pharmacological option to reduce the burden of depression in people with CVD.

According to the Johnson-Neyman test, this small moderation effect is present for GS values under 63.2kg for males and 48.3kg for females. In the elderly population, the GS measurement is more commonly used as a screen for sarcopenia, a very prevalent condition in this type of population. These results indicate that even for GS values lower than the cut-off for sarcopenia (<27kg for men and <16kg for women) (Cruz-Jentoft, 2019), strength seems to be a moderator of depressive symptoms. Even with an elderly person who continues to be at risk of being diagnosed with sarcopenia, interventions that increase their strength may have a small protective effect against depression, attenuating its symptoms.

When analysing the current results, it is important to consider their advantages and disadvantages. As far as we know, this is the first study to examine the moderating role of GS in the relationship between depressive symptoms and the two major cardiovascular events, myocardial infarction and stroke. Additionally, this study used an objective measure of physical fitness (i.e., GS) as a moderator, assessed by trained personnel. Self-reported questionnaires are frequently used in large sample studies to quantify physical activity or even, in some cases, physical fitness, which typically yields higher values than objective measures (Olds, 2019). Despite these strengths, several limitations must be acknowledged. First, the diagnosis of cardiovascular events, myocardial infarction and stroke were self-reported, which may lead to memory bias. Also, we did not measure the number of previous CVEs and did not you include current medication of participants. Second, the study's cross-sectional design restricts the interpretation of the current findings in a cause-and-effect way despite the big multinational sample. Lastly, another limitation was the inability to account for several

confounding variables, including important risk factors such as the history of depression, coronary heart disease, cigarette smoking and excessive alcohol consumption. Future research should consider testing more complex moderation models, where other variables are analyzed that may also be playing a moderating effect on these relationships. Other covariates that were not included in this study should also be included in these models. In any case, these results reinforce the evidence that, in the clinical context, strength training could be integrated into rehabilitation programs for this type of population.

Conclusion

GS, a proxy of muscular fitness, slightly buffers the association between cardiovascular events (myocardial infarction and stroke) and depressive symptoms. This supports the idea that physical activity, namely muscle-strengthening activities, may be incorporated into primary and secondary preventive strategies to reduce the burden of depression in people with CVD.

Study III. Moderating effect of grip strength in the association between diabetes mellitus and depressive symptomatology

Abstract

Background: Diabetes mellitus and depression rank among the leading causes of disease burden and are present in the top 10 causes of disability-adjusted life years worldwide. Numerous studies have shown that both depression and diabetes have a detrimental effect on the quality of life, and when they coexist, the effect is considerably worse. This study aimed to analyse how grip strength moderates the relationship between diabetes and depressive symptoms among middle-aged and older adults. *Methods:* 41,701 participants (18,003 men) were studied in wave 8 of the cross-sectional population-based Survey of Health, Aging, and Retirement in Europe (2019/2020) data. A dynamometer was used to test grip strength twice on each hand. Depressive symptoms were measured using the 12-item EURO-D scale. *Results:* The relationship between diabetes and depressed symptoms is negatively moderated by grip strength (male: B= -0.03, 95% CI = -0.04, -0.03; female: B= -0.06, 95% CI = -0.07, -0.06). Furthermore, the significant zone grip strength moderation values for males and females were less than 48.7 kg and 38.9 kg, respectively. *Conclusions:* Muscular strength moderated depressive symptoms, attenuating its association with diabetes. This supports the premise that physical activity, namely muscle-strengthening exercises, should be included in diabetes treatment programs.

Keywords: depression; elderly; grip strength; moderation; diabetes

Introduction

Chronic hyperglycemia is a hallmark of diabetes mellitus (DM), a metabolic disorder involving the metabolism of carbohydrates, proteins, and fats that has been extensively investigated (Sapra, 2023). Over the next ten years, the prevalence of DM is anticipated to rise by 25% globally, making it a rising public health concern (Saeedi et al., 2019).

Depression is a significant comorbid condition in DM (Wirkner, 2022). A sense of prolonged sadness and loss of interest are symptoms of depression, a mood illness. The typical symptoms include feelings of melancholy, emptiness, or irritability, along with physical and cognitive changes that majorly impact the person's ability to operate. (Chand, 2023). A key contributor to disability, depression lowers the quality of life, raises the chance of early death, and heavily strains healthcare systems (Archer, 2020). Different estimates show that depression could affect more than 300 million people worldwide (Chodavadia, 2023).

DM and depression rank among the leading causes of disease burden worldwide and are present in the top 10 causes of disability-adjusted life years worldwide (Habib, 2022). Evidence supports a bidirectional association between DM and depression (Alzoubi, 2018). DM increases the risk of depression by 15– 28% (Chireh, 2019). On the other hand, depression was confirmed as a risk factor for DM (34% and 60% risk increase) (Kozela, 2023). Numerous studies have shown that both depression and DM have a detrimental effect on the quality of life, and when they coexist, the effect is considerably worse (Bădescu, 2016; Jing, 2018; Paudel, 2023; Zurita-Cruz, 2018). Even when other known DM risk factors are considered, such as a poor diet, family history, inflammation, the use of some antidepressants, and a sedentary lifestyle, the elevated risk for DM associated with depression persists (Hunter, 2018).

Physical activity is any bodily movement produced by skeletal muscles that results in energy expenditure (Caspersen, 1985). Provides various benefits, including preventing chronic diseases, lowering the risk of depression, increasing physical strength, and reducing mental stress (Mahindru, 2023). Thus, among people with DM, physical activity may not only help alleviate depressive symptoms (Kandola, 2019) but also assist in achieving glycaemic control (Arsh, 2023). Regular physical activity helps regulate normal glucose uptake into peripheral tissues and increases insulin receptors and insulin sensitivity, thus contributing to the blood glucose control (Kim, 2018). From all the health-related components of physical fitness (Caspersen, 1985), muscular strength has been researched recently regarding its relationship with middle-aged and older adults' mental health (Volaklis, 2019). Muscle strength seems to be inversely correlated with depression and cognitive performance in middle-aged and older adults (Cabanas-Sánchez, 2022; Shin, 2022), emphasising the value of exercise and physical fitness in preventing depression. Grip strength (GS) has been considered a legitimate and trustworthy measure of overall muscle strength and one's physical and mental health (Oh, 2023).

Given that the prevalence of both DM and depression is increasing in the middle-aged and older adults'group (Laiteerapong, 2018; Zhang, 2023) and the causes and relationship remain rather complex and understudied (Sartorius, 2018), this study aimed to analyse how GS moderates the relationship between DM and depressive symptoms among middle-aged and older adults.

Methods

Participants and Procedures

Data from the Survey of Health, Aging, and Retirement in Europe (SHARE) wave 8 data (2019/2020) was used. Borsch-Supan (2013) provided a full explanation of the SHARE survey and methodology. This survey gathers data on adults 50 and above every two years in European countries and Israel. The target population consists of all people living in residential households, plus their (possibly younger) partners. Those who do not reside at the sampled address (e.g. because it was a seasonal or vacation residence), are physically or mentally unable to participate, died before the start of the field period, cannot speak the specific language of the national questionnaire, were excluded. The SHARE protocol was approved by the University of Mannheim Ethics Committee and the Ethics Council of the Max-Planck-Society for the Advancement of Science. The study's participants all provided their written, informed consent.

There were 41701 participants (30224 aged ≥65), 18003 men and 23698 women,, with a mean age of 70.65 (9.1) and coming from 29 different countries (Austria, Germany, Sweden, the Netherlands, Spain, Italy, France, Denmark, Greece, Switzerland, Belgium, Israel, the Czech Republic, Poland, Ireland, Luxembourg, Hungary, Portugal, Slovenia, Estonia, Croatia, Lithuania, Bulgaria, Cyprus, Finland, Latvia, Malta, Romania, and Slovakia).

Measures

The outcome measure was depressive symptoms. The EURO-D 12-item scale was used to quantify depressive symptoms. Scores range from 0 to 12, with higher numbers denoting more severe depressive symptoms. A cut-off ≥4 points indicates clinically significant depression (Gallagher, 2013; Prince, 1999b). The scale's validation and justification are discussed elsewhere (Prince, 1999b). The exposure measure was DM.

The existence or absence of DM that a doctor had previously diagnosed was inquired of the participants. GS was the moderator in use. It was measured twice on each hand using a dynamometer (Smedley, S Dynamometer, TTM, Tokyo, 100 kg), switching between the left and right hands (Roberts, 2011). The inner lever of the dynamometer was set to the hand. Participants kept their upper arm tightly against their bodies while standing or sitting, with the elbow at a 90-degree angle, the wrist in neutral, and the elbow snugly against their body. Participants exerted the dynamometer's maximum pressure for 5 seconds. Before the assessment, participants had the option to practice. GS variable contained the maximum value of the GS measurement of both hands. Values of two measures that differed by more than 20 kg were considered invalid. Measurements of GS that were equal to or more than 100 kg were excluded, as well as measurements where GS was only assessed once in one hand. Sex and age were the self-reported covariates.

Statistical Analysis

Descriptive statistics (mean, standard deviation, and frequency) were calculated for all variables. The depressive symptomatology of men and women according to DM diagnosis, as well as the association between GS and depressive symptomatology, were compared using an independent sample t-test and a Pearson correlation analysis, respectively. Using the suggestions for moderation made by Baron and Kenny (Baron, 1986), a moderated analysis of GS (moderator, W) on the connection between DM (categorical, X) and depressive symptoms (continuous, Y) was conducted. The moderation analysis was carried out using Andrew Hayes' PROCESS macro-3.5. The Johnson-Neyman method was used to evaluate statistically significant interactions and find regions of significance. This process was also used to determine a threshold of statistical significance. Analysis was stratified by sex and adjusted for age. Data analysis

was performed using IBM SPSS Statistics version 28 (SPSS Inc., an IBM Company, Chicago, Illinois, USA). For all tests, the statistical significance was set at $p<0.05$.

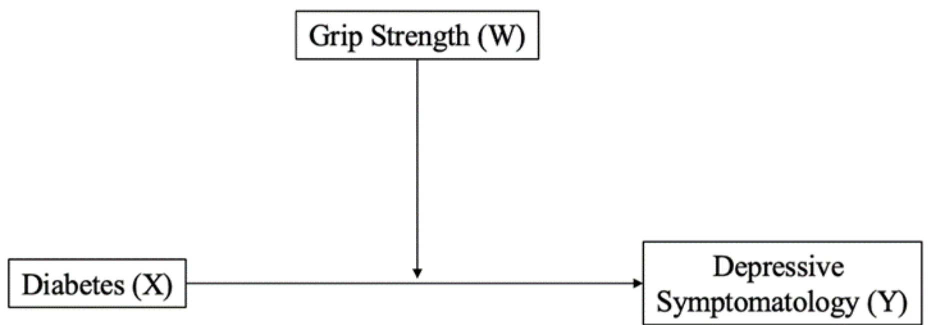


Figure 1. A conceptual diagram of the relationship between diabetes (X) and depressive symptomatology (Y) moderated by grip strength (W).

