Aus der Klinik und Poliklinik für Psychosomatische Medizin und Psychotherapie

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Mental health in women and men:

The interplay of biological, psychological, and social-environmental risk- and protective factors in internalizing disorders

Psychische Gesundheit bei Frauen und Männern:

Das Zusammenspiel von biologischen, psychologischen, sozialen und umweltbedingten Risiko- und Schutzfaktoren für internalisierende Störungen

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Abbreviations

AIC	Akaike Information Criterion
APC	Age-Period-Cohort
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CIDI	Composite International Diagnostic Interview
CRHR1	Corticotropin-Releasing Hormone Receptor 1
CVD	Cardiovascular Disease
COPD	Chronic Obstructive Pulmonary Disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
ESR	Excessive Symptom Reporting
GAD-7	Generalized Anxiety Disorder-7
GDR	German Democratic Republic
GESA	GEnder Sensitive Analyses of mental health trajectories and implications for prevention
GHS	Gutenberg Health Study
HAPC	Hierarchical Age-Period-Cohort
HRQL	Health-Related Quality of Life
HPA axis	Hypothalamic-Pituitary-Adrenal axis
hs-CRP	high-sensitivity C-Reactive Protein
IGFBP-3	Insulin-Like Growth Factor Binding Protein-3
IGF-1	Insulin-Like-Growth factor-1
KORA	Cooperative Health Research in the Region Augsburg
MONICA	Monitoring of Trends and Determinants of Cardiovascular Disease
MGCFA	Multi-Group Confirmatory Factor Analysis
MI	Measurement Invariance
PHQ-4	Patient Health Questionnaire-4
PHQ-9	Patient Health Questionnaire-9
PTSD	Post-Traumatic Stress Disorder
RMSEA	Root Mean Square Error of Approximation
SES	Socioeconomic Status
SHIP	Study of Health in Pomerania
SRMR	Standardized Root Mean Square
WHO	World Health Organization
WHR	Waist-to-Hip Ratio

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1 General Introduction

With the high numbers of mental disorders worldwide, mental (ill-)health has become a serious public health concern and hence a major topic of interest. In Europe, approximately 4% of all deaths are caused by mental and behavioral disorders. Furthermore, individuals with severe mental disease have a higher premature mortality rate compared to the general population (1). In Germany, with 5.9%, mental and behavioral disorders were the fourth leading cause of death within the population in 2021 (2).

Depression and anxiety belong to the most common (internalized) mental disorders. They are often comorbid and can be labelled under the umbrella term *mental distress*. In the German population, depression symptoms were present among 10.1% of the population, and 8.1% reported having received a diagnosis of depression from a physician or psychotherapist (3). A diagnosis of depression in the last year according to the Composite International Diagnostic Interview (CIDI) was found for 7.1% of the individuals. For women, depression or symptoms of depression were more often present than for men (regardless of measurement applied). With regard to anxiety, data from 2008-2011 revealed a prevalence of 15.4% of any anxiety disorder and 2.3% of a generalized anxiety disorder in the previous year (4). Anxiety disorders were more common among women than men. Combined with suicidal ideation (present among 8% of the German population (5)) these are the most frequent disorders in the population. Mental ill health has numerous negative consequences, for example on an individual's physical health (e.g., less healthy lifestyle and health behaviors such as low physical activity, poor diet, smoking, alcohol and/or substance abuse (6) as well as an increased number of years lived with disability and years of life lost (7)). Furthermore, internalized disorders (especially depression and anxiety) compromise quality of life and psychosocial functioning (8) and indirectly cause lower well-being (9). Besides this 'human burden', mental ill health also causes an 'economic burden'. Depression and anxiety are associated with considerable economic costs owing to lost work productivity and increased healthcare resource utilization (10, 11). Risk for suicidal ideation (stronger present among women) and behavior (stronger present among men) increase with number of mental disorders (12) and pose a great threat for possibly avoidable premature mortality.

In the development of mental disorders, biological, psychological, somatic, and social or cultural/environmental components interact. Individuals have a diverging vulnerability to develop mental disorders or experience recurrence of a disorder. An interplay between these vulnerabilities, risk factors (e.g., stressful events), and the presence or absence of protective factors (e.g., social support) will influence the likelihood of a person developing or experiencing recurrence of a mental disorder. The differences in developing or experiencing recurrence of mental disorders and the consequences of ill-mental health between women and men might be explained by differences in biological, psychological, and social related risk- and protective factors for women and men. In this dissertation, I focus on differences in prevalence rates, risk- and protective factors, and consequences of mental ill-health between women and men.

The current work first presents a general theoretical framework including an overview of health differences between women and men, a description of internalized mental disorders with a focus on mental distress, depression, anxiety, and suicidal ideation in women and men, and an explanation of the biopsychosocial model that has been consulted to integrate the different approaches to foster our understanding of mental health differences between women and men (Chapter 2). The following chapters present the conducted empirical studies for this dissertation. In Chapter 3, a systematic review article "*Similarities and differences of mental*

health in women and men: A systematic review of findings in three large German cohorts" informs on the main findings on mental health within Germany stratified for women and men to regain more insights into current knowledge gaps. In Chapter 4, "*Depressive symptoms predict the incidence of common chronic diseases in women and men in a representative community sample*", the predictive value of depressive symptoms on physical health is examined. Chapter 5, "*Does social support prevent suicidal ideation in women and men? Gender-sensitive analyses of an important protective factor within prospective community cohorts*" focuses on social support as a protective factor. In Chapter 6, "*Gender differences in the prevalence of mental distress in East and West Germany over time: a hierarchical age-period-cohort analysis*" an overview of mental distress over time within East- and West-Germany is given. Chapter 7 concludes with a general discussion relating the main findings of the four empirical studies and interpreting them in the light of the biopsychosocial model as well as from a gender perspective. Furthermore, clinical implications and limitations of the studies are discussed. Lastly, an outlook on important features for future research highlighting the relevance of separate studies for women and men in mental health research is given.

2 Theoretical Background

This chapter provides a general theoretical framework including an overview of the origin of health differences between women and men and the current state of (epidemiological) research on mental health differences between women and men. Section two provides a description of internalized mental disorders with a focus on mental distress, depression, anxiety, and suicidal ideation in women and men. In section three, the biopsychosocial model is introduced, which has been consulted in section four to get a better understanding of mental health differences between women and men. Section five focuses on physical health in women and men in light of the biopsychosocial model and lastly, section six concludes with the current state of research on mental morbidity and mortality.

2.1 History of the investigation of health differences in women and men

Biological differences between sexes are rooted in anatomy, physiology, genetics, and hormones. These differences have for a long time been neglected in medical research due to a male default in medicine. Into the ‘90s, women were not required to be included in clinical research, leading to an underrepresentation of women in clinical studies (1). Although the topic has increasingly come to public attention (2), until recent years, women remained to be understudied in medical research. A review from 2018 examining the inclusion of women in randomized control trials in medical studies in the USA and comparing them with 2004 and 2009 reported no significant changes in the inclusion of women (3). This was confirmed in other studies (4). Furthermore, when including women in preclinical studies, only one-fourth to one-third of the studies reported at least one outcome by sex or explicitly included sex as a covariate in statistical analysis (5, 6). This has had far-reaching implications, for example in the area of medical drugs. Medical drugs have been mostly tested with men and the efficacy, dosage, and side effects of many drugs are therefore less well known for women (7), which is highly problematic since studies revealed differences in pharmacokinetics between women and men (8, 9). A recent review examining sex differences in pharmacokinetics as the cause of differences in adverse drug reactions revealed elevated blood concentrations and longer elimination times to predict adverse drug reactions in women, but not in men (10). Besides pharmacokinetics, differences in sexual hormones between women and men were found to be associated with illnesses. Levels of sexual hormones that differ between women and men were shown to be associated with the immune system (11, 12), with adipose tissue (13, 14), and with liver metabolism (15, 16) accounting for differences in prevalence and outcomes in related diseases. The combination of sexual hormones and genetics was revealed to account for differences in neurodegenerative disorders in women and men (e.g., Parkinson's disease), in mental disorders, and in behavioral traits (17, 18). Lastly, some diseases are only present in women or men. Diseases only present in women, for example, endometriosis, were discovered relatively late, less present in research and are therefore still insufficiently described (e.g., in terms of prevalence rates and symptoms variety) (19).

Further, symptom differences between women and men exist and are understudied. Already in the ‘80s, a study in the USA found that women reported a greater variety of symptoms, illnesses and injuries compared to men when visiting a physician (20). However, men received more diagnoses than comparable women and women were more likely to receive an unspecified diagnosis. This could be caused by women presenting with other symptoms of a specific disease than men with the consequence of the disease not being recognized by the physician. A well-known example is acute myocardial infarction in which women are less likely

to present with chest pain compared to men, but more likely to report fatigue, neck pain, syncope, nausea, right arm pain, dizziness, and jaw pain (21, 22). In the past, for cardiologists, the symptom of chest pain has been the primary sign of acute myocardial infarction. Consequently, women were not-, under- or later diagnosed compared to men (23). This contributed to higher mortality in women due to heart attacks. Also for other (cardiovascular) diseases symptoms differ between women and men e.g., (ischemic and hemorrhagic) stroke (24), which contributed to a greater relative risk of coronary death in women (e.g., as a consequence of diabetes (25)). Symptom differences between women and men are also present in several mental disorders. In the case of major depression, a Canadian study demonstrated that women reported significantly more symptoms than men (26); women were especially more likely to report an increased appetite, being often in tears, loss of interest, and experiencing thoughts of death. With regard to schizophrenia and schizoaffective disorder, women with schizophrenia more often reported a history of childhood physical abuse and they experienced more psychotic and depressive symptoms compared to men (regardless of their history of childhood physical abuse) (27). Lastly, for bipolar disorders small symptom differences in women and men were found, men reported more mania at the onset of the bipolar disorder than women and were more likely to report behavioral problems and being unable to hold a conversation during mania (28)

Lastly, health differences between women and men can also be attributed to health behavior and social and environmental factors. First of all, men and women differ with regard to the utilization of healthcare. Men are less likely to visit physicians (29) or other doctor's offices or emergency departments than women and they are less likely to engage in preventive care (30). Furthermore, differences in health information-seeking behavior between women and men were present. In fact, women researched more information on health compared to men (31). Also, health behaviors (smoking, physical activity, alcohol consumption and dietary patterns) differ between women and men and unhealthy behaviors contribute more strongly to all-cause mortality in men compared to women (32, 33). With regard to social factors, social relations (marital status) and socioeconomic status (SES) were found to explain the sex gap in mortality, besides functional impairments (diseases), biological markers (e.g., inflammation, total cholesterol, and glycosylated hemoglobin) and health behaviors (33). Higher mortality in men is reduced when controlling for SES (men more often have higher levels of education and are less likely to be affected by poverty).

2.2 Mental health, mental distress, and mental disorders

Mental health is an integral part of a person's general health and well-being and is acknowledged by the World Health Organization (WHO) as a basic human right (34). The WHO conceptualizes mental health as a " state of mental well-being that enables people to cope with the stresses of life, realize their abilities, learn well and work well, and contribute to their community" (35). Mental illness and mental well-being are related yet distinct phenomena (36, 37) and have different causal factors and mediators (37). Mental health thus comprises more than only the absence of mental illness. The term *mental* or *psychological distress* is often applied to symptoms ranging from depression and general anxiety symptoms to personality traits and behavioral problems. However, it is nowadays largely defined as a state of emotional suffering characterized by symptoms of depression and anxiety (38, 39). While *mental distress* refers to distress in response to an external stressor, *psychological disorders* consist of a pattern of persistent behavioral or psychological symptoms that influence several areas of life.

Mental or psychological distress and mental disorders are strongly associated with significantly lower positive mental health (40) and diminish quality of life and work productivity (41). Further, mental disorders increase the risk of physical illnesses (41) and are among the leading causes of nonfatal burden of disease globally (42). Moreover, mental disorders reduce the life expectancy of a large proportion of the general population (41). Lastly, mental disorders constitute a substantial economic burden for societies (43). All of these aspects have caused mental distress and mental disorders to become a major public health concern.

2.2.1 Internalized and externalized mental disorders

Mental disorders can manifest in various ways and their symptoms differ in intensity and frequency. Mental disorders can be broadly grouped into *internalizing* and *externalizing disorders.* Internalization is linked with negative emotionality (a tendency to experience anxiety, anger, and alienation) (44); internalized disorders are characterized by symptoms that are experienced internally. Internalized disorders include mood disorders (e.g., major depressive episode, dysthymia with hierarchy) and anxiety disorders (e.g., panic disorder, specific phobia, social phobia, agoraphobia with or without panic disorder, generalized anxiety with hierarchy, post-traumatic stress disorder (PTSD) (45). Individuals suffering from internalized disorders often feel hopelessness, experience negative thoughts, withdraw from social interactions or isolate themselves. By contrast, externalization is linked with a lack of *constraint* (a tendency to engage in risky behavior, to act on impulse, and to endorse non-traditional values) (44). Externalized disorders are thus characterized by having difficulties regulating one's emotions (e.g., exhibiting aggressive behavior) or engaging in risky activities (substance abuse). Externalized disorders therefore include attention-deficit, conduct, alcohol-use, and drug-use disorder) (45).

Internalized disorders can be difficult to diagnose because their symptoms are often not clearly visible and many individuals suffering from internalized disorders do not seek help. Externalized disorders may be difficult to diagnose while individuals may be in denial or do not recognize the extent of their problems and are therefore reluctant to seek help. Further, internalized and externalized disorders often co-occur, e.g., a person with an internalized mood disorder might use drugs or alcohol as a means of coping and herewith develop a substance abuse disorder. This co-occurrence complicates diagnosis and treatment. The causes of internalized and externalized disorders are complex and multifactorial. While internalized disorders were found to have a shared genetic risk (46), this observation could not yet be extended to externalized disorders. Besides genetics, biological (e.g., stress response (47)), social (e.g., social isolation or loneliness (48), but also childhood trauma (49)), and environmental (e.g., income inequality (50)) factors play a role in the development of mental disorders.