Results

The descriptive analysis is presented in Table 1. Women (45.6%) reported having depressive symptoms more frequently than men (29.6%). Men, however, were more likely than women to report having been diagnosed with DM (16.2% vs. 12.7%).

Table 1. Sample characteristics for the total sample and by sex.

	Mean (SD) or n (%)		
	Total (n=41701)	Male (n=18003)	Female (n=23698)
Age (years)	70.65 (9.1)	71.1 (8.8)	70.3 (9.4)
Grip strength (kg)	32.0 (11.2)	40.7 (10.0)	25.5 (6.7)
EURO-D score (n)	2.3 (2.2)	1.9 (1.9)	2.6 (2.3)
Diabetes			
Yes n (%)	5932 (14.2)	2918 (16.2)	3014 (12.7)
No n (%)	35769 (85.8)	15085 (83.8)	20684 (87.3)
Depression			
Yes n (%)	16130 (38.7)	5331 (29.6)	10799 (45.6)
No n (%)	25571 (61.3)	12672 70.4)	12899 (54.4)

Abbreviations: SD, standard deviation;

Table 2 presents the relationship between GS and depressive symptoms. GS was negatively correlated with depressive symptoms for the entire sample ($r = -0.254$, $p<0.001$) as well as for males and females separately ($r = -0.193$, $p<0.001$ VS $r = -0.210$, $p<0.001$).

Table 2. Pearson correlation between grip strength and depressive symptomatology.

	Depressive symptoms (EURO-D 12 score)					
	Total		Male		Female	
	r	p-value	r	p-value	r	p-value
Grip strength	-0.254	<0.001	-0.193	<0.001	-0.210	<0.001

The depressive symptoms of patients with and without DM are presented in Table 3. The mean depressive symptomatology was higher in people with DM than those without DM, regardless of sex (males: 2.53 vs 1.76, $p<0.001$; females: 3.55 vs 2.50, $p<0.001$).

Table 3. Comparison of depressive symptomatology according to the presence or absence of diabetes.

	Depressive symptoms (EURO-D 12 score)					
	Total		Male		Female	
	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value
With diabetes	2.71 (2.32)	<0.001	2.18 (2.08)	<0.001	3.22 (2.43)	<0.001
Without diabetes	2.25 (2.12)		1.85 (1.92)		2.54 (2.21)	

The moderating role of GS (W) in the relationship between DM (X) and depressive symptoms (Y) is shown in Table 4. (male: B= -0.03, 95% CI = -0.04, -0.03; female: B= -0.06, 95% CI = -0.07, -0.06) means that higher GS resulted in a reduced

correlation between DM and depressive symptoms. Additionally, the Johnson-Neyman test showed that the GS moderation values for males and females in the significant zone were less than 48.7 kg and 38.9 kg, respectively.

Table 4. Moderation analysis of grip strength for the relationship between diabetes and depressive symptomatology stratified by sex.

	Depressive symptoms (EURO-D 12 score)					
	Total sample		Male		Female	
	B	95% CI	B	95% CI	B	95% CI
Diabetes (X)	0.94	0.77, 1.11	0.67	0.35, 0.98	0.98	0.67, 1.29
Grip Strength (W)	-0.04	-0.05, -0.04	-0.03	-0.04, -0.03	-0.06	-0.07, -0.06
Diabetes*Grip Strength	-0.02	-0.02, -0.01	-0.01	-0.02, 0.00	-0.02	-0.03, -0.01

Abbreviations: CI, confidence interval

Discussion

This study investigated how GS affects the relationship between depressive symptomatology and DM in middle-aged and older individuals. According to the findings, depressive symptoms were significantly higher in both men and women with DM and GS was significantly associated with lower depressive symptoms. When getting a DM diagnosis, GS reduced depressive symptoms, moderating the relationship between them and DM.

Depression is more common in women than in men. According to research, women are roughly twice as likely as men to experience depression throughout their lifetime (Kuehner, 2017). This sex difference in depression prevalence aligns with our results reporting that women suffer more from depression than men (45.6% and 29.6%, respectively). The reasons for this disparity are multifaceted and may involve a combination of biological, psychological, and sociocultural factors (Remes, 2021).

Our results have shown a negative correlation between GS and depressive symptoms, meaning that as GS increases, the severity of depression tends to decrease.

Various studies also observe this association (Zasadzka, 2021; Zhang, 2022). The exact mechanisms underlying this correlation have yet to be fully understood, but several potential explanations exist. For groups with co-occurring mental and physical health issues, and once that it is often considered a proxy for overall physical health and functional fitness, GS might offer four advantages: (1) It might lessen depressive symptoms through biological and psychosocial mechanisms, (2) It might enhance physical health by treating the comorbid illness itself or by avoiding its secondary effects, (3) It may be that individuals with better physical health, including muscle strength, have a more robust physiological response to stress and are better equipped to cope with depressive symptoms, (4) it might also reflect individuals who are involved in physical activities that confer mental health and well-being benefits (Arsh, 2023).

The guidelines of scientific societies indicate that a substantial proportion of patients are diagnosed with a psychiatric disorder (Jung, 2021). Given the chronic nature of DM, along with the daily management tasks and potential complications, people with DM have a higher risk of developing depression compared to the general population (Deischinger, 2020). The constant need for self-management can be stressful and overwhelming, contributing to frustration and anxiety. Our research reveals that in men and women, participants with DM tended to present higher scores of depressive symptomatology than those without it. This increased risk can be attributed to various factors related to living with DM. Through dysregulation of the hypothalamic-pituitary-adrenal axis, hyperactivity of the autonomic nervous system, and inflammatory processes, depression and type 2 DM share biological roots. Type 1 DM patients may be more vulnerable to depression if they have a long-lasting disease from a young age when their personalities are also forming (Habib, 2022).

A moderator is a variable that can influence or modify the relationship between two other variables, in this case, DM and depressive symptomatology. Our findings demonstrate that for both males and females, GS modifies the link between depressive symptomatology and DM. B's negative value reveals that the association is unfavourable. This indicates that rather than negating the link between these two variables, the moderating effect weakens it. According to these findings, those who have DM typically experience more depression than those who do not (higher score values for depressive symptoms). Nevertheless, among those who do, individuals with greater muscular strength, as determined by GS, tend to experience less suffering (show lower scores of depressive symptoms) than those with lesser muscular strength. According to the Johnson-Neyman test, this moderation effect is present for GS values below 48.7 kg for men and 38.9 kg for women.

Several things could justify that individuals with more muscular strength may be less susceptible to the detrimental psychological effects of DM. A physically active lifestyle and improved mental health frequently correlate with a stronger GS (Pan, 2022). Based on preliminary data, resistance training appears beneficial for enhancing the majority of life quality domains, handgrip strength, lower and upper limb muscle strength, and depression in middle-aged and older adults (Kashi, 2023). Regular exercise, including strength training, can lessen stress and lessen the symptoms of depression. In parallel, strength exercise can boost self-efficacy and self-confidence while helping to improve GS (Medrano-Ureña, 2020). These psychological elements may protect from the emotional strain of managing DM. Also, exercise and strength training, in general, are efficient stress-reduction methods (Churchill, 2022). Regular strength training may help people with DM cope better with the pressures of the condition, thus lowering the risk of depression.

The moderating impact of GS on depressive symptomatology may not be the same for every DM patient. It's conceivable that the degree to which GS moderates the association between DM and depression varies depending on things like DM severity (the moderating effect may be more prominent in people with poorly controlled DM or those who have had the condition for a longer period), individual resilience (the effect of DM on depression may depend on an individual's psychological resilience, coping mechanisms, and social support system), and ageing (GS usually weakens with age and younger people with DM may experience a different moderating impact than middle-aged and older persons).

The strengths and limitations of the existing results should be considered when analysing them. Regarding limitations, the study's cross-sectional design cannot prove causality because it is mainly descriptive. The direction of causality or the existence of underlying causal mechanisms cannot be determined. However, they can spot relationships or correlations between variables. Another limitation was the inability to account for several confounding factors, such as smoking use/abuse, educational level, diet or physical activity levels. Regarding strengths, this is the first investigation, as far as we are aware, on the moderating effect of GS in the association between depressive symptoms and DM. In this study, physical fitness was measured by an objective measure (i.e., GS) acting as a moderator and assessed by an impartial physical fitness test. Objective measures provide precise and accurate data, reducing the potential for measurement error or bias. They offer clear and quantifiable results that can be consistently obtained across different assessments and evaluators (Ramsey, 2021). It also constitutes a strength that this study was with a multinational sample. Multinational samples capture a wide range of cultural, social, and economic viewpoints and produce conclusions more generally applicable to a global environment. Because they are less

likely to be impacted by peculiar or regional characteristics, results from international samples are frequently more solid and reliable. The validity of results is strengthened by consistency across various populations (Faber, 2014).

Research into the relationship between muscular strength and depression in people with DM is underway. This study highlights the possibility that, even when diagnosed with DM, persons with higher grip strength values may have a mitigating effect on depressive symptoms. There is already evidence that suggests GS may lessen depression in people with DM, but further studies are required to understand the processes at work and to pinpoint the precise circumstances in which this moderation takes place. This link is complicated and not entirely clear. It's crucial to understand that DM patients' despair is not solely influenced by their GS. Future research in this area should consider that other elements, like glycemic control, healthcare access, social support, and psychological elements, can also greatly impact how depression develops and is treated in this population. A specific focus should be placed on middle-aged and older individuals because DM and depression are becoming more prevalent in this age group. Due to the anticipated rise in the population's senior citizens, who have a high prevalence of DM, this is especially significant.

Conclusion

GS, a proxy of muscular fitness, slightly buffers the association between cardiovascular events (myocardial infarction and stroke) and depressive symptoms. This supports the idea that physical activity, namely muscle-strengthening activities, may be incorporated into primary and secondary preventive strategies to reduce the burden of depression in people with CVD.

DISCUSSION

This research project aimed to analyze whether GS moderates the relationship between chronic diseases (cancer, CVD, and DM) and depressive symptomatology among middle-aged and older adults in Europe. According to the findings, while the effect seems modest and the relationship between chronic diseases, depression, and muscle strength are intricate and dynamic, GS seems to play a moderating role in these associations. Despite the existing relationship between depression and chronic diseases (cancer, CVD and DM), GS moderates this relationship, attenuating the effects of these diseases on depressive symptoms.

Our results report that women suffer more from depression than men. Gender differences in depression have been extensively studied over the past few decades, revealing that women are approximately twice as likely as men to experience depression throughout their lifetime, irrespective of cultural factors (Kuehner, 2017). The reasons for this disparity are multifaceted and may involve a combination of biological, psychological, and sociocultural factors (Remes, 2021). Concerning biological causes that may account for this difference, especially regarding physical health, it is notable that in this project's analysis, the prevalence of chronic diseases (cancer, cardiovascular disease, and DM) consistently appeared to be lower in women compared to men. This observation raises the hypothesis that, within this sample, while women have a lower prevalence of chronic diseases, they may face higher exposure to psychological and sociocultural factors contributing to their increased susceptibility to depression. Particularly in economically developed countries, which constitute the majority of the sample, women appear to experience greater stress, influenced by lifestyle choices, individual coping mechanisms, trauma, and early life experiences - factors predominantly classified as psychological influences (Matud, 2020). Sociocultural factors may also

contribute to individuals, particularly women, residing in developed countries facing heightened exposure to social isolation, loneliness, urbanization, and disconnection from nature (Brandt, 2022).

Our findings indicate a slight negative correlation between GS and depressive symptoms, suggesting that as GS rises, the severity of depression tends to decrease. These results align with other large-scale multinational studies conducted among middle-aged and older adults living with chronic diseases. Indeed, the link between muscle strength and depression is frequently documented in the literature (Oh, 2023; Wang, 2022; Zasadzka, 2021).

Across the three studies presented, a statistically significant difference was observed in depressive symptomatology between individuals diagnosed with a chronic disease (such as cancer, CVD, or DM) and those without such a diagnosis. This suggests that, as anticipated, individuals living with cancer, CVD, or DM are more susceptible to depression compared to those without these conditions. Specifically, cancer appears to be correlated with depressive symptomatology, with its severity being more pronounced in middle-aged and older adults (Wang, 2020). While not specifically examined in the present study, this association seems to persist irrespective of the specific type of cancer, sample size, and sociodemographic characteristics (Aminisani, 2017; Zhang, 2021). Previous research has also established a strong correlation between CVD and depression (Okunrintemi, 2019). Similarly, DM is associated with an increased risk of developing depression compared to the general population (Deischinger, 2020). Our findings are consistent with these previous findings.

A moderator is a variable capable of influencing or altering the relationship between two other variables: chronic diseases and depressive symptomatology. Our findings indicate that, although the effect size is small, GS acts as a moderator in the

relationship between cancer, CVD, DM, and depressive symptomatology for males and females. The relatively small moderation effect observed across all three studies could be attributed to the sample size (resulting in high variance) and the omission of other potential contributors to depression in the analysis.

It is plausible that the relationship, examined through a simple moderation model in our current studies, is complex, dynamic and influenced by several other variables. Nevertheless, despite the complexity of underlying factors contributing to depression, we consistently observe the moderation effect, suggesting that the effect may be substantial for certain individuals. Despite these limitations, all three studies identified a statistically significant moderating effect, underscoring the importance of incorporating muscular strength, particularly GS, into future moderation models to assess these relationships.

It is noteworthy that even among individuals diagnosed with a chronic disease, those with higher levels of muscle strength, as measured by GS, exhibit lower levels of depressive symptoms. Our results indicate that the moderation effect is more pronounced at lower muscle strength levels than higher levels. This insight could be valuable for professionals working in clinical settings with individuals affected by the diseases studied here or associated risk factors.

It's reasonable to expect that not every individual with cancer, CVD, or DM will experience the same degree of benefit from the moderating influence of GS on depressive symptomatology. Various factors may influence the extent to which GS modifies the relationship between chronic diseases and depression. For instance:

- Individual resilience: The impact of chronic disease on depression may hinge on an individual's psychological resilience, coping mechanisms, and social support system (Mei, 2023). Those with robust resilience and strong

support networks may experience a lesser impact of chronic disease on depression, potentially altering the effectiveness of GS as a moderator;

- Ageing: Given that GS typically declines with age, younger individuals with chronic diseases may encounter a different moderating effect than older adults (Laird, 2019). The influence of GS on depression may vary across different age groups due to differences in physical capabilities and resilience to age-related changes.
- Disease severity: The moderating effect of GS may be more pronounced in individuals with poorly managed disease symptoms or those who have lived with the condition for an extended period (Ma, 2021). The severity of the chronic disease and its impact on overall health may influence the degree to which GS mitigates depressive symptoms.

Considering these factors, it's essential to recognize the nuanced interplay between GS, chronic diseases, and depression, as well as the diverse experiences of individuals affected by these conditions.

Regardless the fact that there is a moderation effect (in a cross-sectional analysis) does not imply that, for a given individual, increasing strength will reduce the risk of depression. This would assume a causal mechanism that these studies, given their methodology, cannot assess.

As far as we are aware, these studies represent the first attempts to analyze the potential moderating effect of GS on the relationship between chronic diseases (such as cancer, CVD, and DM) and depression. This information is significant, as existing literature highlights the importance of considering not only an individual's age and gender but also any potential chronic diseases when examining the relationship between muscular strength and depression (Marconcin, 2020). Furthermore, prior studies

examining the association between muscle strength and depression did not account for other diagnoses, particularly chronic diseases such as those assessed in our analysis (Kim, 2022; Marques, 2021; Oh, 2023). Indeed, previous studies typically utilized samples of middle-aged and older adults, but these individuals were not necessarily diagnosed with a chronic disease (Marques, 2020; Zheng, 2022).

GS is correlated with strength in other body compartments and functions, making it a marker for overall strength. For instance, it is commonly utilized in the diagnostic criteria for sarcopenia. The cutoff values for muscle strength in diagnosing sarcopenia are <27 kg for men and <16 kg for women (Cruz-Jentoft, 2019). The Johnson-Neyman test, employed in all three studies, demonstrated that this moderation effect holds for GS values below <48.5 kg for men and <38.9 kg for women. Thus, there's a strong likelihood that, regardless of gender, even individuals who improve their strength (as measured by GS) above the sarcopenia cutoff value may experience additional "protection" against depression. Physically, the objective would be to increase an individual's strength until they reach the minimum muscular strength cutoff. Incorporating a psychological perspective while maintaining this objective, it's essential to recognize that even if this threshold is not yet attained, efforts to enhance strength may already contribute to reducing depressive symptomatology. Nevertheless, future investigations are warranted to elucidate the true preventive significance of these values.

Although the moderation effect of GS in the relationship between cancer, CVD, DM, and depression appears to be a multifaceted phenomenon involving various interactions with physical and psychological factors, several hypotheses can be proposed regarding potential explanatory mechanisms. It is plausible to suggest that muscular strength may alleviate depressive symptoms through both physiological and psychosocial mechanisms.

Regarding physiological mechanisms, depression has been associated with systemic inflammation, often stemming from conditions such as DM, cancer, and CVD (Beurel, 2020). It is plausible that muscle strength plays a role in mitigating inflammation, thereby reducing inflammatory markers in the body. For individuals grappling with cancer, CVD, or DM, bolstering muscular strength may alleviate depression symptoms by dampening inflammatory responses. Furthermore, muscle strength has been shown to release increased neurotransmitters such as norepinephrine, dopamine, and serotonin, which uplift mood and alleviate depressive symptoms (Basso, 2017).

Concerning cancer, the release of endorphins, acting as natural anxiolytics and mood elevators, is attributed to muscle strength (Ferioli, 2018). Studies have demonstrated that muscular strength elevates levels of brain-derived neurotrophic factor (Sleiman, 2016), a protein crucial for neuronal growth and maintenance, and fosters endorphin release, which naturally enhances mood and mitigates depressive symptoms in cancer patients. Enhanced levels of brain-derived neurotrophic factor have been correlated with improved mood and cognitive function, potentially aiding in depression reduction among cancer patients (Ng, 2023). Moreover, muscle strength seems to improve immunological function, often compromised in cancer patients (Gustafson et al., 2021), thereby reducing susceptibility to infections, and fortifying the body against cancer therapies' adverse effects, consequently enhancing overall health and potentially alleviating depressive symptoms. Additionally, research indicates that strength training can elevate general energy levels and mitigate cancer-related fatigue, a common side effect of cancer treatment (Misiąg, 2022).

Muscle strength is also linked to enhanced cardiovascular health by augmenting blood flow and cardiac function and reducing blood pressure (Pinckard, 2019), a pivotal risk factor for CVD. Improved blood flow to the brain may elevate mood and bolster

cognitive performance, potentially alleviating depression symptoms in individuals with cardiovascular diseases.

In DM, muscle strength augments the body's capacity to metabolize glucose and respond to insulin (Thyfault, 2020). Given that fluctuating blood sugar levels can exacerbate depressive symptoms, this is particularly beneficial for individuals with DM. Strengthening muscles may indirectly alleviate depression by enhancing metabolic health in these individuals.

In relation to psychosocial mechanisms and given that a physically active lifestyle improves mental health and frequently correlates with stronger GS (Pan, 2022), individuals with higher levels of muscular strength might be better at managing the difficulties brought on by chronic diseases. Maintaining a healthy lifestyle is often imperative for managing chronic diseases, and prioritizing physical strength can be viewed as a proactive measure. Engaging in strength training not only enhances neuroplasticity (Sun, 2019) – the brain's ability to adapt and reorganize in response to new experiences - but also empowers patients with cancer, CVD, and DM by instilling a sense of control over their health, thereby bolstering their self-efficacy beliefs. Furthermore, developing muscular strength can improve physical appearance and body image, potentially boosting self-esteem and cultivating a more positive self-concept. Individuals with chronic diseases may grapple with body image concerns linked to their condition, such as weight fluctuations or changes in physical appearance due to medication side effects.

Moreover, participating in group strength training programs can provide valuable social support for individuals with chronic diseases (Kennedy, 2022). Establishing connections with others facing similar health challenges can mitigate feelings of loneliness and isolation, both of which exacerbate the risk of depression.

In addition to improving sleep quality, which positively influences mood and mental well-being, regular strength training, particularly strength training, can enhance the overall quality of life (Kovacevic, 2018) and equip individuals with chronic diseases with healthy coping strategies to navigate the psychological and physical hurdles associated with their condition.

These psychological elements may protect from the emotional strain of managing a chronic disease.