Studies have reported differences in prevalence rates between internalized and externalized orders between women and men. The prevalence of any lifetime internalizing disorder was significantly higher in women than in men, yet this was not the case for all individual internalizing disorders (45). Conversely, the prevalence of any lifetime externalizing disorder was significantly higher in men compared to women (45). These differences are stark and appear in almost exactly opposite directions between the two groups of disorders; women had two-fold higher odds of internalizing disorders than men, while this was the inverse for externalizing disorders. Furthermore, women had a roughly two-times higher projected lifetime risk of internalizing disorders than men, whereas men had a two-times higher projected lifetime

risk of externalizing disorders than women (45). Already in the ‘80s women were found the report a greater variety of symptoms, illnesses and injuries and more often a combination of physical and mental symptoms compared to men when visiting a physician (20) and were therefore more likely to receive a diagnosis of (an internalized) mental disorder. This remained stable over time. Currently, women are still more likely to receive a diagnosis of an internalized mental disorder (e.g., depressive disorder, anxiety disorder, and sleeping problems) and antidepressants and anxiolytics are more often prescribed for women than for men (51).

2.2.2 Depression, anxiety, and suicidal ideation

Depression is an emotion with functional and adaptive aspects (52). As a normal expression of mood, depression refers to a combination of *misery and lethargy*. Depression can also be considered a syndrome, referring to a constellation of depressive symptoms as described in DSM-5 (53). The definition of depression as a disorder is based on symptoms forming a syndrome and causing functional impairment (54). It’s a severe, oftentimes chronic, disorder that in a severe form leads to high dysfunction. Anhedonia, the diminished ability to experience pleasure, is characteristic of depression disorder, but also neurovegetative (e.g., fatigue and loss of appetite) as well as neurocognitive (e.g., ability to concentrate) symptoms mark depression (see Figure II. 1 for an overview of depression symptoms). Depression is one of the most frequent and harmful mental disorders with an estimated lifetime risk of 15–18% (54). The likelihood of recurrence is high, the risk increases with every episode, and, overall, almost 80% of patients experience at least one further episode in their lifetime. According to Eurostat, 7.2% of European citizens reported having a chronic depression in 2019. This was a small increase (+0.3%) compared to 2014 (55). In Germany, 11.6% of citizens reported chronic depression in 2019. Herewith Germany belonged to the leading five countries with regard to the prevalence of chronic depression in Europe.

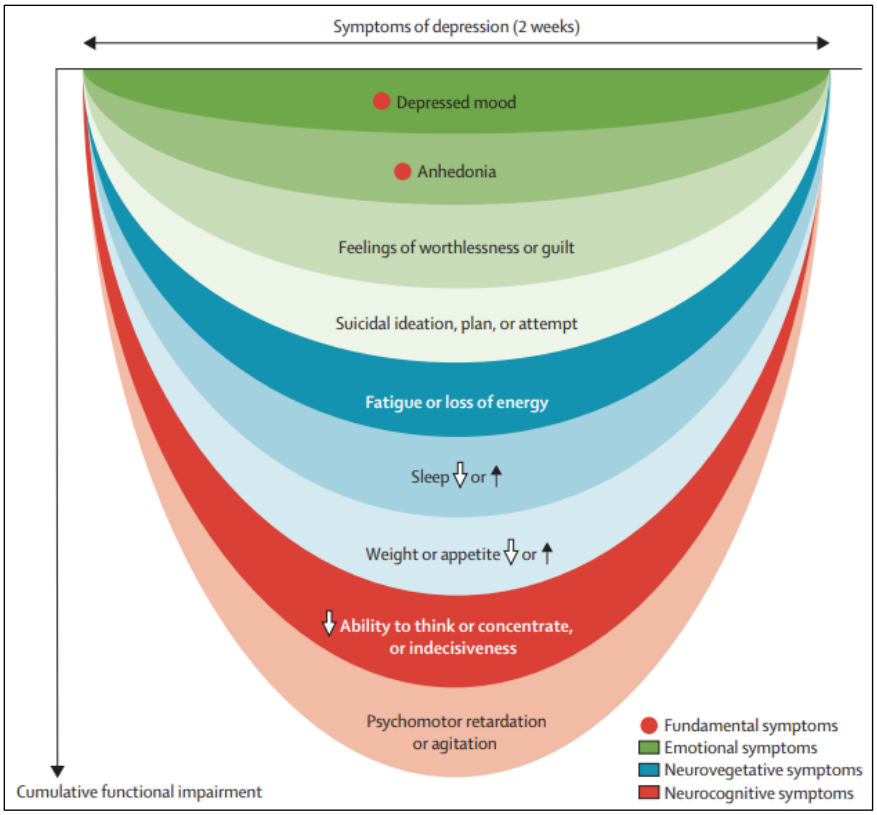

Figure II.1. Key symptoms of Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 for depression. Figure retrieved from publication *Depression* from Malhi and Mann in 2018 (p. 2).

Anxiety disorders are characterized by persistent, excessive worrying of or fear about everyday situations. Besides excessive worry, symptoms of anxiety include restlessness, irritability, fatigue, and difficulties sleeping and concentrating. Depression and anxiety are among the most common mental disorders. Both belong to the broader category of internalized disorders. Further, they are highly comorbid (54). A worldwide survey reported that 45.7% of individuals with lifetime major depressive disorder had a lifetime history of one or more anxiety disorders (56). This comorbidity was also found at the symptom level; 53% of patients with major depression had significant anxiety symptoms and were considered to have an anxious depression (57). Further, depression and anxiety often coexist during the same time period; 41.6% of individuals with a 12-month prevalence of major depression reported one or more anxiety disorders over the same time (56). The comorbidity of depression and anxiety differs with respect to the specific anxiety disorder; lifetime comorbidity with depression was estimated to range from 20% to 70% for individuals with social anxiety disorder (58), around 50% for individuals with panic disorder (58), and from 48% to 72% for individuals with generalized anxiety disorder (59). These percentages vary depending on whether the first diagnosis was a depression or anxiety disorder (59). A shared genetic risk exists between internalizing disorders and is strongest between major depression disorder and generalized anxiety disorder (46). A meta-analysis examining depression and anxiety from a neurobiological perspective revealed shared structural and functional brain alterations in circuits involving emotion regulation processes across depression and anxiety (60). Another meta-analysis found brain alterations with regard to cognitive control that were similar in people with depression and anxiety disorder (61). Due to the high comorbidity of depression and anxiety disorder and their symptoms and the shared structural and functional brain alterations,

depression and anxiety are often examined together under the umbrella term *mental distress* (38).

Suicidal ideation, thoughts or ideas about suicide, can also be a symptom of depression or exist without depression. Suicidal ideation can be passive or active. Passive suicidal ideation refers to thoughts of death without having any specific plan or intent to harm oneself, whereas active suicidal ideation involves thoughts of wanting to harm oneself and making specific plans to do so. The overall lifetime prevalence rate of suicidal ideation lies around approximately 9.2% (62). Expressions of suicidal ideation indicate great emotional distress. Suicidal ideation also interacts with depression and anxiety; individuals with anxious major depressive disorder were more likely to have suicidal thoughts (56, 57). Suicidal thoughts and behaviors cover a continuum which ranges from passive death wishes to dangerous attempts and deaths by suicide (63). The notion of the fundamental importance of social connectedness is a cornerstone of both the earliest and the most recent theoretical conceptions of risk and protective factors for suicidal thoughts and behaviors over the life span: At the end of the 19th century, Émile Durkheim analyzed statistics from several European countries that were directly or indirectly related to suicide rates. His seminal work „Le suicide“ (64) examined both societies in a historical context concerning their basic structural features, and individuals and their behavior in illustrative case studies. Durkheim distinguished different types of suicide (egoistic, altruistic, and anomic suicide). In all cases, the cause is to be sought in the relationship of the individual with the wider society. It was in this context that Durkheim coined the important term anomie. According to its Greek origin anomía (ἀνομία), anomie could be translated as lawlessness, normlessness or disorder. Durkheim used it as a descriptor of the state of the individual or a group lacking social ties. By means of the example of suicide, he stated that feelings of solidarity and social connectedness are literally vital in the sense that individuals cannot endure a life without them. Likewise, some of the most influential etiological theories have highlighted social connectedness and community as central protective factors, for instance, the Interpersonal Psychological Theory of Suicide (65), the Interpersonal Theory of Suicide (66), and the Integrated Motivational-Volitional model of suicide (67).

2.3 Biopsychosocial Model for mental health

In presuming there is always an interaction between the mind and the body, the biopsychosocial model of health was introduced by the internist and psychiatrist George Engel (68). This model was proposed by Engel as an alternative to the biomedical model that did not include social, psychological and behavioral dimensions of diseases. Engel recognized the great advances in biomedicine, but argued nevertheless that the biomedical model was limited, and insufficient for many aspects of medical science and healthcare. The biomedical model did not consider a person’s experience of illness, a person’s account of and attitude towards the illness (e.g., if a person regards the condition as an illness), the care of the patient as a person, the effect of the condition on living with this condition and it possibly changing course, and it did not consider the healthcare system. In the biopsychosocial model, these perspectives were integral parts of the overall approach to health or illness, respectively.

The biopsychosocial model includes the words *bio* referring to biological factors or physiological pathology, *psycho* referring to psychological factors such as thoughts, emotions, and behaviors, and *social* referring to socio-economical, socio-environmental, and cultural factors. Physiological pathology comprises biological and genetic determinants of health including age, sex, genotype, and inherited conditions. These factors determine one’s physical

structure, nervous system, body chemistry, and intelligence. Psychological factors are the aspects of mental and emotional well-being that also relate to behavior. Besides, thoughts, emotions, and behaviors they include distress, dysfunctional cognition, fear/avoidance beliefs, and coping methods. Social factors include for example work issues, family circumstances and economic disadvantages/benefits. Hence, the biopsychosocial model is an interdisciplinary model that considers the interconnection between biological, psychological, and socio-environmental factors. This model suggests that to understand a person's medical condition one should not only consider biological factors, but also psychological and social factors. Health and illness behaviors are the products of biological characteristics (e.g., genes), behavioral factors (e.g., lifestyle, stress, and health beliefs), and social conditions (e.g., cultural influences, family relationships, and social support). The model assumes that health and illness exist on a continuum. A person should be treated not only for their physical illness but rather, a focus on healthy behavior is equally important. Changes in beliefs, behavior, and helping patients develop coping mechanisms contribute to improving someone's health in a sustained way. Due to an ongoing interaction between the mind and the body, one's physical health influences one's mental health and vice versa.

The model, however, received multiple criticisms. On the one hand, the model itself was criticized as it was argued that the model lacked specific content and philosophical coherence and was too general. On the other hand, the validity of the model was criticized as it was said the model lacked scientific validity. Ghaemi (2009) being one of the opponents of the biopsychosocial model argues in his critique 'The Rise and Fall of the Biopsychosocial Model' that the model is too general and tells us nothing specific of value, hence is inefficient. The model was developed during a time in which there were ideological conflicts on what the causes of illnesses were. The biopsychosocial model solves this conflict by stating the cause of illness, and hence - in theory - both its prevention and treatment are biological, psychological and social. Ghaemi interprets the model to mean that all three levels (biological, psychological, and social) are more or less equally relevant in all cases at all times and it is unclear how to prioritize one aspect over another. However, in some persons or for some conditions the bio-aspect might be most important (e.g., bacterial infections and anti-biotic cures), whereas for other conditions the social aspect plays a crucial role. Kendler (69) who reviewed Ghaemi's work concluded that the biopsychosocial model has been inadequate for the scientific paradigm since it lacks validity and philosophical coherence. This validity is difficult to accomplish. The complex relations between the causes and effects of biological, psychological, and social factors to influence one's health status or occurrence of diseases are difficult to examine altogether. It requires elaborate and detailed information on persons/patients, which is not always available (or too time-consuming). However, Kendler argues the model does serve a useful clinical and teaching function in psychiatry and medicine. Thus, the model has often been criticized for being an overarching framework and thereby being too general and vague. As a solution, Bolton & Gillet (70) propose to rethink and reinvigorate the model and move away from the one overarching general model. The content should rather lie in the *scientific and clinical specifics*, e.g., the scientific and clinical content of the model should relate to specific conditions and stages of conditions. They propose individual models, for example, a biopsychosocial model of cardiovascular disease (CVD), diabetes or depression. In this way, one could still theorize biopsychosocial interactions in health and disease.

Yet, the biopsychosocial model is still very relevant and has become a renewed focus when studying mental health. An overview of the biopsychosocial model for mental health is displayed in Figure II. 2. The biopsychosocial model can be specified for depression and

anxiety (often combined under the umbrella term *mental distress* (38)). Biological (e.g., genetic factors and neurochemical response to stress), psychological (e.g., traumata, emotion regulation), somatic (diseases), and social and cultural (instability and insecurity, but also environmental factor) risk factors are included in the psychobiological vulnerability to depression, anxiety, and suicidal ideation (71-73). Gender plays an important role in all these aspects, since women, for example, have a greater psycho-biological vulnerability to depression and are exposed to more stressful, traumatizing life events and circumstances that heighten the risk of depressive disorders (71). Also, sex hormones (particularly oestradiol and progesterone) might play a significant role in differences in the prevalence, severity, and burden of anxiety between women and men (74). The gender paradox of suicidal ideation and behavior (e.g., the preponderance of deaths by suicide among men which is highest in Europe versus the higher prevalence of non-fatal suicide attempts and suicidal ideation in women) (75) can also be explained by an interaction between biological, psychological, social, and cultural factors.