Strengths and limitations

When evaluating the conclusions of this thesis, it's crucial to consider its strengths and weaknesses. Overall, while the present thesis provides valuable insights into the moderation effect of GS on the relationship between chronic diseases and depression, acknowledging these strengths and limitations is essential for a comprehensive interpretation of the findings.

One potential source of bias is the reliance on self-reported diagnoses of cancer, CVD, and DM, which may introduce inaccuracies or inconsistencies. Additionally, crucial details such as the individuals' current medication regimen, the specific type of DM (type I or II), the number of prior CVD events, or the subtype of cancer were not assessed, which could have provided valuable context and insight into the relationship between chronic diseases and depressive symptomatology.

Moreover, the study's cross-sectional design restricts the ability to establish causal relationships between variables, highlighting the need for future longitudinal studies to elucidate the underlying mechanisms. Furthermore, assessing depressive symptoms using the EURO-D scale may introduce limitations, as the longitudinal stability of this measure

requires further investigation by future research (de la Torre-Luque, 2019). For this reason, it was not methodologically advisable for the study design to be longitudinal.

Although the participants were middle-aged and older, separate analyses could have been conducted according to age groups (< 65 years and age ≥ 65 years). This approach would have helped to ascertain whether the moderation effect varies according to age. A further drawback was the use of different covariables depending on the study. Some significant covariates received no analysis at all, such as a history of depression, coronary heart disease, cigarette smoking, excessive alcohol consumption, and body mass index. This deliberate methodological choice appears to simplify a relationship that we know in advance is complex. However, it allowed us to ensure a significant sample power. We acknowledge that many of the unanalyzed covariates are linked to chronic diseases, muscular strength, and depression, potentially altering these relationships. However, due to the nature of the available data, including them would have significantly reduced the sample size. We prioritized ensuring a substantial multinational sample size.

Despite these limitations, the studies in this thesis also have several strengths. One strength lies in the large international sample utilized in the studies, providing broad representation and potential generalizability of findings. Additionally, including the Johnson-Neyman test allowed for a nuanced examination of the moderation effect of GS across different cutoff values, enhancing the depth of analysis.

To the best of our knowledge, this research is the first to examine the moderating role of GS in the relationship between depressive symptoms and three chronic diseases (cancer, CVD, and DM). Furthermore, GS, an objective measure of physical fitness evaluated by qualified staff, was used as a moderator. Large-sample studies often rely on self-reported questionnaires to measure physical activity and, in certain circumstances, physical fitness, which typically yield higher values than objective tests (Olds, 2019).

Indeed, the utilization of an international sample is another notable strength of this study. Multinational samples provide insights that are more widely applicable on a global scale, as they encompass diverse cultural, social, and economic perspectives. Notably, remarkable or regional features are less likely to impact the results from international samples, rendering them more consistent and reliable (Faber, 2014).

Perspectives and future research

Certainly, investigating the longitudinal stability of the EURO-D structure would be an important component of future research to consider, especially given the known tendency for depressive symptomatology to become chronic with age. This aspect becomes particularly relevant due to the cross-sectional design of the study. By examining how the structure of the EURO-D scale holds up over time, researchers can gain valuable insights into the trajectory and persistence of depressive symptoms among middle-aged and older adults. This longitudinal approach would contribute to a deeper understanding of the progression of depressive symptomatology and its implications for mental health interventions and treatment strategies over the lifespan (de la Torre-Luque, 2019). Future research should examine the EURO-D scale's invariance across different age groups and nations. Demonstrating the scale's invariance is crucial for conducting cross-cultural comparative research on depressive symptoms effectively. By ensuring the scale's validity and reliability across diverse populations, researchers can mitigate potential methodological artefacts and cultural biases, thus enhancing the comparability and generalizability of findings. This approach will facilitate a more comprehensive understanding of depressive symptomatology across various cultural and demographic contexts (Castro-Costa, 2008; Maskileyson, 2021; Prince, 1999a).

The findings of this thesis suggest that, even within the context of cancer, DM, and CVD, muscle strength seems to exert a protective influence against depressive symptoms. While existing evidence indicates that GS may mitigate depression in individuals with chronic diseases, further research is warranted to fully understand the underlying mechanisms and identify the specific conditions under which this moderation effect occurs. The literature highlights the necessity for additional studies to explore the mechanisms underlying the relationship between depression and GS, as well as potential moderators such as age, sex, and the presence of chronic disease. By delving deeper into these factors, researchers can enhance our understanding of how muscle strength intersects with depressive symptomatology in chronic illness, thereby informing targeted interventions and therapeutic approaches. (Ganipineni, 2023).

The connection between depression and chronic diseases is indeed complex and multifaceted. It's essential to recognize that depression in individuals with chronic diseases is influenced by various factors beyond just muscle strength. Future studies in this field should consider the broader context and acknowledge that other factors, such as physical activity levels, glycemic control, access to healthcare, and psychological factors, may also play significant roles in the development and management of depression in this population.

Future research should incorporate experimental designs to enable a clearer cause-and-effect interpretation of these relationships. By doing so, researchers can better elucidate the mechanisms underlying the relationship between chronic diseases and depression, as well as the potential moderating effects of factors like muscle strength.

Given the increasing prevalence of chronic diseases and depression among middle-aged and older individuals, this population should receive particular attention in future research endeavours. Understanding the complex interplay between these factors

is crucial for developing effective interventions and strategies to prevent and manage depression in individuals with chronic diseases.

CONCLUSION

Due to the stigma surrounding mental health disorders, depression often goes underdiagnosed and undertreated. According to our findings, GS moderates the association between depression and chronic diseases, including cancer, CVD, and DM, in both men and women. Individuals diagnosed with one of these conditions tend to exhibit higher scores for depressive symptomatology compared to those without them. However, among those diagnosed, individuals with higher levels of muscle strength, as determined by GS, demonstrate lower scores for depressive symptomatology than those with lower levels of general strength. Additionally, our results suggest that this moderation effect is even more pronounced for individuals with low levels of muscle strength.

Given the multifaceted nature of the moderation effect, which involves various relationships with physiological and psychological factors, it is reasonable to assume that not all patients with cancer, CVD, or DM will experience the same benefits from GS's moderating influence on depressive symptomatology. Further research is needed to understand the true preventive implications of this relationship. Nonetheless, increasing overall muscle strength - particularly through GS - appears to be a valuable non-pharmacological strategy for mitigating the significant effects of depression in this specific population.

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APPENDICES

Appendix 1. SHARE ethics approvals.

M A X - P L A N C K - G E S E L L S C H A F T

Ethikrat – Kommission des Präsidenten

Max-Planck-Gesellschaft, Postfach 10 10 62, 80084 München

Ethikrat der MPG
Der Vorsitzende
Prof. Dr. R. Wolfrum

Geschäftsstelle GV
Ulrich Braun Ref. VII b
Tel.: 089 21 08 - 1843

June 8th 2021

To
Daniel Schmidutz (M.A.)
Munich Center for the Economics of Aging (MEA)
Max Planck Institute for Social Law and Social Policy
Amalienstrasse 33
80799 Muenchen, Germany

Opinion of the Ethics Council of the Max Planck Society on the "SHARE" Project

The SHARE project has been running since 2002. It was originally established at the Mannheim Research Institute for the Economics of Aging (MEA) of the University of Mannheim. Since 2011, it is being operated under the umbrella of the Max Planck Society at the Max Planck Institute for Social Law and Social Policy and is centrally coordinated by the Munich Center for the Economics of Aging. As a result, the research-ethical assessments of the project, which were previously carried out by the University of Mannheim (see ethics committee decisions dated 13.12.2004, 16.12.2008 and 28.6.2010), were taken over by the Ethics Council of the Max Planck Society. The Council first dealt with parts of the project at its meeting on 19.10.2011 – not conclusively – and later at its meetings on 15.2.2012, 13.6.2012, 19.2.2014, 23.2.2016, 14.6.2018, 29.5.2020 and 8.6.2021(Waves 4-9) in detail. In the process, the overall concept with its interdisciplinary and international approach was also scrutinized in an appropriate scope. The Ethics Council came to the unanimous conclusion that the overall project design as well as the subprojects it assessed – e.g., the 1st and 2nd SHARE Corona Survey (SCS), the SHARE-HCAP sub-study, the SHARELIFE questionnaire or the sampling and analysis of dried blood spots since Wave 4 – did not raise any research-ethical concerns as regards design and foreseen practical implementation. Upon recommendation of the Ethics Council, data protection concerns were clarified with the Data Protection Officer of the Max Planck Society.

Numerous approvals and votes by other ethics committees in the participating SHARE countries – in particular, with regard to the international sampling and analysis of dried blood spots in Wave 6 – have confirmed the project to be compliant with relevant legal, especially statutory norms, as well as with research-ethical guidelines, e.g., the set of ethical principles regarding human experimentation developed for the medical community by the World Medical Association (Declaration of Helsinki, last revised at the 64th WMA Meeting held in Fortalezza/Brazil in October 2013).

The Ethics Council of the Max Planck Society extends its best wishes to the persons responsible for the continued success of the project.

Ulrich Braun
Office of the Ethics Council
On behalf of the Chairman Prof. Dr. Dres. Hc. Rüdiger Wolfrum

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Appendix 2. Euro-D Scale.

MH002	In the last month, have you been sad or depressed?	1. Yes 5. No
MH003	What are your hopes for the future?	1. Any hopes mentioned 2. No hopes mentioned
MH004	In the last month, have you felt that you would rather be dead?	1. Any mention of suicidal feelings or wishing to be dead 2. No such feelings
MH005	Do you tend to blame yourself or feel guilty about anything?	1. Obvious excessive guilt or self blame 2. No such feelings 3. Mentions guilt or self blame, but it is unclear if these constitute obvious or excessive guilt or self-blame
MH006 (if MH005 = 3)	So, for what do you blame yourself?	1. Example(s) given constitute obvious excessive guilt or self-blame 2. Example(s) do not constitute obvious excessive guilt or self-blame, or it remains unclear if these constitute obvious or excessive guilt or self-blame
MH007	Have you had trouble sleeping recently?	1. Trouble with sleep or re cent change in pattern 2. No trouble sleeping
MH008	In the last month, what is your interest in things?	1. Less interest than usual mentioned 2. No mention of loss of interest 3. Non-specific or uncodeable response
MH009 (if MH008 = 3)	So, do you keep up your interests?	1. Yes 5. No
MH010	Have you been irritable recently?	1. Yes 5. No
MH011	What has your appetite been like?	1. Diminution in desire for food 2. No diminution in desire for food 3. Non-specific or uncodeable response
MH012 (if MH011 = 3)	So, have you been eating more or less than usual?	1. Less 2. More 3. Neither more nor less
MH013	In the last month, have you had too little energy to do the things you wanted to do?	1. Yes 5. No

MH014	How is your concentration? For example, can you concentrate on a television programme, film or radio programme?	1. Difficulty in concentrating on entertainment 2. No such difficulty mentioned
MH015	Can you concentrate on something you read?	1. Difficulty in concentrating on reading 2. No such difficulty mentioned
MH016	What have you enjoyed doing recently?	1. Fails to mention any enjoyable activity 2. Mentions ANY enjoyment from activity
MH017	In the last month, have you cried at all?	1. Yes 5. No

Appendix 3. Copy of the published version of Study II.