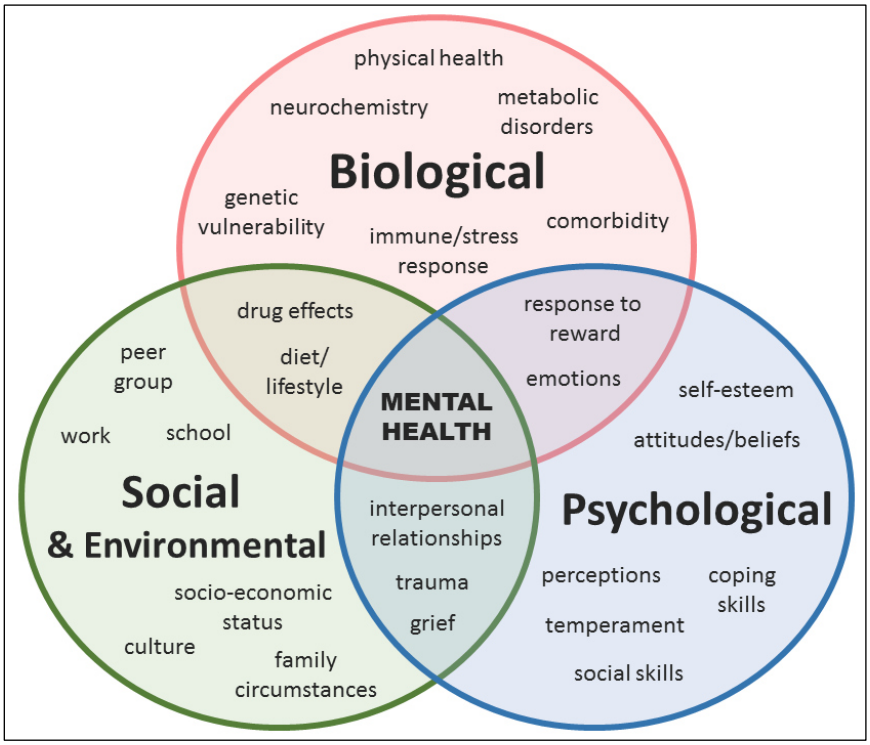

Figure II.2. The Biopsychosocial model for mental health. Based on *The Need for a New Medical Model: A Challenge for Biomedicine* from Engel in 1977.

2.3.1 Biogenetic and biological risk and protective factors for depression, anxiety, and suicidal ideation

With regard to biogenetic and biological risk factors, a main focus in depression research lies on the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis (proceeding from the hypothalamus), a neuroendocrine mechanism, mediates the effects of stressors by regulating numerous physiological processes, such as metabolism and immune responses. In case of a stressful event or situation, the sympathetic nervous system secretes epinephrine and norepinephrine that enact changes in the body as a response to the stressful event or situation

(e.g., increased heart rate or perspiration). Hereafter the HPA axis is stimulated since the hypothalamus responds to signals like elevated norepinephrine levels. The hypothalamus now secretes corticotropin-releasing hormone into the bloodstream which increases the activity of the sympathetic nervous system. It also gives a sign to the hypophysis to secrete andrenocorticotropic hormone into the bloodstream. As soon as this hormone reaches the adrenal cortex, andrenocorticotropic hormone binds to receptors on the surface of the adrenal cortices. This in turn leads to intracellular interactions resulting in the adrenal glands secreting glucocorticoids like the hormone cortisol (76, 77). Hence, the primary function of the activated HPA axis is to release glucocorticoids that activate short-term physiological responses to stress. For severe depression changes in the HPA axis were found, namely an increased amount of plasma cortisol due to excessive stress-related cortisol release and impaired glucocorticoid-receptor-mediated feedback inhibition (54). If a state of distress persists too long, it can lead to a dysregulation of the stress feedback system which in turn can lead to an individual being in a permanent condition of hyperarousal (52). This state of hyperarousal changes the functioning of the central nervous system (78). Prolonged or chronic conditions of stress and hyperarousal can result in neurotoxicity: changes in the central nervous system that cause malfunctions of the normal and flexible coping mechanisms for reducing stress, these mechanisms are no longer effective. In chronic and recurring depression, episodes often seem to arise even though no significant life events that lead to stress are manifest. So, they are independent of external stress factors and probably caused by a deficit in the mechanisms of coping with stress. Not only for depression, but also for anxiety associations between changes in the HPA axis and generalized anxiety disorder were found (79). Especially the glucocorticoid receptor function is impaired in anxiety disorders (80). An impaired ability to mount an adequate cortisol response is associated with greater psychological distress in general (81). Another example is the important role inflammation plays in depression and anxiety. High levels of pro-inflammatory cytokines predict future risk for depression and are associated with clinical anxiety (82). Neuroinflammation promotes a toxic environment unsuitable for proper brain activity and is harmful to mental health.

2.3.2 Psychological risk and protective factors for depression, anxiety, and suicidal ideation

A growing body of evidence supports the interplay between biological and psychological factors. Studies have shown that adverse childhood experiences, especially severe traumatic events such as child maltreatment (neglect, physical abuse, emotional abuse, and/or sexual abuse) increase the vulnerability to depression and anxiety. Such psychological traumatic experiences may in turn affect biological functioning. They can lead to neurobiological changes in stress regulation pathways with lasting effects triggered by epigenetic alterations (83). Such epigenetic alterations can also cause emotional dysregulation and cognitive deficits such as impaired executive function (84).

A predominantly psychological factor strongly influencing differences between individuals with and without depression and anxiety disorder and suicidal ideation is emotion regulation. Emotion regulation is defined as the use of cognitive or behavioral strategies in order to modify the circumstances in which an emotion occurs, the experience of an emotional response (including its intensity and duration), or the way in which an emotion is overtly expressed (85). Coping strategies are often divided into problem-focused coping and emotion-focused coping. The first refers to individual behavior to manage stressful situations by modifying or eliminating the sources of stress (86, 87). The latter refers to regulative efforts to diminish the emotional consequences of stressful events. Sometimes meaning-focused coping (or appraisal-based

coping) is mentioned as a third overarching category of emotion regulation mechanisms. It implies a coping process that generates positive emotions through individual beliefs, values and goals (88). Maladaptive emotion regulation strategies can lead to negative outcomes in the long run, whereas adaptive emotion regulation strategies more often assure positive outcomes. Examples of maladaptive emotional regulation strategies are rumination (repetitive and negative self-referential thought about causes and consequences of mood that involves a detrimental pattern of attention allocation) (89) or expressive suppression (attempting to control emotional responses by avoiding expressing them outwardly) (85). Adaptive emotion regulation strategies are, for example, reappraisal, acceptance, and problem-solving. Reappraisal can be described as thinking about a stressful event from a different perspective in a way that minimizes its negative impact. Acceptance can be understood as recognition of the value of oneself and others, to have an open attitude towards one's emotions and thoughts and external events (90). Problem-solving strategies are based on problem-focused action; it is defined by thoughts or ideas and direct action taken to solve the problem.

Maladaptive emotion regulation strategies (e.g., rumination) are found to be associated with impaired mental health, while adaptive strategies such as positive appraisal or positive focusing were associated with better mental health (91). In a study examining coping strategies of individuals with major depressive disorder and individuals with social anxiety disorder, results revealed that both groups, compared to never-disordered controls, more often applied rumination and excessive suppression strategies (92). They less frequently used reappraisal. Rumination was also in other studies found to be associated with depression (93). Moreover, an increased risk of developing depression exists when individuals use rumination strategies as a response to stressful events (94). Difficulties with emotion regulation were also found for individuals with generalized anxiety disorder (95). A meta-analysis on emotion regulation strategies (including acceptance, avoidance, problem-solving, reappraisal, rumination, and suppression) revealed avoidance, rumination, and suppression to be positively associated with anxiety and depression. Problem-solving was found to be a protective factor; it was negatively associated with anxiety and depression. For depression, reappraisal also showed a negative association with depression, but only a marginal negative association with anxiety. Acceptance was not associated with depression or anxiety (96). Furthermore, expressive suppression and cognitive reappraisal were found to mediate associations between self-compassion and social anxiety (97). Emotion regulation strategies also play a role in suicidal ideation. Theories have described that suicidal ideation and suicidal behavior are maladaptive strategies to reduce chronic and intense negative affect (98). In general, people who reported suicidal ideation and attempted suicide were found to use less useful coping strategies in response to stressful situations (99). A systematic review also concluded that difficulties in regulating one's emotions were associated with suicidal ideation (and also suicidal behavior) (100). Especially problems with emotional clarity were found to be associated with suicidal ideation and negative affect (e.g., anxiety, depression) (101). Thwarted belongingness as a known predictor of suicidal ideation and was found to be a mediator between several emotion regulation domains and suicidal ideation in young adults (102). In contrast to the negative impact of expressive suppression, Gross and John (2003) have found that those who primarily engage in cognitive reappraisal are more likely to share their emotions (both positive and negative) with others and maintain close relationships with friends. They also apply more self-regulation strategies in the form of coping and have a stronger social network compared to expressive suppressors (85).

2.3.3 Social and cultural differences in depression, anxiety, and suicidal ideation

Differences in mental health relating to social and cultural factors cover an enormous spectrum of relevant factors. It ranges from relevant factors on an individual level such as one's family status / relations, received social support, and/or SES (e.g., education level, employment, income) to society-level factors such as social norms and issues, prejudice and stigmatization, labor market, but also historical and socialization differences. These factors are mostly intertwined and work together to influence the prevalence of mental disorders, ways in which health and illness are perceived, and help-seeking behavior.

Demographic aspects, especially age, play an important role in depression, anxiety, and suicidal ideation. Many studies have focused on the emergence of mental disorders across ages and the differences in prevalence, symptomatic, and burden of mental disorders in different age groups. A large-scale worldwide meta-analysis including 192 epidemiological studies concluded that the new onset of mental disorders often takes place at a young age (103), in many of those affected already before the age of 25. The new onset of mood disorders, however, starts mostly around the age of 31. The median age of new onset of generalized anxiety disorder lies around the age of 32. The median of new onset of depression disorder lies around 30. A study comparing several European countries revealed an overall pattern of a steady increase in the cumulative proportion of internalizing disorders with an increase in age (45). A study in Great Britain examined the prevalence of suicidal ideation over the lifespan. This study revealed suicidal ideation to be three times more common in younger adults than in those aged 55-74 (104). Risk factors for suicidal ideation were comparable across age groups. A review study on prevalence rates of depression and anxiety across age groups found an indication for a decrease in depression, anxiety, and mental distress across age groups (105). However, results were not consistent and it is discussed whether these are actual age or merely cohort effects.

Social relations play an important role in mental health. Especially close social relations as can be found in a partnership (marriage, living with a partner) were shown to improve psychological well-being, whereas parenthood increases psychological distress (106). A systematic review and meta-analysis including only longitudinal studies revealed an increased risk of depression for people living alone (107). Furthermore, living alone and having never been married, currently not married, and currently single (in some studies interpreted as social isolation) were associated with an increased risk of social anxiety disorder (108). Living alone was also found to be associated with suicidal ideation and suicide attempts (109). A further important social factor is loneliness, which can be described as a complex set of feelings encompassing reactions to the absence of intimate and social needs (110). It is a concept referring to the subjective aspect of the social condition of isolation. Loneliness was found to be positively associated with the new onset of depression and anxiety (111). Loneliness was also found to be associated with suicidal ideation (109), self-harm (111), and to have a major impact on suicide attempts (109). These findings confirm Durkheim's theory stating that suicide rates are inversely correlated with social integration and hereby highlight the importance of the social dimension in suicidal ideation and behavior (64). Joiner's Interpersonal Theory of Suicide emphasizes the importance of social connection and highlights thwarted belongingness (a feeling of not being an integral part of a group) and perceived burdensomeness as key elements in the emergence of suicidal ideation and further suicidal processes (65). A person can achieve social belonging by experiencing social support from their direct or indirect environment and support from the direct environment has indeed been shown to improve mental health and psychological well-being (112). Social support was found to be negatively

associated with depression, anxiety, bipolar disorder, and schizophrenia (113, 114). Especially perceived social support within the family context was found to be a protective factor for depression and anxiety (115). A meta-analysis including research on risk- and protective factors of suicidal ideation and behavior covering 50 years of research concluded that the protective factor of social support is examined very differently in studies and the differences in time spans accounted for diverging results (116).

Review studies and meta-analyses including both prevalence and incidence studies concluded that persons with a lower socioeconomic are at a higher risk of depression (117). Furthermore, socioeconomic factors such as a low level of education and unemployment were positively associated with diagnoses of major depression and generalized anxiety (118). SES is often linked to suicidal ideation and suicidal behavior. Low education and unemployment or precarious employment lead to an increase in suicidal ideation and suicide attempts (119), especially in the younger population (120). In the case of SES, a link between psychological and social factors was found, the emotion strategy reappraisal predicted lower anxiety for people with a low SES, but not for people with a high SES (121).