Article

Moderating Effect of Muscular Strength in the Association between Cardiovascular Events and Depressive Symptoms in Middle-Aged and Older Adults—A Cross Sectional Study

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Abstract: Background: Depression and cardiovascular diseases are two main health conditions contributing to the global disease burden. Several studies indicate a reciprocal association between them. It is still unclear how changes in overall muscle strength may impact this association. This study aimed to analyse how muscular strength moderates the relationship between cardiovascular events and depressive symptoms among middle-aged and older adults. Methods: Wave 8 of the population-based Survey of Health, Ageing, and Retirement in Europe (2019/2020) cross-sectional data, which included 41,666 participants (17,986 men) with a mean age of 70.65 (9.1) years old, was examined. Grip strength was measured twice on each hand using a dynamometer. The 12-item EURO-D scale was employed to gauge depressive symptoms. Results: Grip strength negatively moderates the link between cardiovascular events and depressive symptoms (male: B = −0.03, 95% CI = −0.04, −0.03; female: B = −0.06, 95% CI = −0.06, −0.05). Additionally, the grip strength moderation values in the significant zone for males and females were less than 63.2 kg and 48.3 kg, respectively. Conclusions: Muscular strength modifies depressive symptoms and lessens their correlation with cardiovascular diseases. Muscle-strengthening activities could be incorporated into primary and secondary preventive strategies to reduce the burden of depression in people with CVD.

Keywords: depression; elderly; grip strength; moderation; cardiovascular diseases

Citation: Veiga, D.; Peralta, M.; Gouveia, É.R.; Nascimento, M.d.M.; Carvalho, L.; Encantado, J.; Marques, A. Moderating Effect of Muscular Strength in the Association between Cardiovascular Events and Depressive Symptoms in Middle-Aged and Older Adults—A Cross Sectional Study. *Geriatrics* **2024**, *9*, 36. https://doi.org/10.3390/geriatrics9020036

Academic Editor: Phyo Kyaw Myint

Received: 12 November 2023
Revised: 18 January 2024
Accepted: 11 March 2024
Published: 12 March 2024

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1. Introduction

Depression and cardiovascular diseases (CVD) are two main health conditions contributing to the disease burden globally [1]. Depression can harm mental and physical health, hamper daily activities, and negatively impact the quality of life [2]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the diagnosis of depression requires five or more symptoms to be present within a 2-week period [3]. One of the symptoms should, at least, be either a depressed mood or anhedonia. The secondary symptoms are appetite or weight changes, sleep difficulties, psychomotor agitation or retardation, fatigue or loss of energy, diminished ability to think or concentrate, feelings of worthlessness or excessive guilt, and suicidality. Although depression is one of the top causes of disability worldwide, most people who have depression still do not

obtain effective treatment [4]. Although there is significant variance between countries, the lifetime risk of depression is (at least) 10% [5,6], and in patients with CVD, depression is estimated to be one in five [7]. According to statistical reports, nearly 45% of patients with CVD struggle with major depressive disorder [8]. Furthermore, having comorbid depression is independently linked to a worse prognosis for people with CVD [9].

Both CVD and depression share common pathogenic mechanisms [10]. Increased levels of inflammatory markers [11], abnormalities in sympathetic and parasympathetic activity [12] and irregularities in hormone and neurotransmitter levels (such as cortisol and serotonin) [13] have all been linked to depression and CVD. Additionally, there are data indicating that the co-occurrence of these diseases may be influenced by similar genetic variables [14]. Therefore, it is plausible that CVD is an important risk factor for depression. A cardiovascular disease diagnosis or ongoing condition can result in substantial emotional anguish, worry, and depression. Furthermore, mood and mental health can be directly impacted by the physiological effects of cardiovascular disease on the brain and body as a whole [15]. Depression is associated with physiological changes, including increased inflammation, altered autonomic nervous system activity, and hormonal imbalances, which can contribute to the development and progression of CVD [16]. Prior research has demonstrated a significant rate of co-morbidity between depression and CVD, indicating a reciprocal association between the two conditions [17–19]. Delivering physical exercise or physical activity may not only improve depression severity, but also directly tackle the constitutive elements of cardiovascular risk [20]. Several investigations have suggested that muscle strength is a plausible mechanism for these associations, as it has a protective effect on the development of CVD [20–23]. Also, both dynapenia (muscle weakness) and depressive symptoms are common in the elderly population [24], although women seem to live longer and have more years free of dynapenia than men [25]. Dynapenia is often accompanied by increased inflammation and oxidative stress. Chronic inflammation and oxidative stress are common features of both depression and CVD [26]. Among middle-aged and older adults, grip strength (GS) may mediate the relationship between depression and the estimated 10-year risk of CVD [27]. GS is a measure of overall body strength, and it is also a maximum hand static force measure commonly used to capture muscular strength and monitor the health status of the general population, especially in older individuals [28].

As the world's population ages and life expectancy rises, it is increasingly important to consider middle-aged and older adults' health, including depression and CVD. There is substantial complexity in the associations between depression, GS, and CVD. Although some of these links are understood, it is still unclear how changes in GS, as a proxy for overall muscle strength, may impact the association between CVD and depression. The research question was established: among European middle-aged and older adults of both sexes, does GS have a moderating role in the relationship between depressive symptoms and CVDs? Towards the hypothesis that GS weakens the link between depressive symptoms and CVDs among European middle-aged and older adults of both sexes, this study aimed to analyse how GS moderates the relationship between two major cardiovascular events, myocardial infarction and stroke, and depressive symptoms among middle-aged and older adults by sex.

2. Materials and Methods

2.1. Participants and Procedures

Data from wave 8 (2019/2020) of the population-based Survey of Health, Ageing, and Retirement in Europe (SHARE) served as the foundation for this research. The SHARE methodology was previously detailed in [29]. It is a biennial survey that gathers data from several European nations and Israel. The target population consists of all people living in residential households who are 50 years of age or older, plus their (possibly younger) partners. Those who do not reside at the sampled address (e.g., because it was a seasonal or vacation residence), are physically or mentally unable to participate, died before the start of

the field period, or cannot speak the specific language of the national questionnaire, were excluded. The Ethics Council of the Max Planck Society for the Advancement of Science and the University of Mannheim Ethics Committee accepted the SHARE protocol. Written informed consent was obtained from all participants involved in the study.

A total of 41,666 participants (17,986 men and 23,680 women), with a mean age of 70.65 (9.1) years old, from 29 different countries (Austria, Germany, Sweden, the Netherlands, Spain, Italy, France, Denmark, Greece, Switzerland, Belgium, Israel, the Czech Republic, Poland, Ireland, Luxembourg, Hungary, Portugal, Slovenia, Estonia, Croatia, Lithuania, Bulgaria, Cyprus, Finland, Latvia, Malta, Romania, and Slovakia) made up the final sample.

2.2. Measures

2.2.1. Depressive Symptoms

Depressive symptoms, the outcome measure, were assessed with the 12-item EURO-D scale. Scores vary from 0 to 12, with higher scores indicating more severe symptoms of depression. A cut-off of $\geq$4 points indicates clinically significant depression [30,31]. The validation and explanation of the scale are covered elsewhere [31].

2.2.2. Cardiovascular Events

The exposure measure was being previously diagnosed with a cardiovascular event (stroke and/or myocardial infraction). Participants were asked to report being previously diagnosed with a cardiovascular event (stroke and/or myocardial infraction) by a medical doctor.

2.2.3. Grip Strength

The moderator employed was GS. Using a dynamometer, it was measured twice on each hand (Smedley, S Dynamometer, TTM, Tokyo, Japan, 100 kg), switching between the left and right hand [32]. Participants held their upper arm tightly against their bodies while standing or sitting, with the elbow at a 90-degree angle, the wrist in neutral, and the inner lever of the dynamometer set to the hand. After practicing, participants exerted the dynamometer's maximum pressure for 5 s. The GS variable contained the maximum value of the GS measurement of both hands. The values of two measures that differed by more than 20 kg were considered invalid. Measurements of GS that were equal to or more than 100 kg were excluded, as were measurements where GS was only assessed once in one hand.

2.2.4. Co-Variables

Covariates included sex, physical activity, hypertension, age, and country, which were self-reported. Physical activity was measured as "frequency of moderate physical activity" (e.g., gardening, cleaning the car, going for a walk) and "frequency of vigorous physical activity" (e.g., sports, heavy housework, a job involving physical labour). The response alternatives for both moderate and vigorous activity were: (1) more than once a week, (2) once a week, (3) up to three times a month, and (4) hardly ever or never. The last two response options were grouped into one category called less than once a week.

2.3. Statistical Analysis

Descriptive statistics, including mean and standard deviation for continuous variables and frequency for categorical variables, were calculated. The *t*-test (for continuous variables) and chi-square (for categorical variables) were used to compare participants' characteristics between sexes. An independent sample *t*-test and a Pearson correlation analysis were used to compare the depressive symptoms of men and women according to cardiovascular event diagnosis and to determine the relationship between GS and depressive symptoms. Based on the moderation methods suggested by Baron and Kenny [33], a moderated analysis of GS (moderator, W) on the connection between cardiovascular events (categorical, X) and depressive symptoms (continuous, Y) was conducted, and unstandardized coefficients

were presented. The moderation analysis was carried out using Andrew Hayes' PROCESS macro-3.5. The Johnson–Neyman method was used to evaluate statistically significant interactions and find regions of significance. This process was also used to determine a threshold of statistical significance. The analysis was stratified by sex and adjusted for age. Data analysis was performed using IBM SPSS Statistics version 28 (SPSS Inc., an IBM Company, Chicago, IL, USA) for Apple Mac®. For all tests, the statistical significance was set at $p < 0.05$.

3. Results

Table 1 presents the descriptive analysis. More women (30.5%) than men (18.3%) reported having depressive symptoms above cutoff. In contrast, more men (18.4%) than women (12.4%) reported having a history of cardiovascular events (myocardial infarction and/or stroke). A total of 6262 men and women had at reported least one cardiovascular event (5153 myocardial infractions and 1548 strokes in total).