On a higher level, societal factors play a role in people's mental health as well. An important factor is socialization. Socialization processes can be defined as social influences through which individuals acquire values, standards of behavior, attitudes, and skills that are regarded as desirable and appropriate for a certain society (122). These processes enable a person to function within a certain culture or society. Socialization processes thus are society- and culture-dependent and highly influenced by historical events, as well as economic and political systems. This is an important topic that should be taken into account when studying mental health and is especially relevant in Germany which was divided into two countries at the end of the Second World War. In contrast to the Federal Republic of Germany which followed the West European system and was shaped by capitalism, the German Democratic Republic (GDR) was a centralized, socialist society founded following Soviet occupation after World War II. The focus on collectivist values in the GDR (123) versus the focus on individualistic values in the GDR (124) caused extremely different socialization and living conditions. The German reunification in 1990 required the strongest adaptations from East Germany (or the former GDR). Economic, social, and cultural differences have remained to be embedded in Germany differentiating East from West Germany. Before the reunification, personal freedom and mobility were higher in West Germany, whereas the provision of childcare early on in the East promoted regular participation of mothers in paid labor in East Germany (125). These distinctions were not synchronized immediately after reunification. Furthermore, the reunification caused major unemployment, loss of social security, and job insecurity in East Germany. These differences, embedded in and shaped by social contexts, have also led to differences in mental health. A large nationally representative survey reported a higher prevalence of depression and social anxiety in the Western states in 1998/1999 (126). However, the subsequent survey in 2014 revealed no such differences (127). Currently, rates of depression and anxiety are still higher in West Germany compared to East Germany (128). Although not much is known about the dynamics of suicidal ideation in East and West Germany over the years, suicide rates are currently still highest in East German states (129).

2.4 Biopsychosocial factors in depression, anxiety, and suicidal ideation for women and men

With regard to biological factors, the proper functioning of the HPA axis is critical for the maintenance of mental and physical health, as dysregulations of the HPA axis have been linked to several mental and physical disorders. Numerous studies have observed distinct sex differences in the regulation of the HPA axis in response to stress, and it is hypothesized that these differences may partially explain the female predominance in stress-related mental disorders. Preclinical models have clearly shown that the HPA axis in women is activated more rapidly and produces a larger output of stress hormones than in men (130, 131). A review on brain sex differences concluded that these differences are partly caused by direct genetic effects and have grave implications for an individual's mental and physical health (17). Sex hormones differentially affect women and men by altering both their gut microbiome composition and their immune status, particularly microglial cells (82). The existing evidence concerning sex differences in stress and immune responses is mixed. In some studies, women were found to respond better to stressful events and inflammatory conditions. Women resolve local inflammatory responses more rapidly than men (132). Furthermore, adult men seem to respond to typical psychological stressors with a greater increase in cortisol compared to age-matched women (133). Lastly, social isolation causes more mortality in men mediated by greater immune activation (134). Other studies show disadvantages for women with regard to inflammatory responses. In women, systemic inflammation impairs mood and affective behavior more than in men (135). Besides, women seem to exhibit more robust stress responses and more potent immune responses compared to men (136).

Psychological factors, especially early stress such as childhood adversity and later outcomes such as emotion regulation strategies differ between women and men and influence mental health in women and men. Overall, child abuse has stronger negative consequences for women than for men; as effect sizes of overall child abuse on poor physical health in adulthood were larger for the sample of women compared to the sample of men (137). Also, the effects of physical and sexual abuse on depression and anxiety in adulthood were larger for women (138). Furthermore, a history of childhood physical or sexual abuse (139) and a history of emotional abuse (140) were, in both women and men, associated with suicidal ideation in adulthood. Rumination as an emotion regulation strategy is more often applied by women than men (141, 142). Furthermore, women were more likely to report the strategies of catastrophizing and positive refocusing (141) as well as active coping and emotional support (142). With regard to reappraisal and acceptance, results are mixed. For several emotional regulation mechanisms associations with depression were found. Rumination was for both women and men positively associated with depression (141, 142). Furthermore, catastrophizing and self-blame (141) as well as suppression (142) were for both women and men positively associated with depression, whereas positive appraisal functioned as a protective mechanism for depression (141). Sex hormones might influence the selection and consequences of emotion regulation strategies. For women, estradiol levels were associated with rumination as an emotion regulation strategy, but not with suppression or reappraisal. High estradiol and high progesterone combined with reappraisal as well as low estradiol combined with rumination predicted negative affect in women (143). Lastly, with regard to suicidal ideation and suicidal behavior, a study revealed that women who attempted suicide used less useful coping strategies as a response to stressful situations than men who had attempted suicide (99). Furthermore, for men, life meaning can act as a buffer between coping style and suicidal manifestations (96).

A broad range of social and environmental factors differ between women and men and affect one's mental health. Relationship status was for both women and men found to be associated with mental health, e.g., marriage, having a partner or living together with a partner were found to be beneficial for mental health. However, for both women and men relationship status and mental health were moderated by relationship quality (144). For women, being in a poor-quality relationship was associated with greater levels of anxiety (144). Furthermore, depression was more often present in single mothers, which could partly be explained by differences in exposure to stress and reduced social support (145). Suicidal ideation and suicide risk is higher among individuals not having a partner, this is especially a strong risk factor for men (146). With regard to age, the new onset of internalizing disorders, especially depression, differs between women and men in the sense that from adolescence onwards women have a higher risk of newly developing depression (147, 148). This elevated risk persists until the mid-50s. For men, from 60 years onwards, the internalizing disorders appear to plateau (12). The higher prevalence rates of internalizing disorders for women compared to men can thus be traced back to the higher risk of the first onset of internalizing disorders, but not to differential persistence or recurrence of disorder (148). SES has been shown to be inversely related to the risk of anxiety and depressive disorders among women (149, 150). The higher risk of depression and especially the persistence of depression in women can partly be explained by the higher levels of *double burden* (combining child rearing and domestic tasks with work and career) experienced by women (151, 152). Similar results were found for women with anxiety disorders. Women had a significantly lower SES than men and reported a higher negative impact of substantial reductions in income (153). Furthermore, lower SES (unemployment and lower income) had a stronger effect on suicide risk for men than for women (146).

2.5 Biopsychosocial model in somatic health

Besides its relevance for mental health, the biopsychosocial model is also extremely relevant for psychosomatic medicine. Prospective epidemiological studies suggest that risks for many major illnesses, physical and mental, start early in development, many in childhood, and that risks include *social factors* such as poverty and other forms of social exclusion, some specific *family-level factors* such as neglect and abuse, and *lifestyle factors* such as exercise and diet. Several reviews and meta-analyses revealed associations between childhood maltreatment and physical and mental illnesses later in life. Associations were observed between physical and emotional abuse and neglect and drug use, suicide attempts, and sexually transmitted infections and risky sexual behavior (154). All forms of child maltreatment (any child maltreatment, sexual abuse, physical abuse, emotional abuse, neglect, and exposure to intimate partner violence) were associated with depressive disorders (155). Several forms of child maltreatment (any child maltreatment, sexual abuse, physical abuse, and neglect) were also significantly associated with anxiety disorders. Significant associations were also found between several forms of child maltreatment and PTSD. Overall, child abuse was associated with an increased risk of poor physical health in adulthood. Neurological and musculoskeletal problems yielded the largest effect sizes, followed by respiratory problems, CVD, gastrointestinal and metabolic disorders (137). Furthermore, child abuse was associated with obesity in adult life (156). This was found for abuse in general as well as for each kind of physical, emotional, and sexual abuse. The association was stronger for severe abuse versus light/moderate abuse. As possible pathways, experts discuss the induction of mental and emotional perturbations, maladaptive coping responses, stress, inflammation and metabolic disturbances. Lifestyle factors, comprising behaviors and associated beliefs, attitudes and

values, have been increasingly implicated as risk-, or conversely as protective factors, for a wide range of physical and mental health conditions. For CVD, the classic risk factors such as dyslipidemia, hypertension, and diabetes mellitus have been extended by lifestyle risk factors such as dietary habits and obesity, physical inactivity, and smoking, often via pathways of inflammation or oxidative stress (157). Recent research on social factors as causes or risks for poor health — the so-called 'social determinants of health' — is probably the most well-known, new face validation of the need for a broad biopsychosocial model. Furthermore, the social gradient in health, i.e., the correlation between indices of social status and health outcomes is now well-established; and much is now known about the social determinants of health (158).

2.6 Mental ill-health and mortality

Empirical evidence supports that mental disorders are a risk factor for reduced life expectancy or mortality, respectively. Findings on years of life lost due to mental disorders differ between studies and tend to depend on the follow-up time of the study, year of the study, type of mental disorder(s) included, and country. Data from the Global Burden of Disease including 20 mental and substance use disorders in 187 countries revealed that the burden of mental and substance use disorders increased by 37.6% between 1990 and 2010 (159). This observation could, however, be explained mostly by population growth and an aging population. In 2010, 0.5% of all years of life lost to premature mortality were caused by mental and behavioral disorders. A meta-review (review of systematic reviews) focusing on all-cause (including suicide) mortality in mental disorders revealed that all mental disorders samples had higher mortality risks than the general population samples (160). A review and meta-analysis including results from 148 studies found a pooled relative risk of mortality in those with mental disorders of 2.2 and 14.3% of deaths worldwide being attributable to mental disorders (41). Of these, 135 studies revealed that mortality was significantly higher among people with mental disorders than among the comparison population and based on 24 studies the median years of life lost was 10. A 17-year follow-up of a nationally representative survey in the USA demonstrated a shortened life expectancy of approximately 8 years for people with mental disorders (161). A large-scale longitudinal study in the Scandinavian countries harnessing national psychiatric case registers, reported a shortened life expectancy of at least ten years for persons with a diagnosis of an affective disorder, a diagnosis in the schizophrenia spectrum, a substance abuse disorder, or a personality disorder (162). All-cause mortality was significantly elevated for mood disorders, psychoses, and anxiety (41). According to the German statistical office, mental and behavioral illnesses accounted for 59,990 deaths in Germany in 2021 (163).

Personality disorders, schizophrenia, and substance use disorders were assigned the highest increased risk for mortality based on all medical conditions and diseases (162). Although mortality risk was higher for psychoses than for depression (41), depression accounted for the largest number of loss of healthy life years (159). A review including only studies of the general population, assessing mental disorders using structured or semi-structured diagnostically oriented interviews, response rates above 60%, and a sample size larger than 500 respondents, revealed an increased risk in all-cause mortality due to depressive disorders of approximately 70% (relative risk of 1.7) (164). A meta-analysis including 25 studies encompassing 106,628 participants of whom 6,416 were depressed reported a relative risk of mortality of 1.8 in depressed participants (major depression as well as subclinical forms of depression) compared to non-depressed subjects (165). However, the relative risk was not

corrected for chronic illnesses or lifestyle factors, which are known to be extremely important confounding variables (as described above).

Mortality caused by mental disorders can, for the most part, be attributed to natural/medical causes, especially chronic diseases (41, 161). A small part of mortality caused by mental disorders (5.4%-17.5%) can be attributed to unnatural causes (e.g., accidents or suicides). Mortality caused by mental disorders is often due to CVD (161, 162, 166), especially coronary heart disease. The increase in expected mortality due to CVD was found to increase two- to three-fold in all diagnostic mental disorder groups (162). Furthermore, the most common deaths for persons with mental disorders were due to CVD (33.9%) (161). Besides CVD, mortality caused by mental disorders can be attributed to cancer (21.0%) (161, 162), respiratory or pulmonary disease (13.5%) (161, 166), and infectious diseases (162). However, only a trend for an increased risk of mortality was found after controlling for demographic factors, SES, health system factors (e.g., health insurance), and baseline clinical characteristics (e.g., health status and BMI) (161).

The risk of elevated mortality caused by mental disorders differs between women and men. A Finish study revealed an association between mental disorder and elevated mortality, a relative risk of 1.6 in men and 1.4 in women (166). For women with a diagnosis of an affective disorder, a diagnosis in the schizophrenia spectrum, a substance abuse disorder, and a personality disorder the life expectancy was approximately 15 years shorter, whereas for men it was approximately 20 years shorter (162). In Germany, mental and behavioral illnesses accounted for more deaths in women (61.9%) than in men (163). With regard to mortality due to natural/medical causes, deaths caused by depression were attributed to CVD (especially coronary disease) in men, whereas they were attributed to respiratory disease in women (166).

In addition to natural causes, elevated mortality caused by mental disorders is attributed to unnatural causes, especially self-harm and suicide (42, 166, 167). Data from the Global Burden of Disease revealed suicide to be the 13th leading cause of death globally (168) and accounted for 5% of deaths in women and 6% of deaths in men in persons aged 15-49 years old. Suicide was more prevalent in regions with advanced healthcare systems, raising concerns regarding the correct identification and unbiased reporting of suicide deaths. Affective or mood disorder (i.e., depression and bipolar disorder) and personality disorder posed the highest risk of suicide (160, 162). The elevated risk of death from injuries and suicide was among women the highest for mood disorders, whereas among men it was highest for (neurotic) depression (166).

3 Study 1: Similarities and differences of mental health in women and men: A systematic review of findings in three large German cohorts

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3.1 Introduction

Mental disorders have become major public health concerns affecting quality of life, work productivity and life expectancy (1) of a large proportion of the general population. Representative German studies have shown that approximately one in three women and one in four or five men had a diagnosis of a mental disorder in the previous 12 months (2). For most internalizing disorders (e.g. major depression and eating disorders), women are more frequently affected (3, 4), whereas for externalizing disorders (e.g. substance abuse) men are more frequently affected.