Table 1. Characteristics of the total sample and divided by sex.

	Mean (95% CI) or % (95% CI)			
	Total (n = 41,666)	**Male (n = 17,986)**	**Female (n = 23,680)**	***p*-Value**
Age (years)	70.65 (70.56, 70.73)	71.12 (70.99, 71.25)	70.29 (70.17, 70.41)	<0.000
GS (kg)	32.04 (31.93, 32.14)	40.68 (40.54, 40.83)	25.47 (25.38, 25.55)	<0.000
EURO-D score	2.32 (2.30, 2.34)	1.90 (1.87, 1.93)	2.63 (2.60, 2.66)	<0.000
EURO-D ≥ 4				
Yes [% (95% CI)]	25.3 (24.8, 25.7)	18.3 (17.8, 18.9)	30.5 (29.9, 31.1)	<0.000
No [% (95% CI)]	74.7 (74.3, 75.2)	81.7 (81.1, 82.2)	69.5 (68.9, 70.1)	
Hypertension				
Yes [% (95% CI)]	45.1 (44.7, 45.6)	44.9 (44.1, 45.6)	45.3 (44.7, 46.0)	<0.000
No [% (95% CI)]	54.9 (54.4, 55.3)	55.1 (54.4, 55.9)	54.7 (54.0, 55.3)	
MPA				
<1×/week	18.5 (18.1, 18.8)	17.6 (17.0, 18.2)	19.1 (18.6, 19.6)	<0.000
1/week	14.9 (14.6, 15.3)	15.0 (14.5, 15.5)	14.9 (14.4, 15.3)	
>1/week	66.6 (66.2, 67.1)	67.4 (66.7, 68.1)	66.0 (65.4, 66.6)	
VPA				
<1×/week	52.3 (51.8, 52.8)	48.5 (47.7, 49.2)	55.2 (54.6, 55.8)	<0.000
1/week	15.2 (14.8, 15.5)	15.0 (14.5, 15.5)	15.3 (14.9, 15.8)	
>1/week	32.5 (32.1, 33.0)	36.5 (35.8, 37.2)	29.5 (28.9, 30.1)	
CVE *				
Yes [% (95% CI)]	15.0 (14.7, 15.4)	18.4 (17.9, 19.0)	12.4 (12.0, 12.8)	<0.001
No [% (95% CI)]	85.0 (84.6, 85.3)	81.6 (81.0, 82.1)	87.6 (87.2, 88.0)	

Abbreviations: GS, grip strength; CVE, cardiovascular events; * CVE is history of cardiovascular events (myocardial infarction and/or stroke).

The correlation analysis between GS and depressive symptoms showed that GS was significantly and negatively correlated with depressive symptoms for the total sample ($r = -0.254$, $p < 0.001$), as well as for males ($r = -0.193$, $p < 0.001$) and females ($r = -0.210$, $p < 0.001$) separately.

Table 2 compares depressive symptoms between participants according to the history of cardiovascular events (myocardial infarction and/or stroke). Regardless of sex, participants with a cardiovascular event had higher mean depressive symptoms than participants without CVD (males: 2.53 vs. 1.76, $p < 0.001$; females: 3.55 vs. 2.50, $p < 0.001$).

Table 2. Comparison of depressive symptoms according to the history of cardiovascular events (myocardial infarction and/or stroke).

	Depressive Symptoms (EURO-D 12 Score)						
	Total		Male		Female		*p*-Value
	Mean (SD)	Cohen's *d*	Mean (SD)	Cohens *d*	Mean (SD)	Cohens *d*	
CVE history	3.01 (2.39)	2.14	2.53 (2.21)	1.93	3.55 (2.47)	2.23	<0.001
No CVE history	2.19 (2.09)		1.76 (1.85)		2.50 (2.19)		

Abbreviations: CVE, history of cardiovascular events (myocardial infarction and/or stroke); SD, standard deviation.

Table 3 presents the small moderating effect of GS (W) on the association between cardiovascular events (X) and depressive symptoms (Y). The link between cardiovascular events and depressive symptoms was negatively moderated by GS (male: B = −0.03, 95% CI = −0.04, −0.03; female: B = −0.06, 95% CI = −0.06, −0.05), meaning that greater GS led to a weaker association. The Johnson–Neyman test also revealed that the GS moderation values in the significant zone for males and females were less than 63.2 kg and 48.3 kg, respectively.

Table 3. Moderation analysis of grip strength for the relationship between cardiovascular events and depressive symptoms stratified by sex.

	Depressive Symptoms (EURO-D 12 Score)					
	Total Sample		Male		Female	
	B	95% CI	B	95% CI	B	95% CI
CVE (X)	1.05	0.89, 1.21	1.13	0.84, 1.42	1.03	0.74, 1.33
Grip Strength (W)	−0.04	−0.04, −0.04	−0.02	−0.03, −0.02	−0.05	−0.05, −0.04
CVE * Grip Strength	−0.01	−0.02, −0.01	−0.01	−0.02, −0.01	−0.01	−0.03, −0.01

Abbreviations: CI, confidence interval; CVE, cardiovascular events. * CVE is history of cardiovascular events (myocardial infarction and/or stroke).

4. Discussion

This study aimed to analyse how GS moderates the relationship between two major cardiovascular events, myocardial infarction and stroke, and depressive symptoms among middle-aged and older adults. Results revealed that GS was positively related to lower depressive symptoms in middle-aged and older individuals. Furthermore, GS had a small moderating role in the association between CVEs and depressive symptoms in both men and women, possibly weakening its link to CVD.

Gender differences in depression have been extensively addressed over the past few decades. Our results support the evidence that women suffer more from depression than men (30.5% and 18.3%, respectively), which is in line with the majority of research that has found that women tend to experience depression twice as frequently as males do, independently of the culture [5]. The reasons for the disparities in depression between men and women include biological, psychological, and social factors [34].

Although using different methodologies, the negative correlation between GS and depression in this study matches other large-scale multinational studies carried out with older people [35,36]. The association of GS with depressive symptoms seems significant and inverse in individuals with and without chronic diseases, namely, CVD [37]. The findings also suggested that participants with a cardiovascular event diagnosis tend to present higher scores of depressive symptoms than those without it, both males and females. Depression seems to be highly prevalent in cardiac patients [38]. The fact that the longer a person lives with CVD, the greater the cumulative psychological impact [39], the functional impairment caused by CVD can decrease the ability to engage in desired activities and

lead to depression [40], and intensive treatments, medications, or invasive procedures used to manage severe CVD can have physical and psychological side effects [41] could possibly explain how the duration and intensity of CVD can affect depression and vice versa. There may be a physiological connection between CVD and depression, as prior research demonstrates the close relationship between these two clinical diseases [42]. Although these relationships can be complex and multifaceted, several physiological mechanisms can also help explain the connections between these conditions and GS. Cardiovascular health is linked to GS through the muscle–heart axis (myokines production) [43]; high GS may indicate a lower overall inflammatory and oxidative burden (contributing to better cardiovascular and mental health) [44]; muscle strength exercises promote neuroplasticity and brain health, helping to mitigate the risk of depression by enhancing brain function and structure, as well as reducing the risk of cardiovascular diseases by improving cerebral blood flow and reducing vascular risk factors [45]. Still, most of the underlying mechanisms underpinning the connection between these two illnesses are unknown [46]. For instance, compared to people without CVD, CVD patients are more likely to experience depression.

GS moderated the relationship between depressive symptoms and cardiovascular events (myocardial infarction and stroke), slightly buffering this association for both males and females. According to the findings, people with cardiovascular events tend to suffer more from depression (presenting higher score values of depressive symptoms), and although the effect was small, having greater GS protected against depressive symptoms. It is important to note that, although the effect is significant, as it is small, intervention studies are needed that can analyse this moderation effect in terms of clinical practice. Nevertheless, once nearly 45% of patients with CVD present depressive symptoms [8] and it is estimated that depression is one in five in this population [7], improving muscular strength may be an effective non-pharmacological option to reduce the burden of depression in people with CVD.

According to the Johnson–Neyman test, this small moderation effect is present for GS values under 63.2 kg for males and 48.3 kg for females. In the elderly population, the GS measurement is more commonly used as a screen for sarcopenia, a very prevalent condition in this type of population. These results indicate that even for GS values lower than the cut-off for sarcopenia (<27 kg for men and <16 kg for women) [47], strength seems to be a moderator of depressive symptoms. Even for an elderly person who continues to be at risk of being diagnosed with sarcopenia, interventions that increase their strength may have a small protective effect against depression, attenuating its symptoms.

When analysing the current results, it is important to consider their advantages and disadvantages. As far as we know, this is the first study to examine the moderating role of GS in the relationship between depressive symptoms and the two major cardiovascular events, myocardial infarction and stroke. Additionally, this study used an objective measure of physical fitness (i.e., GS) as a moderator, assessed by trained personnel. Self-reported questionnaires are frequently used in large sample studies to quantify physical activity or even, in some cases, physical fitness, which typically yields higher values than objective measures [48]. Despite these strengths, several limitations must be acknowledged. First, the diagnosis of cardiovascular events, myocardial infarction and stroke, were self-reported, which may lead to memory bias. Also, we did not measure the number of previous CVEs and did not include the current medication of the participants. Second, the study's cross-sectional design restricts the interpretation of the current findings in a cause-and-effect way, despite the large multinational sample. Lastly, another limitation was the inability to account for several confounding variables, including important risk factors such as the history of depression, coronary heart disease, cigarette smoking, and excessive alcohol consumption. Future research should consider testing more complex moderation models, where other variables are analysed that may also be playing a moderating effect on these relationships. Other covariates that were not included in this study should also be included in these models. In any case, these results reinforce the evidence that, in the clinical

context, strength training could be integrated into rehabilitation programmes for this type of population.

5. Conclusions

GS, a proxy of muscular fitness, slightly buffers the association between cardiovascular events (myocardial infarction and stroke) and depressive symptoms. This supports the idea that physical activity, namely muscle-strengthening activities, may be incorporated into primary and secondary preventive strategies to reduce the burden of depression in people with CVD.

Author Contributions: Conceptualisation, D.V., M.P. and A.M.; methodology, D.V. and M.P.; software, D.V.; validation, L.C., J.E. and M.d.M.N.; formal analysis, D.V. and M.P.; investigation, É.R.G.; resources, A.M.; data curation, L.C., J.E. and M.d.M.N.; writing—original draft preparation, D.V.; writing—review and editing, A.M. and É.R.G.; visualisation, M.d.M.N.; supervision, A.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The SHARE protocol was approved by the Ethics Committee of the University of Mannheim and by the Ethics Council of the Max-Planck-Society for the Advancement of Science, verifying the procedures to guarantee confidentiality and data privacy.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data are freely accessible. The data can be accessed through the SHARE project website—https://share-eric.eu/ (accessed on 15 July 2023).

Acknowledgments: We would like to acknowledge all SHARE Survey participants for their generous time when participating in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

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Appendix 4. Copy of the published version of Study III.

Article

Moderating Effect of Grip Strength in the Association between Diabetes Mellitus and Depressive Symptomatology

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Abstract: Diabetes mellitus and depression rank among the leading causes of disease burden and are present in the top ten causes of disability-adjusted life years worldwide. Numerous studies have shown that both depression and diabetes have a detrimental effect on the quality of life, and when they coexist, the effect is considerably worse. This study aimed to analyse how grip strength moderates the relationship between diabetes and depressive symptoms among middle-aged and older adults. In total, 41,701 participants (18,003 men) in wave 8 of the cross-sectional population-based Survey of Health, Ageing, and Retirement in Europe (2019/2020) data were studied. A dynamometer was used to test grip strength twice on each hand. Depressive symptoms were measured using the 12-item EURO-D scale. The relationship between diabetes and depressive symptoms is negatively moderated by grip strength (male: B = −0.03, 95% CI = −0.04, −0.03; female: B = −0.06, 95% CI = −0.07, −0.06). Furthermore, the significant zone grip strength moderation values for males and females were less than 48.7 kg and 38.9 kg, respectively. Muscular strength was a moderator of depressive symptoms, attenuating its association with diabetes. This supports the premise that physical activity, namely muscle-strengthening exercises, should be included in diabetes treatment programs.

Keywords: depression; elderly; grip strength; moderation; diabetes

Citation: Veiga, D.; Peralta, M.; Gouveia, É.R.; Carvalho, L.; Encantado, J.; Teixeira, P.J.; Marques, A. Moderating Effect of Grip Strength in the Association between Diabetes Mellitus and Depressive Symptomatology. *Sports* **2024**, *12*, 3. https://doi.org/10.3390/sports12010003

Academic Editor: Corrado Lupo

Received: 19 October 2023
Revised: 21 November 2023
Accepted: 18 December 2023
Published: 20 December 2023

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1. Introduction

Chronic hyperglycemia is a hallmark of diabetes mellitus (DM), a metabolic disorder involving the metabolism of carbohydrates, proteins, and fats that has been extensively investigated [1]. There are two main types of diabetes. Type 1 DM is an autoimmune disease that leads to the destruction of insulin-producing pancreatic beta cells [2]. The two main causes of type 2 DM are the incapacity of insulin-sensitive tissues to react to insulin correctly and impaired insulin production by pancreatic β-cells [3]. Over the next ten years, the prevalence of DM is anticipated to rise by 25% globally, making it a rising public health concern [4].

Depression is a significant comorbid condition in DM [5]. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), the diagnosis of depression requires five or more symptoms to be present within a 2-week period [6]. One of the symptoms should, at least, be either a depressed mood or anhedonia. The secondary symptoms are appetite or weight changes, sleep difficulties, psychomotor agitation or retardation, fatigue or loss of energy, a diminished ability to think or concentrate, feelings of worthlessness or excessive guilt, and suicidality. A key contributor to disability, depression lowers the quality of life, raises the chance of early death, and heavily strains healthcare

systems [7]. Different estimates show that depression could affect more than 300 million people worldwide [8,9].

DM and depression rank among the leading causes of disease burden worldwide and are present in the top ten causes of disability-adjusted life years worldwide [10]. Evidence supports a bidirectional association between DM and depression [11]. DM increases the risk of depression by 15–28% [12]. On the other hand, depression was confirmed as a risk factor for DM (34% and 60% risk increase) [13]. Numerous studies have shown that both depression and DM have a detrimental effect on the quality of life, and when they coexist, the effect is considerably worse [14–17]. Even when other known DM risk factors are considered, such as a poor diet [18], family history [19], inflammation [19], the use of some antidepressants [20], and a sedentary lifestyle [21], the elevated risk for DM associated with depression persists [22].

Physical activity, defined as any bodily movement produced by skeletal muscles that results in energy expenditure [23], provides various benefits, including preventing chronic diseases, lowering the risk of depression, increasing physical strength, and reducing mental stress [24]. A person's capacity to do physical activity is correlated with a set of traits known as physical fitness [25]. The health-related components of physical fitness are cardiorespiratory endurance, muscular endurance, muscular strength, body composition, and flexibility. From all the health-related components of physical fitness [23], muscular strength has been researched recently regarding its relationship with middle-aged and older adults' mental and physical health [26]. Among people with DM, strength training may not only help alleviate depressive symptoms [27], but also assist in achieving glycaemic control [28]. Regular physical activity helps regulate normal glucose uptake into peripheral tissues, increases insulin receptors, and improves insulin sensitivity [29], thus contributing to the blood glucose control [30]. Strength training has anti-inflammatory properties [31], aids in beneficial changes in body composition [32], and makes weight management easier [33]. In addition, muscle strength seems to be inversely correlated with depression and cognitive performance in middle-aged and older adults [34,35], emphasising the value of exercise and physical fitness in preventing depression. Grip strength (GS), the force used by the hand and fingers to grasp and hold onto an object, is a numerical assessment of the strength of the muscles used in handgrip activities [36]. GS, a measure of muscle strength that is associated with physical activity levels [37], has been considered a legitimate and trustworthy measure of overall muscle strength and the state of one's physical and mental health [38].

Given that the prevalence of both DM and depression is increasing in the middle-aged and older adults' group [39,40], and the causes and relationship remain rather complex and understudied [41], this study aimed to analyse how GS moderates the relationship between DM and depressive symptoms among middle-aged and older adults.

2. Materials and Methods

2.1. Participants and Procedures

Data from the Survey of Health, Ageing, and Retirement in Europe (SHARE) wave 8 data (2019/2020) were used. The SHARE methodology has been previously described [42]. This survey gathers data on adults aged 50 and above every two years in European countries and Israel. The target population consists of all people living in residential households, plus their (possibly younger) partners. Those who do not reside at the sampled address (e.g., because it was a seasonal or vacation residence), are physically or mentally unable to participate, have died before the start of the field period, or cannot speak the specific language of the national questionnaire were excluded. The SHARE protocol was approved by the University of Mannheim Ethics Committee and the Ethics Council of the Max-Planck-Society for the Advancement of Science. The study's participants all provided their written informed consent.

There were 41,701 participants (30,224 with age $\geq$ 65), 18,003 men and 23,698 women, with a mean age of 70.65 (9.1) and coming from 29 different countries (Austria, Germany,

Sweden, The Netherlands, Spain, Italy, France, Denmark, Greece, Switzerland, Belgium, Israel, the Czech Republic, Poland, Ireland, Luxembourg, Hungary, Portugal, Slovenia, Estonia, Croatia, Lithuania, Bulgaria, Cyprus, Finland, Latvia, Malta, Romania, and Slovakia).

2.2. Measures

The outcome measure was depressive symptoms. The EURO-D 12-item scale was used to quantify depressive symptoms. Scores range from 0 to 12, with higher numbers denoting more severe depressive symptoms. A cut-off $\geq$ 4 points indicates clinically significant depression [43,44]. The scale's validation and justification are discussed elsewhere [44]. The exposure measure was DM. The existence or absence of DM that had previously been diagnosed by a doctor was inquired of the participants. GS was the moderator in use. It was measured twice on each hand using a dynamometer (Smedley, S Dynamometer, TTM, Tokyo, 100 kg), switching between the left and right hands [45]. The inner lever of the dynamometer was set to the hand. Participants kept their upper arm tightly against their bodies while standing or sitting, with the elbow at a 90-degree angle, the wrist in neutral, and the elbow snugly against their body. Participants exerted the dynamometer's maximum pressure for 5 s. Before the assessment, participants had the option to practice. The GS variable contained the maximum value of the GS measurement of both hands. Values of two measures that differed by more than 20 kg were considered invalid. Measurements of GS that were equal to or more than 100 kg were excluded, as well as measurements where GS was only assessed once in one hand. Sex and age were the self-reported covariates.

2.3. Statistical Analysis

Descriptive statistics (mean, standard deviation, and frequency) were calculated for all variables. The depressive symptomatology of men and women according to DM diagnosis, as well as the association between GS and depressive symptomatology, were compared using an independent sample *t*-test and a Pearson correlation analysis, respectively. Using the suggestions for moderation made by Baron and Kenny [46], a moderated analysis of GS (moderator, W) on the connection between DM (categorical, X) and depressive symptoms (continuous, Y) was conducted (Figure 1). The moderation analysis was carried out using Andrew Hayes' PROCESS macro-3.5. The Johnson-Neyman method was used to evaluate statistically significant interactions and find regions of significance. This process was also used to determine a threshold of statistical significance. Analysis was stratified by sex and adjusted for age. Data analysis was performed using IBM SPSS Statistics version 28 (SPSS Inc., an IBM Company, Chicago, IL, USA). For all tests, the statistical significance was set at $p < 0.05$.

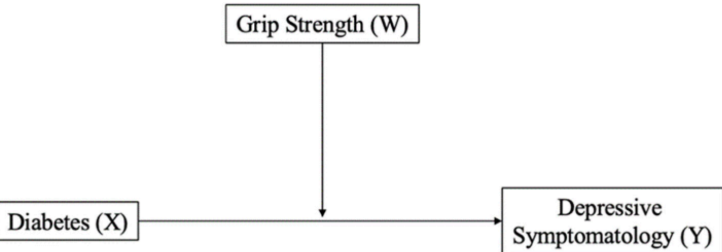

Figure 1. A conceptual diagram of the relationship between diabetes (X) and depressive symptomatology (Y) moderated by grip strength (W).

3. Results

The descriptive analysis is presented in Table 1. Women (45.6%) reported having depressive symptoms more frequently than men (29.6%). Men, however, were more likely than women to report having been diagnosed with DM (16.2% vs. 12.7%).

Table 1. Sample characteristics for the total sample and by sex.