Mental health differences between women and men have been attributed to sex and gender differences. Rooted in genetics, anatomy, and physiology (5), sex represents a biological construct. In contrast, gender comprises psychosocial variables that differentiate women and men (6) elucidating societal conditions and offering explanatory models. Gender can be differentiated according to 1) gender roles: behavioral norms attributed to women and men in a given society; 2) gender identity: how people see themselves on the dimensions of femininity-masculinity; 3) gender relations: how individuals interact with or are treated by others based on ascribed or experienced gender; and 4) institutionalized gender: distribution of power between women and men in institutions in society which shapes social norms and justifies different expectations and opportunities for women and men (5). Sex differences in mental health can be explained by sex hormones (7, 8) and dysregulations in the HPA axis (7, 9), especially for stress-related psychiatric disorders. Gender differences in mental health can be explained by e.g. gender-based violence (10), low self-esteem (7) and belonging to a gender minority (11). The interplay between sex and gender is an important factor in mental health. Sex and gender interact in the development of diseases (12, 13) (e.g. depressive disorders (14)) and coping strategies (15). The association between biological sex and mental health in Europe is moderated by socioeconomic and family-related factors (16), which explain about 20% of the differences in mental health between women and men. Such factors are for example employment (16, 17), education, housekeeping or looking after children and income (16, 18). The inverse association between socioeconomic position and morbidity and mortality has been termed social gradient of health (19). While multiple inequalities between women and men (e.g. gender pay gap, lower pension due to maternity leaves and part-time employment) are known, interactions between sex and socioeconomic position, which may put women at a disadvantage have been understudied (19).

Sex and gender differences vary across countries and regions (20). In a study including 48 countries, males have consistently reported higher self-esteem than females, but the strength of this effect differed between countries (21). Furthermore, sex, gender and cultural differences for self-reported emotional intensity (arousal) were found between the Chinese and German culture (22). However, in a study on the universality of emotions across 37 countries, no differences were found between women and men (23); in all countries men reported more powerful emotions (e.g. anger), whereas women tended to report powerless emotions (e.g. fear or sadness). A study focusing on similarities and differences in three psychological domains (cognitive domain, social and personality and well-being) combined numerous meta-analyses and identified only small differences between women and men (24). These differences remained consistent across countries. Regional differences regarding material living standards and employment conditions may also affect women and men differently (20). In examining mental health, it is therefore important to consider differences between countries and regions.

In Germany, large population-based cohort studies have been implemented in order to identify risk and protective factors for health in the general population. Major ongoing cohorts have been established between 1983 and 2007. These include the representing different German regions, respectively, the southern, north-eastern and middle part of Germany. KORA (Cooperative Health Research in the Region Augsburg) focusses on the fields of epidemiology, health economics, and health in the region Augsburg (formerly Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA)), the Study of Health in Pomerania (SHIP) and the Gutenberg Health Study (GHS), care research (25), SHIP contains a broad range of health and quality of life indicators (26) and GHS focusses on uncovering risk factors for several conditions, such as CVD and mental diseases (27). The three cohort studies followed representative samples of participants stratified by sex and age, which were drawn in comparable ways from their respective regions (28) (GHS: *N* = 15,010 respondents, 35-74 years; KORA: *N* = 18,079 respondents 25-74 years; SHIP: *N* = 12,324 respondents 20-79 years). The three German regions differ regarding socioeconomic and economic parameters: Unemployment rates are highest, discretionary incomes, and life expectancy lowest in Greifswald (SHIP). As the eastern and western states of Germany have evolved in different political and economic systems following World War II, these regions show pronounced differences regarding full-time employment rates among mothers resulting in different gender pay gaps (28).

These three cohorts also include mental health variables and are therefore particularly suitable to derive knowledge on sex, mental health and their relationships to physical health. The GESA consortium (Gender Sensitive Analyses of mental health trajectories and implications for prevention) has recently been established to enable future conjoint analyses (28). The purpose of this systematic review is to analyze published findings from the three cohorts and to identify sex-specific prevalence rates of mental disorders and to identify risk and protective factors and regional effects.

3.2 **Methods**

Published studies were identified through searches of the databases PubMed and Web of Science. We included studies from initiation of each cohort until June 2019. KORA started in 1996 (25) following its precursor MONICA which had started in 1984, SHIP started in 1996 (26) and GHS started in 2007 (27). Keyword, title, authors and abstract information were used. The search terms were `*KORA*`, `*Cooperative Health Research in the Augsburg Region*`, `*SHIP*`, `*Study of Health in Pomerania*`, `*GHS*` or `*Gutenberg Health Study*` combined with `*mental health*`, `*sex*` or `*gender*`. English and German publications were considered. Unpublished papers, abstracts, dissertations and book chapters were not included. The search took place from April until June 2019.

To decide whether an article fulfilled the criteria, the first rough selection was made by inspecting the title and abstract of the article. To identify relevant studies, the following inclusion criteria were used:
1) studies using KORA, SHIP or GHS data;
2) cross-sectional and longitudinal/prospective studies addressing mental health;
3) studies containing sex, respectively gender.

Furthermore, it was required that the articles either 1) contained descriptive statistics on mental health variables including statistical tests that probed for differences between women and men, or 2) tested factors related to mental health with separate analyses for women and men, respectively analyses with an interaction term for sex. We only selected papers that included mental health as a dependent variable. This first group of articles was used to describe prevalence rates of mental health for women and men. The second group of articles was analyzed to describe explanatory factors for mental health between women and men. Of the selected articles the literature list was meticulously examined and further relevant articles were selected. Articles including analyses with mental health as dependent variable, but only including sex as a control factor, were not taken into account. Articles containing descriptive statistics for mental health aspects, but without differences between women and men (statistically tested) were excluded. Lastly, we excluded methodological papers. The selection procedure is displayed in detail in Figure III.1.

Mental health is a broad concept. In this article, we were guided by the definition of WHO including mental, physical and social well-being, not just the absence of mental disorders (29). Similarly, Galderisi and colleagues *(30)* interpreted mental health as a dynamic state of well-being changing through lifetime and depending on life events. Therefore, not only mental disorders, but also mental health aspects such as well-being, somatic symptoms, loneliness and resilience were taken into account in this review.

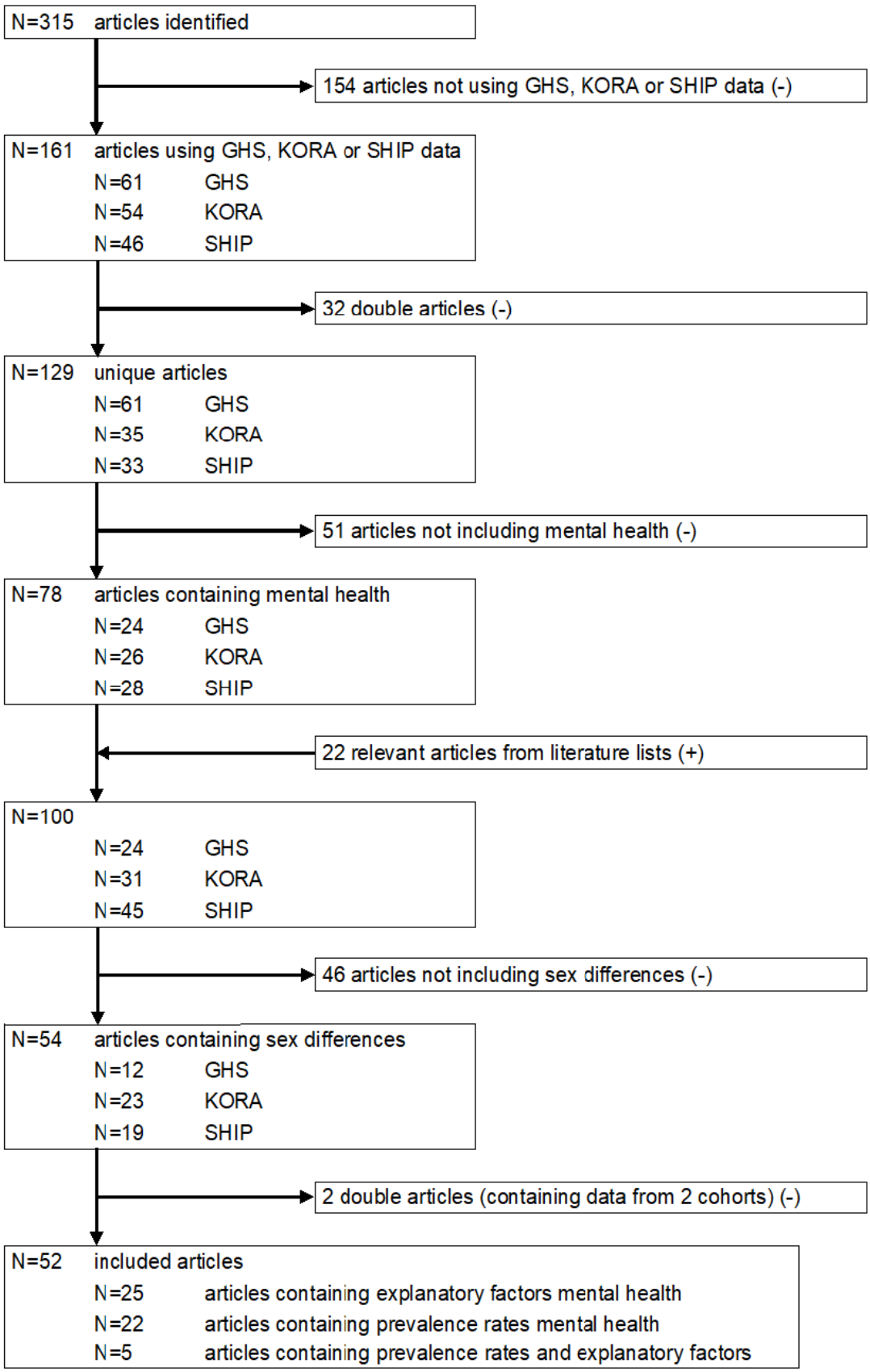

Figure III.1. Overview of identified, screened and included articles.

3.3 Results

Our search strategy has identified 52 articles reporting GHS, KORA or SHIP data on mental health and sex differences. We found articles reporting prevalence rates of mental health [*N* = 22], explanatory factors for mental health [*N* = 25] and articles reporting both [N = 5].

Articles assessing gender differences based on gender identity and gender relations were not found, but some articles included variables indicating gender aspects related to gender roles and institutionalized gender. Previous research indicated gender differences in power, responsibilities and in dimensions of the self (4), contributing e.g. to lower income of women, more responsibilities in childcare and more domestic work. In another previous study a gender index based on secondary data specified taking care of children, being unemployed, working few hours and lower education as indicators for feminine gender roles (31). Such socioeconomic and family-related factors were included as possible gender factors.

3.3.1 Prevalence of mental health complaints

The articles reported a broad range of prevalence rates of mental health indicators for women and men. The articles are consistent in their findings, but most prevalence rates were only reported in one or two of the three cohorts, based on specific diagnostic instruments. The results are listed in Table III.1.

Table III.1. Results prevalence rates mental health for women and men.

Authors, year	Study	*N*	Mental health construct	Measurement scale, cut-off value (range)	Total	Women[1]	Men[1]	p-value[2]
Grabe et al., 2009 (37)	SHIP	3,300	depression	CID-S[6]: two items, ≥1 (0-2)	4,310	807 (36.8%)	507 (23.9%)	**p<.05**
			anxiety	CID-S[6]: five items, ≥1 (0-5)	4,310	1223 (55.8%)	823 (38.9%)	**p<.05**
			somatization	CID-S[6]: one item, ≥1 (0-1)	4,310	384 (17.5%)	308 (14.5%)	**p<.05**
Grabe et al., 2009 (51)	SHIP	3,045	traumatic event	PTSD module of SCID[7], ≥1[7a]	3,045	830 (52.8%)	833 (56.5%)	**p<.05**
			PTSD[3]	PTSD module of SCID[7], ≥6 (0-17)[7b]	1,663	43 (5.2%)	24 (2.9%)	**p<.05**
Spitzer et al., 2009 (52)	SHIP	3,171	PTSD[3]	PTSD module of SCID[7], ≥1 (0-17)[7c]	3,171	42 (2.5%)	20 (1.3%)	**p≤.007**
Michal et al., 2010 (45)	GHS	4,912	suicidal ideation	Item PHQ-9[8], ≥1 (0-3)	4,912	223 (9.2%)	151 (6%)	**p<.001**
Appel et al., 2011 (36)	SHIP	2,157	depressive symptoms	BDI-II[9], continues (0-63)	2,157	7.0±7.9	5.7±6.3	**p<.001**
			MDD[4]	M-CIDI[10]	2,157	253 (22.3%)	117 (11.5%)	**p<.001**
Michal et al., 2011 (57)	GHS	4,900	depersonalization	CDS-2[11], ≥3 (0-6)	4,900	20 (0.8%)	21 (0.8%)	p=.96
Spitzer et al., 2011 (32)	SHIP	1,772	mental health problems	CID-S[6], ≥1 (0-12)	1,772	372 (40.9%)	261 (30.2%)	**p≤.001**
Wiltink et al., 2011 (33)	GHS	5,000	mental distress[5]	PHQ-9[8], ≥10 (0-27); PHQ panic module[12], ≥2 (0-4); Mini-Spin[13], ≥6 (0-12); GAD[14]-2, ≥3 (0-6)	4,753	453 (19.4%)	304 (12.6%)	**p≤.001**
Beutel et al., 2012 (56)	GHS	4,928	type D personality	DS14[15], ≥10 (0-28)	4,928	561 (23.1%)	534 (21.3%)	p=.13
Grabe et al., 2012 (38)	SHIP	2,035	depressive symptoms	BDI-II[9], continues outcome (0-63)	2,035	7.0±7.9	5.7±6.5	**p<.001**
Grabe et al., 2012 (35)	SHIP	1,974	depressive symptoms	BDI-II[9], continues outcome (0-63)	1,974	7.0±7.8	5.6±6.2	**p<.001**
Häfner et al., 2012 (50)	KORA	1,369	sleep disturbances, no depressed mood	USI[16], ≥3 (1-6); DEEX[17], ≥12 women; ≥10 men (0-24)	1,369	157 (22.1%)	95 (14.4%)	**p<.01**
Perna et al., 2012 (58)	KORA	3,347	resilience	RS-11[18], upper third	3,347	536 (30.5%)	501 (31.5%)	p=.17
Ladwig et al., 2013 (53)	KORA	3,000	full PTSD[3]	PDS and IES[19]	3,000	32 (2.1%)	19 (1.3%)	**p<.001**
Michal et al., 2013 (34)	GHS	4,937	depression	PHQ-9[8], ≥10 (0-27)	4,937	212 (8.7%)	145 (5.8%)	**p<.001**
Michal et al., 2014 (48)	GHS	9,751	severe sleep problems	Item PHQ-9[8], ≥2 (0-3)	9,751	548 (11.4%)	354 (7.2%)	**p<.001**

Schneider et al., 2014 (46)	KORA	1,2888	committing suicide	Death certificates	12,898	18 (0.3%)	30 (0.5%)	**p=.001**
Zebhauser et al., 2014 (41)	KORA	1,022	mild/moderate depression	Geriatric Depression Scale-15[20], ≥4 (0-15)	1,058	87 (17.2%)	60 (10.9%)	**p=.011**
			anxiety	GAD-7[14], ≥10 (0-21)	1,005	53 (10.6%)	24 (4.8%)	**p=.005**
			low life satisfaction	Item Satisfaction With Life Scale[21], ≤4 (0-10)	1,022	32 (6.3%)	24 (4.7%)	p=.24
			low resilience	RS-11[18], lowest two thirds	993	356 (71.8%)	333 (67.0%)	p=.10
Zebhauser et al., 2015 (55)	KORA	346	living alone and loneliness	Item living alone (dichotom); UCLA-Loneliness-Scale-12[22], ≥21 (0-36)	346	76 (29.6%)	29 (32.6%)	p=.59
Beutel et al., 2017 (54)	GHS	14,661	severe loneliness	Item frequency alone, =4 (0-4)	14,413	165 (2.3%)	83 (1.2%)	**p<.001**
Goltz et al., 2017 (44)	SHIP	3,926	depression and obesity	PHQ-9[8], ≥10 (0-27); WHR[23], > 0.85 females; > 1.0 males	3,926	77 (3.8%)	25 (1.3%)	**p<.010**
Rose et al., 2017 (49)	GHS	7,930	fatigue	PBS[24], ≥50 (0-100)	7,948	1,266 (35.8%)	918 (20.9%)	**p<.001**
Atasoy et al., 2018 (43)	KORA	9,340	depressed mood	DEEX[17], ≥12 women; ≥10 men (0-24)	9,340	1,702 (37.6%)	1,814 (37.7%)	p=.96
Beutel et al., 2018 (40)	GHS	12,061	new onset of depression	PHQ-9[8], ≥10 (0-27)	10,036	232 (5.0%)	205 (3.8%)	**p=.003**
König et al., 2018 (42)	SHIP	2,265	lifetime MDD[4]	M-CIDI[10]	2,265	267 (22.5%)	119 (11.0%)	**p<.001**
Beutel et al., 2019 (47)	GHS	7,974	somatic symptom load	PHQ-12[25], ≥4 (0-24)	7,974	1,121 (28.8%)	1,073 (16.1%)	**p<.001**
Schlax et al., 2019 (39)	GHS	1,2484	depressive symptoms	PHQ-2[8], ≥2 (0-6)	12,484	1,598 (26.4%)	1,281 (19.9%)	**p<.001**

[1]Number and percentage or mean and standard deviation.
[2]Bold printed values significant.
[3]Post-traumatic stress disorder.
[4]Major depressive disorder.
[5]Depression, panic, social anxiety or generalized anxiety.
[6]Composite International Diagnostic Screener (CID-S): 12 yes/no questions addressing different diagnostic domains.
[7]PTSD module of the Structured Clinical Interview for DSM-IV (SCID) measures experience of traumatic event and PTSD symptoms, including criterion A2 (experiencing high distress during/after event), criterion B (five re-experiencing symptoms), criterion C (seven avoidance symptoms), and criterion D (five arousal symptoms);
[7a]Experiencing more than one traumatic event varying from combat or war zone experience to rape or abuse and illness.
[7b]Experiencing 1 re-experience (0-5), 3 avoidance (0-7) and 2 hyperarousal (0-5) symptoms.
[7c]Experiencing 1 re-experience (0-5) (no avoidance (0-7) or hyperarousal (0-5)) symptoms.
[8]Patient Health Questionnaire 2 or 9 (PHQ-2 or PHQ-9) screens, diagnoses, monitors and measures severity of depression with 2 or 9 items (4-point-Likert rating scale, 0-3).
[9]Beck Depression Inventory-II (BDI-II) measures presence and severity of depressive symptoms with 21 items (4-point-Likert rating scale, 0-3).
[10]Munich-Composite International Diagnostic Interview assesses psychiatric disorders over the lifespan according to DSM-IV criteria.

[11]Brief Cambridge Depersonalization Scale (CDS-2) measures frequency and duration of depersonalization symptoms with 2 items (4-point-Likert rating scale, 0-3).
[12]Brief PHQ Panic Module screens panic disorders with 4 dichotomous items.
[13]Mini-Social Phobia Inventory (Mini-Spin) detects social anxiety with 3 items (5-point-Likert rating scale, 0-4)
[14]Generalized Anxiety Disorder 2 or 7 (GAD-2 or GAD-7) screens for anxiety disorders with 2 or 7 items (4-point-Likert rating scale, 0-3)
[15]Type D scale (DS14) comprises two reliable subscales with 7 items each for negative affectivity and social inhibition (5-point-Likert rating scale, 0-4)
[16]Adapted version of Uppsala Sleep Inventory (USI) measures initiating and maintaining sleep with 2 items (3-point-Likert rating scale, 1-3)
[17]DEpression and EXhaustion subscale (DEEX scale) measures presence and severity of depression and anxiety with 8 items (4-point-Likert rating scale, 0-3). Sex-specific cut-off points were applied (≥12 for women, and ≥10 for men)
[18]Resilience scale 11 (RS-11) with 11 items (7-point-Likert scale, 1-7); highest one third indicates resilience, lowest two thirds indicates low resilience (thirds based on data).
[19]Post-traumatic Diagnostic Scale and impact of event scale indicate respectively experience of a traumatic event (criteria A, 11 events) and symptoms of PTSD (criteria B, C and D; re-experiencing, avoidance and arousal). Exposure to 1 traumatic event and 1 re-experience, 1 avoidance and 1 hyperarousal symptom indicate full PTSD;
[20]Geriatric Depression Scale-15 measures depression among elderly with 15 dichotomous items.
[21]Satisfaction With Life Scale: one item measuring satisfaction with life on a 0 to 10 rating scale.
[22]UCLA loneliness scale-12 measures loneliness with 12 items with a 4-point-Likert rating scale (0-3).
[23]Waist-to-hip ratio (WHR) is calculated by dividing the waist circumference through the hip circumference and therefore can adapt divergent values.
[24]Personal Burnout Scale (PBS) measures physical and mental exhaustion with 6 items with a 5-point-Likert rating scale (1-5). Data were transformed to a metric scale (1=0; 2=25; 3=50; 4=75; 5=100).
[25]Patient Health Questionnaire 12 (PHQ-12) contains the somatic symptom module of the Patient Health Questionnaire-15 (PHQ-15): 12 items with a 3-point-Likert rating scale (0-2).

In general, women reported more mental health problems than men (32, 33). Regardless of the measurement scale, depression or depressive symptoms were reported more often by women than by men (34-39). This also applied to new onset of depression (40) and additionally to specific subgroups, e.g. elderly (41). Major depressive disorders were more frequently present among women compared to men (36, 42). However, when the depression and exhaustion subscale was used, no difference between women and men in reporting depressed mood was found (43). Depression combined with obesity was more often seen in women (44). Depending on operationalization, depression or depressed mood in women ranged from 8.7% (GHS) to 36.8% (SHIP) and in men from 5.8% (GHS) to 37.7% (KORA). Suicidal ideation was more often present in women (9.2% GHS) compared to men (6.0% GHS) (45). However, the risk of committing suicide was higher for men (0.5% KORA) than for women (0.3% KORA) (46). Lastly, anxiety was more often present among women (55.8% SHIP) compared to men (38.9% SHIP) (37), this also applied to elderly women (10.6% KORA) and men (4.8% KORA) (41).

Women reported more somatic complaints compared to men (37, 47). This varied from 17.5% (SHIP) to 28.8% (GHS) for women and from 14.5% (SHIP) to 16.1% (GHS) for men. Sleeping problems (48) and fatigue (49) were more often reported by women. In addition, the combination of sleep disturbances and depressed mood was more frequent among women (50). Men reported more traumatic life events than women (51), whereas women developed more often (lifetime) PTSD after experiencing such an event (51-53). In women, PTSD ranged from 2.1% (KORA) to 5.2% (SHIP). In men, PTSD ranged from 1.3% (KORA and SHIP) to 2.9% (SHIP). Loneliness was also more frequently prevalent in women than in men (54). For women in the age groups 35-44 years and 55-64 years, living alone was strongly associated with loneliness (54). For elderly who lived alone, no difference was found for loneliness between women and men (55). Other indicators of mental health, such as presence of Type D disorder (56) and depersonalization-derealization (57) did also not differ between women and men. For elderly, no difference between women and men was found regarding resilience (41, 58) and life satisfaction (41).

3.3.2 Factors associated with mental health

A broad range of factors was associated with mental health. We categorized the results in five categories: 1) social and gender-related factors, 2) lifestyle, 3) interplay of physical and mental health, 4) Body Mass Index (BMI) and diabetes and 5) genetic and biological factors. An overview of the results can be found in Table III-2. The main findings are described below.

3.3.2.1 Social and gender-related factors

The three cohorts have been drawn as local representative samples of the general population, stratified for sex, age, and urban-rural residence. In all cohorts, women had a lower income than men. Furthermore, men were more often married or living with a partner, whereas more elderly women were living alone. In addition, life expectancy differed between the regions; life expectancy was highest in the middle of Germany and lowest in the northeast of Germany. The demographic and socioeconomic differences between the cohorts influenced associations with mental health.

Social support and social isolation were often associated with mental health. Lack of social support was a strong predictor for somatic symptoms for both women and men (47). For older women and men, a smaller social network was associated with loneliness (41). For women,

low social support was associated with higher mental and physical distress (59) and women without a partner reported more excessively somatic symptoms (60) and were more often socially isolated (61). The presence of social support turned out to be a protective factor against new onset of depression for both women and men (40). For men, not having a partner was associated with social isolation (61) and living alone was linked to suicidal ideation (62). Additionally, elderly women living alone reported lower subjective well-being (63). Depressed women were more likely to be socially isolated (64), and older women were also more often socially isolated, regardless of suffering from a depression (61). For women as well as men, adverse life events were strong predictors for somatic symptoms (47). For men, negative life events were a risk factor for new onset of depression (40) and associated with the development of PTSD (40). Experience of combat or war zone and nonsexual assaults by known assailants were risk factors for developing full PTSD (65) for women and men. For help seeking when suffering from depression, no differences were found between women and men (66).

With regard to gender-related factors, findings for women and men were similar. SES predicted somatic symptoms for women and men (47). Low income had a negative effect on well-being (63) and was associated with suicidal ideation (62). Having five or more children was associated with a worse mental health status (67) and low educational level and unemployment were related to excessive symptom reporting (ESR) (60). A difference was found in the association between unemployment and suicidal ideation, which was only present for men (62). No effects were found for SES on new onset of depression (40), educational level on well-being (63) and unemployment on somatic symptoms (47). Furthermore, no association between net income and status as homemaker were found (62). In general, educational attainment, income and employment did not have an effect on the increase of depressive symptoms over the last years (68).

3.3.2.2 Lifestyle

Smoking and physical inactivity are known factors to negatively influence physical and mental health. Smoking was a risk factor for new onset of depression, but only in men (40). Besides, smoking was associated with suicidal ideation (62) and with social isolation (61) for men. For physical activity, effects for women and men were found. For both women and men being physically inactive was related to social isolation and for men also to social integration and suffering from depression (61). Another study confirmed that depressed men were more likely to be physically inactive than women (64). For both women and men associations between physical inactivity and suicidal ideation were found (62). Women who were moderately active had a lower mental health-related quality of life (HRQL) score than men who were moderately active (69). For older women physical inactivity was associated with loneliness (41), whereas the association between physical inactivity and low subjective well-being was found for both elderly women and elderly men (63). Low alcohol consumption was associated with ESR for both women and men (60).

3.3.2.3 Interplay of physical and mental health

The interplay between physical and mental health has been examined in many studies included in the current review. For both women and men chronic diseases were associated with worse mental and physical well-being (59). For women the experience of a life threatening disease was associated with the development of full and partial PTSD, for men it was only associated with partial PTSD (65). For women cancer, social phobia, generalized anxiety and

loneliness were risk factors for new onset of depression (40). Sleeping disorder, somatic complaints and negative self-perceived health were associated with depression for women as well as for men (61). For elderly women and men absence of loneliness was a protective factor for depression later in life (70), for elderly men, stronger attachment was an additional a protective factor . Depression, generalized anxiety, panic and social phobia predicted somatic symptoms for women and men (47), for women somatic symptoms were also predicted by loneliness. Increased reporting of somatic symptoms was predicted by diseases in general (metabolic syndrome, circulatory diseases, bronchial diseases, cancer and other diseases) for both women and men (60) and associated with sleep disturbances, worse health perception and presence of psychological symptoms. High levels of somatic complains and pulmonary disease symptoms were associated with suicidal ideation for women and men (62), for men medium level of somatic complaints, myocardial infarction and stroke were additionally associated with suicidal ideation. For women as well as for men, depressive symptoms were associated with suicidal ideation (62).