	Mean (SD) or n (%)		
	Total (n = 41,701)	Male (n = 18,003)	Female (n = 23,698)
Age (years)	70.65 (9.1)	71.1 (8.8)	70.3 (9.4)
Grip strength (kg)	32.0 (11.2)	40.7 (10.0)	25.5 (6.7)
EURO-D score	2.3 (2.2)	1.9 (1.9)	2.6 (2.3)
Diabetes			
Yes n (%)	5932 (14.2)	2918 (16.2)	3014 (12.7)
No n (%)	35,769 (85.8)	15,085 (83.8)	20,684 (87.3)
Depression			
Yes n (%)	16,130 (38.7)	5331 (29.6)	10,799 (45.6)
No n (%)	25,571 (61.3)	12,672 70.4)	12,899 (54.4)

Abbreviations: SD, standard deviation.

Table 2 presents the relationship between GS and depressive symptoms. GS was negatively correlated with depressive symptoms for the entire sample (r = −0.254, $p < 0.001$) as well as for males and females separately (r = −0.193, $p < 0.001$ vs. r = −0.210, $p < 0.001$).

Table 2. Pearson correlation between grip strength and depressive symptomatology.

	Depressive Symptoms (EURO-D 12 Score)					
	Total		Male		Female	
	r	p-Value	r	p-Value	r	p-Value
Grip strength	−0.254	<0.001	−0.193	<0.001	−0.210	<0.001

The depressive symptoms of patients with and without DM are presented in Table 3. The mean depressive symptomatology was higher in people with DM than those without DM, regardless of sex (males: 2.53 vs. 1.76, $p < 0.001$; females: 3.55 vs. 2.50, $p < 0.001$).

Table 3. Comparison of depressive symptomatology according to the presence or absence of diabetes.

	Depressive Symptoms (EURO-D 12 Score)					
	Total		Male		Female	
	Mean (SD)	p-Value	Mean (SD)	p-Value	Mean (SD)	p-Value
With diabetes	2.71 (2.32)	<0.001	2.18 (2.08)	<0.001	3.22 (2.43)	<0.001
Without diabetes	2.25 (2.12)		1.85 (1.92)		2.54 (2.21)	

The moderating role of GS (W) in the relationship between DM (X) and depressive symptoms (Y) is shown in Table 4. (male: B = −0.03, 95% CI = −0.04, −0.03; female: B = −0.06, 95% CI = −0.07, −0.06) means that a higher GS resulted in a reduced correlation between DM and depressive symptoms. Additionally, the Johnson-Neyman test showed that the GS moderation values for males and females in the significant zone were less than 48.7 kg and 38.9 kg, respectively.

Table 4. Moderation analysis of grip strength for the relationship between diabetes and depressive symptomatology stratified by sex.

	Depressive Symptoms (EURO-D 12 Score)					
	Total Sample		Male		Female	
	B	95% CI	B	95% CI	B	95% CI
Diabetes (X)	0.94	0.77, 1.11	0.67	0.35, 0.98	0.98	0.67, 1.29
Grip Strength (W)	−0.04	−0.05, −0.04	−0.03	−0.04, −0.03	−0.06	−0.07, −0.06
Diabetes*Grip Strength	−0.02	−0.02, −0.01	−0.01	−0.02, 0.00	−0.02	−0.03, −0.01

Abbreviations: CI, confidence interval.

4. Discussion

This study investigated how GS affects the relationship between depressive symptomatology and DM in middle-aged and older individuals. According to the findings, depressive symptoms were significantly higher in both men and women with DM, and GS was significantly associated with lower depressive symptoms. When getting a DM diagnosis, GS reduced depressive symptoms, moderating the relationship between them and DM.

Depression is more common in women than in men. According to research, women are roughly twice as likely as men to experience depression throughout their lifetime [47]. This sex difference in depression prevalence aligns with our results reporting that women suffer more from depression than men (45.6% and 29.6%, respectively). The reasons for this disparity are multifaceted and may involve a combination of biological, psychological, and sociocultural factors [48].

Our results have shown a negative correlation between GS and depressive symptoms, meaning that as GS increases, the severity of depression tends to decrease. Various studies also observe this association [49,50]. The exact mechanisms underlying this correlation have yet to be fully understood, but several potential explanations exist. For groups with co-occurring mental and physical health issues, and once it is often considered a proxy for overall physical health and functional fitness, GS might offer four advantages: (1) it might lessen depressive symptoms through biological and psychosocial mechanisms; (2) it might enhance physical health by treating the comorbid illness itself or by avoiding its secondary effects; (3) it may be that individuals with better physical health, including muscle strength, have a more robust physiological response to stress and are better equipped to cope with depressive symptoms; and (4) it might also reflect individuals who are involved in physical activities that confer mental health and well-being benefits [28].

The guidelines of scientific societies indicate that a substantial proportion of patients are diagnosed with a psychiatric disorder [51]. Given the chronic nature of DM, along with the daily management tasks and potential complications, people with DM have a higher risk of developing depression compared to the general population [52]. The constant need for self-management can be stressful and overwhelming, contributing to frustration and anxiety. Our research reveals that in men and women, participants with DM tended to present higher scores of depressive symptomatology than those without it. This increased risk can be attributed to various factors related to living with DM. Through the dysregulation of the hypothalamic-pituitary-adrenal axis, the hyperactivity of the autonomic nervous system, and inflammatory processes, depression and type 2 DM share biological roots. Type 1 DM patients may be more vulnerable to depression if they have a long-lasting disease from a young age when their personalities are also forming [10].

A moderator is a variable that can influence or modify the relationship between two other variables: in this case, DM and depressive symptomatology. Our findings demonstrate that for both males and females, GS modifies the link between depressive symptomatology and DM. B's negative value reveals that the association is unfavourable. This indicates that rather than negating the link between these two variables, the moderating effect weakens it. According to these findings, those who have DM typically experience more depression than those who do not (higher score values for depressive symptoms). Nevertheless, among those who do, individuals with greater muscular strength, as determined by GS, tend to experience less suffering (show lower scores of depressive symptoms) than those with lesser muscular strength. According to the Johnson-Neyman test, this moderation effect is present for GS values below 48.7 kg for men and 38.9 kg for women.

Several things could justify that individuals with more muscular strength may be less susceptible to the detrimental psychological effects of DM. A physically active lifestyle and improved mental health frequently correlate with a stronger GS [53]. Based on preliminary data, resistance training appears to be beneficial for enhancing the majority of life quality domains, handgrip strength, lower and upper limb muscle strength, and depression in middle-aged and older adults [54]. Regular exercise, including strength training, can lessen

both stress and the symptoms of depression. In parallel, strength exercises can boost self-efficacy and self-confidence while helping to improve GS [55]. These psychological elements may provide protection from the emotional strain that comes with managing DM. Also, exercise and strength training, in general, are efficient stress-reduction methods [56]. Regular strength training may help people with DM to cope better with the pressures of the condition, thus lowering the risk of depression.

The moderating impact of GS on depressive symptomatology may not be the same for every DM patient. It is conceivable that the degree to which GS moderates the association between DM and depression varies depending on things like: DM severity (the moderating effect may be more prominent in people with poorly controlled DM or those who have had the condition for a longer period), individual resilience (the effect of DM on depression may depend on an individual's psychological resilience, coping mechanisms, and social support system), and ageing (GS usually weakens with age and younger people with DM may experience a different moderating impact than middle-aged and older persons).

The strengths and limitations of the existing results should be considered when analysing them. Regarding the limitations, the study's cross-sectional design cannot prove causality because it is mainly descriptive. The direction of causality or the existence of underlying causal mechanisms cannot be determined. However, they can spot relationships or correlations between variables. Another limitation was the inability to account for several confounding factors, such as smoking use/abuse, educational level, diet, or physical activity levels. Regarding the strengths, this is the first investigation, as far as we are aware, on the moderating effect of GS in the association between depressive symptoms and DM. In this study, physical fitness was measured by an objective measure (i.e., GS) acting as a moderator and assessed by an impartial physical fitness test. Objective measures provide precise and accurate data, reducing the potential for measurement error or bias. They offer clear and quantifiable results that can be consistently obtained across different assessments and evaluators [57]. It also constitutes a strength that this study was with a multinational sample. Multinational samples, which capture a wide range of cultural, social, and economic viewpoints, produce conclusions more generally applicable to a global environment. Because they are less likely to be impacted by peculiar or regional characteristics, the results from international samples are frequently more solid and reliable. The validity of results is strengthened by consistency across various populations [58].

Research into the relationship between muscular strength and depression in people with DM is underway. This study highlights the possibility that, even when diagnosed with DM, persons with higher grip strength values may have a mitigating effect on depressive symptoms. There is already evidence that suggests that GS may lessen depression in people with DM, but further studies are required to fully understand the processes at work and to pinpoint the precise circumstances in which this moderation takes place. This link is complicated and not entirely clear. It is crucial to understand that DM patients' despair is not solely influenced by their GS. Future research in this area should consider that other elements, like glycemic control, healthcare access, social support, and psychological elements, can also greatly impact how depression develops and is treated in this population. A specific focus should be placed on middle-aged and older individuals because DM and depression are becoming more prevalent in this age group. Due to the anticipated rise in the population's senior citizens, who have a high prevalence of DM, this is especially significant.

5. Conclusions

Muscular strength moderated depressive symptoms, attenuating its association with DM and supporting the premise that physical activity, namely muscle-strengthening exercises, could be included in DM treatment programs. In addition to taking other comorbidities into account when managing DM, depression should also be considered. Priority should be given to the early detection of depressive symptoms in DM patients who are depressed to prevent the sad state from adversely affecting the clinical management of DM. Furthermore, because GS is a simple, quick, and economical test, DM recovery programs

could include physical activity, namely muscle-strengthening exercises, as one strategy to potentially prevent depression.

Author Contributions: Conceptualisation, D.V., M.P. and A.M.; methodology, D.V. and M.P.; software, D.V.; validation, L.C., J.E. and P.J.T.; formal analysis, D.V. and M.P.; investigation, É.R.G.; resources, A.M.; data curation, L.C., J.E. and P.J.T.; writing—original draft preparation, D.V.; writing—review and editing, A.M. and É.R.G.; visualization, P.J.T.; supervision, A.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The SHARE protocol was approved by the Ethics Committee of the University of Mannheim and by the Ethics Council of the Max-Planck-Society for the Advancement of Science, verifying the procedures to guarantee confidentiality and data privacy. The SHARE data collection procedures are subject to continuous ethics review. For more details please see: https://share-eric.eu/fileadmin/user_upload/Ethics_Documentation/SHARE_ethics_approvals.pdf (accessed on 21 June 2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data are freely accessible. The data can be accessed through the SHARE project website—https://share-eric.eu/ (accessed on 21 June 2023).

Acknowledgments: We would like to acknowledge all SHARE Survey participants for their generous time when participating in this study.

Conflicts of Interest: The authors declare no conflict of interest.

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