3.3.2.4 BMI and diabetes

Obesity and diabetes are significant health threats in an aging population. When comparing women and men in the association between BMI and HRQL (physical and mental), women with a higher BMI reported lower physical HRQL later in life than men with a higher BMI (69). Another study found an association between high BMI and less physical HRQL for both women and men (71), but in men with strong social support, this association vanished. No association was found between BMI and mental HRQL for either women or men (71) and no differences were found between women and men (69, 72). Women with type 2 diabetes scored lower on mental HRQL compared to men with Type 2 diabetes (73), regardless of type of diabetic medication (74). Changes in the diabetes trajectory also influenced mental HRQL. Men of 55 years and older with prediabetes at baseline and diabetes at follow-up scored lower on mental HRQL than men with persistent prediabetes (75). Women with normal glucose tolerance at baseline and prediabetes at follow-up scored lower on mental HRQL compared to women who still had normal glucose tolerance at follow-up (75). For women and overweight men weight gain was associated with impaired physical health (76). For women, weight gain was associated with improvements in mental health (76). Men with lower BMI more often suffered from a depression (64) and lower BMI was associated with social isolation (61). In addition, diabetes mellitus and obesity were related to excessive somatic symptom reporting (60). Furthermore, using different indicators for obesity (e.g. waist-to-hip ratio (WHR) or BMI) led to different findings (77).

3.3.2.5 Genetic and biological factors

Genetic and biological factors may affect mental health status and the development of mental health disorders. For mental and physical distress, the s/s-genotype and the s/l-genotype on the serotonin transporter gene in combination with unemployment or chronic diseases was related to higher mental and physical distress for women (59, 78). Elderly women reported better well-being when higher levels of insulin-like growth factor binding protein-3 (IGFBP-3) were present. A discrepancy between women and men was found for insulin-like-growth factor 1 (IGF-1). For women, low IGF-1 levels predicted the incidence of depressive disorders 5-years later, whereas for men high levels of IGF-1 predicted future depression (79). In another study an association between IGF-1 levels and current depression was found for elderly

women, but contrary to the previous results; higher IGF-1 levels were associated with more depression (80). Furthermore, for women lower cholesterol levels were associated with suffering from depression (61). Higher cholesterol levels were associated with increased symptom reporting of somatic symptoms and with hypertension for women and men (60). For men higher C-reactive protein levels were associated with social isolation and the presence of depression (61). The inflammatory marker high-sensitivity C-reactive protein (hs-CRP) was not associated directly with either depression or social isolation, but for men with a depressed mood hs-CRP levels were higher compared to men without depressed mood and without being socially isolated (64). No associations between leptin levels and depressed mood or sleep disturbances were found for either women or men (50). However, in normal weight women, leptin levels were higher for women suffering from both depressed mood and sleep disturbances. Associations between cortisol levels and cognitive functioning depend on time of day measurement of cortisol levels (81). Associations between cortisol levels and loneliness were found in married elderly men, but not in married elderly women (82). A study focusing on the oxytocin receptor gene rs53576 A/A found an association between oxytocin receptor gene and less positive affect (strong excitement/emotion) for men (83). A three way interaction between brain-derived neurotrophic factor: Met allele, biallelic 5-HTTLPR: ss-allele and no/mild childhood abuse was found to influence depression for women (38). For men an interaction effect of physical neglect with Corticotropin-releasing hormone receptor 1 (CRHR1) gene on depression was found (84).

Table III.2. Explanatory factors mental health for women and men from the three cohorts.

Authors, year	Design[1]	N	Wave[2]	Main results[5]
Grabe et al., 2005 (59)	CS	976	SHIP-0 (non-random)	° Low social support associated with high mental and physical distress (f). ° Chronic diseases associated with high mental and physical distress (f,m). ° *S/s*-genotype and *s/l*-genotype on serotonin transporter gene and unemployment related to higher mental and physical distress compared to l/l genotype on the serotonin transporter gene (f). ° *S/s*-genotype and *s/l*-genotype on the *5-HT* and chronic diseases related to higher mental and physical distress compared to *l/l* genotype (f).
von Lengerke et al., 2007 (72)	CS	947	KORA-Survey-2000	° No differences between f and m in associations between different weight groups and mental health-related quality of life (HRQL).
Grabe et al., 2009 (67)	CS	1059	SHIP-0 (subjects aged ≥ 60)	° More years in school, respectively 12 (f) or 10 (f,m) related to better mental status for older people. ° For older people, higher income, respectively in the 3rd quintile (m) or in the 4th and 5th quintile (f,m) related to better mental status. ° Five or more children associated with worse mental status (older f,m). ° A smaller number of teeth negatively associated with mental status (older f).
Lucht et al., 2009 (83)	CS	406	SHIP-I	° Oxytocin receptor gene *rs53576 A/A* associated with less positive affect (m).
Wiczinski et al., 2009 (71)	CS	2732	KORA F3	° Normal weight more often present in younger and higher educated people (f,m). ° Not living with partner related to a higher Body Mass Index (BMI) (m). ° Statutory health insurance associated with a higher BMI (f). ° Higher BMI (direction obese) associated with lower physical HRQL (f,m). ° Interaction between social support and BMI on physical HRQL (m). ° No association between BMI and mental HRQL (f,m).
Grabe et al., 2010 (84)	CS	1638	SHIP-LEGEND[3]	° No interaction effect of emotional neglect and *CRHR1* gene on depression (f,m). ° No interaction effect of abuse and *CRHR1* gene on depression (f,m). ° For male interaction effect of physical neglect and *CRHR1* gene on depression.
Ladwig et al., 2010 (62)	CS	3079	KORA F3	° Low net income, physical inactivity, high level of somatic complaints and pulmonary disease symptoms associated with suicidal ideation (f,m). ° Unemployment, living alone, cigarette smoking, medium level of somatic complaints, myocardial infarction associated with suicidal ideation (m).

Ladwig et al., 2010 (60)	CS	11895	MONICA MONICA MONICA S3	S1 S2	° High cholesterol, obesity, hypertension, low alcohol consumption and diabetes mellitus related to excessive symptom reporting (ESR) (f,m). ° No partner (f), lower educational level and higher unemployment (f,m) associated with ESR. ° Diseases (metabolic syndrome, circulatory diseases, bronchial diseases, cancer and other diseases) related to ESR (f,m). ° Regular sleep disturbances, not a good health perception and psychological symptoms related to ESR (f,m).
Grabe et al., 2011 (78)	CS	4308	SHIP-0		° Confirmation of findings of the original paper of Grabe et al., 2005 with an updated sample.
Häfner et al., 2011 (64)	CS	1547	MONICA MONICA MONICA S3	S1 S2	° Depression associated with social isolation (f), physical inactivity (m) and lower BMI (m). ° Inflammatory marker high-sensitivity C-reactive protein (*hs-CRP*) not associated with depression or social isolation. ° *Hs-CRP* levels higher for people with depression and social isolation (m). ° Inflammatory marker interleukin-6 associated with social isolation (m). ° Interleukin-6 levels higher for people with depression and social isolation (m).
Häfner et al., 2011 (61)	CS	1229	MONICA MONICA MONICA S3	S1 S2	° Higher C-reactive protein levels associated with social isolation and (no) depression (m). ° Higher leptin levels associated with social isolation/integration and depression (m). ° Smoking (m) and no partner (f) associated with social isolation (regardless of having depression). ° No partner (m) and higher age (f) associated with social isolation without depression. ° Sleeping disorder, high somatic complaints and negative self-perceived health associated with depression (regardless social isolation or integration) (f,m). ° Physically inactivity related to social isolation (regardless of having depression) (f,m) and to social integration and having depression (m).
Schunk et al., 2012 (73)	CS	9579	KORA SHIP-0	S4	° Type 2 diabetes related to lower score on mental HRQL (f). ° No differences in associations between no Type 2 diabetes and mental HRQL (f,m).
Grabe et al., 2012 (38)	CS	2035	SHIP-LEGEND[3]		° A three way interaction between 1) *brain-derived neurotrophic factor Met allele*, 2) *biallelic/triallelic 5-HTTLPR ss-allele* and 3) non/mild childhood abuse influenced depression (f).
Häfner et al., 2012 (50)	CS	1369	MONICA MONICA MONICA S3	S1 S2	° No associations between leptin levels and depressed mood or sleep disturbances (f,m). ° Associations between leptin levels and an interaction between depressed mood and sleep disturbances (f). ° Higher leptin levels related to depressed mood and sleep disturbances in normal weight people (f). ° For people with obesity and elevated leptin levels no associations between higher leptin levels and depressed mood and sleep disturbances (f).
Lukaschek, et al., 2013 (65)	CS	3080	KORA S4		° Combat or war zone (f,m), nonsexual assaults by known assailants (f,m), experience of interpersonal conflict (m), sexual assaults by known assailant (m) and life threatening diseases (f) important factors for development of full PTSD. ° For men experience of interpersonal conflict (f,m), life threatening illness (f,m), having a serious accident (m) and sexual or non-sexual assaults by known assailants (f) important factors for development of partial PTSD.

Schomerus et al., 2013 (66)	CS	395	SHIP-0 SHIP-I SHIP-LEGEND[3]	° No differences between f and m in the association between childhood abuse, personality traits and resilience and help-seeking for depression.
Wiltink et al., 2013 (77)	CS	5000	GHS BL	° Obesity measure waist-to-hip ratio (WHR) positively related with depression and somatic-affective symptoms (m). ° Obesity measures BMI and waist-to-height ratio negatively related to cognitive-affective symptoms (f). ° Obesity measure waist circumference negatively associated with cognitive-affective symptoms (m).
Emeny et al., 2014 (80)	CS	985	KORA-AGE[4]	° Higher levels of insulin-like growth factor binding protein-3 (IGFBP-3) associated with higher well-being (elderly f). ° Higher insulin-like-growth factor 1 (IGF-1) levels associated with more depression (elderly f). ° No relation between IGFBP-3 and depression (elderly f,m). ° Active elderly f with the highest IGF-1 and IGFBP-3 levels higher well-being than inactive elderly f with similar IGF-1 levels and IGFBP-3 levels.
Hunger et al., 2014 (75)	CS & LS	1046	KORA S4 KORA F4	° People of 55 years and older with prediabetes at baseline and diabetes at follow-up scored lower on mental HRQL than people with persistent prediabetes (m). ° People of 55 years and older with normal glucose tolerance at baseline and prediabetes at follow-up scored lower on mental HRQL than people with normal glucose tolerance at follow-up (f).
Klug et al., 2014 (70)	CS	969	KORA-AGE[4]	° For elderly people higher attachment (m) and lower loneliness (f,m) scores related to not having late life depression.
Laxy et al., 2014 (76)	LS	3080	KORA S4 KORA F4	° Heavy weight gain associated with impairments in physical health (f, obese m) and improvements in mental health (f).
Sievers et al., 2014 (79)	CS & LS	4079 (CS) 3141 (LS)	SHIP-0 SHIP-I	° Low IGF-1 levels (f) and high IGF-1 levels (m) predict incidence of depressive disorders.
Zebhauser et al., 2014 (41)	CS	1022	KORA-AGE[4]	° People older than 85 years old experience more loneliness than people between 64 and 84 years (f,m). ° Elderly women (>85) experience more loneliness than elderly men. ° For older people associations between a small social network and loneliness (f,m). ° Older age related physical limitations mostly not associated with loneliness (f,m). ° Inactivity related to loneliness (elderly f). ° Depression and anxiety associated with loneliness (elderly f,m). ° More life satisfaction and stronger resilience associated with not being lonely (elderly f,m).
Baumeister et al., 2015 (68)	LS	4228 (SHIP-0) 4251 (SHIP-T)	SHIP-0 SHIP-Trend	° Relative increase of depressive symptoms between 1997-2001 and 2008-2012 stronger for men than for women. ° Strongest change of depressive symptoms between 1997-2001 and 2008-2012 in age group 50-64 years (f,m); smallest change in age group 20-34 years (f,m). ° No difference in prevalence of depressive symptoms between 2008-2012 and 1997-2001 (f,m).

Johar et al., 2015 (81)	CS	733	KORA-AGE[4]		° Lower morning to evening cortisol ratio associated with cognitive impairment (elderly m). ° Late evening cortisol measures and cortisol awakening response not associated with cognitive impairment (elderly f,m).
Schunk et al., 2015 (74)	CS	846	KORA SHIP-0	S4	° Using oral diabetic medication, insulin diabetic medication or oral and insulin diabetic medication associated with lower mental HRQL (f).
Lukaschek et al., 2017 (63)	CS	3602	KORA-AGE[4]		° For elderly low income, anxiety, depression, sleeping problems, physical inactivity and multi-morbidity associated with low subjective well-being (f,m). ° Living alone associated with low subjective well-being (elderly f).
Rabel et al., 2017 (69)	CS & LS	3080	KORA KORA KORA FF4	S4 F4	° Women with a higher BMI later in life less physical HRQL than men. ° Women with no or low physical activity later in life less mental HRQL than men.
Beutel et al., 2018 (40)	LS	12061	GHS GHS FU 2	BL	° Cancer, loneliness, social phobia and generalized anxiety risk factors for new onset of depression (f). ° Smoking and life events risk factors for new onset of depression (m). ° Social support associated with less new onset of depression (f,m).
Beutel et al., 2019 (47)	CS	7974	GHS FU 2		° Lack of social support, adverse life events, depression, generalized anxiety, panic and social phobia strongest predictors for somatic symptoms (f,m). ° Loneliness predictor for somatic symptoms (f).

[1]CS = cross-sectional study, LS = longitudinal study.
[2]SHIP-0 = 1997-2001, SHIP-I = 2002-2006, SHIP-LEGEND = 2007-2010, SHIP-Trend = 2008-2012, KORA S4 (1999–2001), KORA F3 = 2004-2005, KORA F4 (2006–2008), KORA FF4 (2013–2014), MONICA S1 = 1984-1985, MONICA S2 = 1989-1990, MONICA S3 = 1994-1995, GHS BL = 2007-2012, GHS FU 1 = 2009-2014, GHS FU 2 = 2012-2017.
[3]SHIP-LEGEND is an add on study, based on the SHIP-0 cohort.
[4]KORA-AGE includes MONICAS1, MONICAS2 , MONICAS3 and KORA S4. Participants aged 65 years or older at the end of 2008 were selected.
[5]f = female, m = male.

3.4 Discussion

In this systematic review, we compared prevalence rates and determinants of mental health indicators from three large, ongoing German cohorts. The benefits of combining three different cohorts are multiple. First, the cohorts represent the general population in three regions, namely KORA in the south, SHIP in the northeast and GHS in the middle of Germany. In these three regions, the composition of populations differs with respect to socioeconomic and regional characteristics. Therefore, the articles complement each other and the conclusions based on concurrent evidence are stronger. Secondly, the stratified random sample selection in all cohorts provides representative groups for the general adult population in the respective areas of Germany. The proportions of women and men in the cohorts are equal and broad ranges of age are covered. Repeated follow-ups provide the opportunity to study participants longitudinally and determine life-span developments. A third advantage of are the overlapping psychological, medical and laboratory assessments. Lastly, the overall number of participants from the three cohorts together is more than 40,000 (28).

Mental health plays a major role in the concurrent German cohort studies and sex differences are increasingly taken into account in analyses. This is underlined by the differences of prevalence rates of mental distress between women and men. In all cohorts, women reported worse mental health than men (32, 33, 85). Particularly, depression, depressed mood or symptoms were more often present in women (34-39, 42-44). Additionally, as reported in one or two of the three cohorts, new onset of depression (40), anxiety (37), traumatic events and PTSD (51-53), suicidal ideation (45), sleeping problems and fatigue (48, 49), somatic complaints (37, 47) and loneliness (54) were more often reported by women, whereas the risk of committing suicide was stronger in men (46). A recent paper using SHIP data confirmed that women were more often affected by depressive, anxiety, obsessive-compulsive disorder, PTSD, somatoform and eating disorders (12-month and lifetime), whereas men indicated substance use more often (86). These results indicate similarities between cohorts and thus regions in sex-specific prevalence rates of mental health. Furthermore, these findings are consistent with current literature on prevalence rates of mental health in several countries. A meta-analysis on depression including 90 studies from 30 countries reported consistently higher prevalence rates of depression in women compared to men (87). In a review on social anxiety disorder including 14 studies from different countries, women were more often suffering from anxiety and reported elevated severity compared to men (88). A systematic review on suicidal behavior and suicide in Europe and America reported that men commit suicide more frequently, whereas women have more attempts and suicidal behavior (89). Furthermore women reported more often lifetime PTSD (90), somatoform diseases (91) fatigue (92, 93) and loneliness (94, 95). The higher prevalence of loneliness is especially present in older women and consistent across several European countries (96).

With regard to risk and protective factors for mental health, differences and similarities were found between women and men. For women loneliness, social isolation and low social support were risk factors for depression or mental distress (40, 59, 61, 64, 70). This finding was consistent in the three cohorts Further, for women, cancer, social phobia, generalized anxiety (40), sleeping disorders and negative self-perceived health (61) were associated with (new onset of) depression. For men myocardial infarction and stroke were associated with suicidal ideation (62). As men experience cardiovascular events at younger age (97), their consequences may lead to a high burden in daily life which can contribute to an increase of suicidal ideation. Additionally, for men, physical inactivity was associated with depression (61, 64) and smoking with new onset of depression (40), suicidal ideation (62) and social isolation

(61). With regard to biological factors, for women, lower cholesterol levels were associated with depression (61) and higher leptin levels with depressed mood (50). For men, higher interleukin-6 levels and higher hs-CRP levels were associated with depression and social isolation (64), higher leptin levels predicted depression and social isolation (61). For other mental health outcomes, no differences were found between women and men. Chronic and life threatening diseases were associated with more mental and physical distress for women as well as for men in all three cohorts (59, 60, 78). Further, for both women and men associations were found between somatic complaints and depression (61) and suicidal ideation (62), life threatening disease and partial PTSD (65) and pulmonary disease and suicidal ideation (62). Additionally, depression, generalized anxiety, panic and social phobia were predictors of somatic symptoms for both sexes (47). Lastly, no differences between sexes were found in the association of BMI with mental HRQL (69, 71, 72).

Not all mental health aspects and possible risk and protective factors were examined in all cohorts, this makes it more complicated to draw conclusions about regional similarities and differences. The most consistent and detailed findings were found for depression. In all cohorts depression, depressed mood or symptoms of depression were more often present in women compared to men (34-39, 42-44). This gender gap is known to become manifest already in early adolescence and declines in early adulthood, remaining stable afterwards (98). When controlling for demographic and socioeconomic background this gender gap persisted (99). However, many studies question whether men actually experience less depression or if depression among men just remains frequently undetected. In a study on men's attitude regarding depression, normative expectations regarding masculinity equated suffering from depression to a weakness (100). Conforming to such traditional masculine norms is problematic for help-seeking for depression (101). This may also contribute to the higher suicide rate in men. Men are less likely to seek treatment for depression and when they seek treatment, they are less likely to be diagnosed with major depressive disorder (97). This is in part due to different symptoms of depression in women and men. When examining depressed patients, men reported more anger attacks compared to women and scored higher on irritability and overreaction (102). When testing the Gotland Scale for Male Depression (103), irritability appeared to be the best indicator of male depression (104). Studies have also strong associations between alcohol abuse, depression and suicidal behavior interacting with biological factors in men (105) and alcohol consumption as a coping strategy for depression in men (106). Thus, depression in men is often masked by atypical symptoms, such as externalizing depression symptoms. For men, external risk factors for depression were also found in this review (e.g. smoking (40) and physical inactivity (58)), whereas the risk profile for women contained more internal factors (e.g. loneliness (40) and social isolation (64)).

Since gender was not measured directly in the studies reviewed, socioeconomic and family-related factors were examined as gender-related factors. In general, women were more often housewives (38), in maternity leave (38), or unemployed (59) compared to men. On average, men had a higher income and education (38) compared to women. Differences between women and men with regard to gender indicators and mental health were found for unemployment and suicidal ideation (61, 62). For men unemployment was positively associated with suicidal ideation. Other associations between gender indicators and mental health were found for both women and men. Income was negatively associated with suicidal ideation (62), positively with mental health status (67) and for elderly positively with subjective well-being (63). Education was negatively associated with ESR (60) and positively with mental health status (67). Lower SES predicted somatic symptoms (47) and having five or more children was associated with a worse mental health status (67). Lastly, unemployment was

positively associated with ESR (60). Unfortunately, none of the articles examined a moderation or mediation effect of gender-related factors in the relation between sex and mental health. Therefore, it is not possible to determine the contributions of sex and gender. In general interactions between sex and socioeconomic position are understudied (19). A study in Brazil testing mediating effects of socioeconomic factors in the association between sex and mental health revealed that personal income and schooling at the age of 30 mediates the association between sex and depression, anxiety and common mental disorders (107), but not family income or maternal schooling. Testing socioeconomic and family-related factors in associations between sex and mental health in longitudinal studies could contribute notably to the understanding of gender aspects in mental health.

Only very recently, the binary assessment of sex has been supplemented by the third category, diverse sex. Therefore this paper does not discuss gender diversity, although it is known that the mental health of the German LHBTI community (lesbian, gay, bisexual, transgender and intersex individuals) should be further examined (11). Mental health of the LHBTI community has been expected to differ from the overall population (e.g. depression and suicidal behavior (108, 109)) due to the heteronormative orientation of society (110, 111). Increasing social acceptance could lead to more possibilities to express one's gender identity and sexual orientation which could improve the health status of sexual minorities (11). A further limitation in this study is that mental health was measured by self-report questionnaires. Since the measurements tools used are reliable and valid, it will still be a good indication of reality. Different questionnaires were used to assess the same mental health construct. In order to overcome this last limitation, the GESA project, integrating data from these three cohorts to examine mental health, harmonizes data (28). Studying interactions between socioeconomic and vocational factors with sex (e.g. full employment of women in SHIP vs. the role of housewife in KORA and GHS) will help to identify differential impact of socioeconomic inequality.

Overall, this systematic review shows the differences and similarities in prevalence rates and determinants of mental health indicators between women and men, from genetic and biological factors to indicators of the social environment. While our picture is far from complete, gender gaps regarding income, education, or living in a relationship underline the need to differentiate mental health outcomes according to sex-related determinants of mental health. Differing risk and protective factors for mental health require a sex sensitive prevention approach. However, this review shows that current research on mental health still lacks a clear focus on gender roles and identities, which have recently been included in the GHS. Future research should therefore illuminate sex differences and broader sex and gender diversity (112). Therefore, an increased focus on sex and gender in mental health research is of great importance.

4 Study 2: Depressive symptoms predict the incidence of common chronic diseases in women and men in a representative community sample

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4.1 Introduction

Depression is one of the most frequent and harmful mental disorders with an estimated lifetime risk of 15-25%, affecting women about twice as frequently as men (1). As it often takes a chronic course and is associated with elevated morbidity and mortality (1), depression is an enormous public health concern. In aging societies, chronic diseases including CVD, cancer, chronic respiratory disease, and diabetes have become the leading causes of death (2). A growing body of research has identified close associations of depressive symptoms with chronic physical diseases. However, previous research has mostly focused on particular pairs of mental and medical diseases (3-5). In a national Danish registry study, Momen et al. (6) reported a median hazard ratio of 1.37 for an association between 90 pairs of mental disorders and medical conditions. In the prospective English Longitudinal Study of Aging (ELSA), Poole and Steptoe (4) found that depressive symptoms at baseline predicted a 5% increase (per point of depression, assessed with the Center for Epidemiologic Studies Depression Scale of incident chronic disease burden 10 years later.

CVD include coronary artery disease, myocardial infarction, peripheral arterial disease, stroke, and congestive heart failure. Previous studies showed (I) increased risk of CVD in depressed individuals, (II) heightened risk of depression following acute CVD, and (III) worse prognosis when CVD was complicated by depression (7-9). The associations of depression with CVD were more pronounced in women than in men (10).

With regard to chronic obstructive lung disease, several studies have shown higher prevalence rates of depression in chronic obstructive pulmonary disease (COPD) patients compared to the general population (11-13). In this group, the prevalence of depression (PHQ-9 >= 10) was twice as high (16.2% vs. 7.5%) compared to participants without COPD (14). Also for patients with chronic bronchitis, a subgroup of COPD patients, prevalence of depression was twice as high (15.9% vs. 7.6%) compared to participants without chronic bronchitis (15). Evidence supports a bidirectional association of asthma and depression (16). However, the effect of depression on asthma seems to be stronger than the other way around. An Egyptian literature review found that depression predicted the new onset of asthma in adults based on six studies which included 83,684 participants that were followed for 8 to 20 years, with 2,334 cases of incident asthma in total (17). Only two studies reported an effect of asthma on incident depression. Furthermore, a review indicated an adverse effect of depression on the course of COPD (18), and another study described an adverse effect of depression on the course of asthma in older people (19). For COPD, this effect was not influenced by participants' sex (18), but sex differences were not examined for asthma (19).

Diabetes mellitus and depression were often comorbid (20). For both type 1 and type 2 diabetes, the prevalence of depression was higher compared to the general population: it was three times as high in people with type 1 diabetes and twice as high in people with type 2 diabetes (21). The relation between type 2 diabetes and depression is mostly considered to be bi-directional (22-25). In one review, depression was associated with a 60% increased risk of type 2 diabetes, whereas type 1 diabetes was only associated with a 15% increased risk of depression (23). The prevalence of depression was higher in women who had diabetes than in men (21), which reflects the epidemiology of depression in the general population. Findings of sex-specific effects of depressive symptoms on diabetes mellitus are conflicting, indicating either no effects of sex (23) or only an effect for women (26).

With regard to cancer, depression has been reported as a frequent consequence of the experience of this potentially life-threatening and increasingly chronic disease (27, 28). It is

compounded by pain and fatigue symptoms (28). Previous research has underscored the need to investigate associations of cancer and mental distress in a sex-sensitive way (29).Evidence regarding the predictive value of depression for cancer is mixed. While associations of depression with cancer mortality (28, 30-32) and cancer progression (28, 32) were found, the contribution of depression to the etiology of cancer has remained a matter of debate (33, 34). Sex-specific investigations of the effects of depression on cancer incidence are scarce. Examining specific types of cancer, it was shown that for women, depression predicted new onset of breast cancer and for men, depression predicted new onset of prostate cancer (33).

Migraine, an episodic primary headache disorder (35), is considerably more prevalent in women than in men (36) and has also been associated with depression (37-39). Depression was predictive of new onset of (chronic) migraine (38, 40) and it was also a risk factor for increased migraine attacks (41) and chronic daily headaches (38, 42). However, it is unclear whether depression is a predictive factor for migraine in both women and men. While triggering factors and attack thresholds for migraine are modulated by sex hormones (39), it is likely that the effects of depression on migraine differ for sex.

Further, the new onset of diseases is shaped by sociodemographic, psychological, metabolic and behavioral factors. For example, the incidence of chronic diseases increased with age (43). Higher educational attainment reduced the risk of chronic lung diseases (44) and was negatively associated with the incidence of major cardiovascular events (45). In contrast, lower income and lower SES increased the risk of chronic lung diseases (44) and were associated with a higher prevalence of migraine (46) and the risk of diabetes, also through health behaviors (47). Social isolation is a known risk factor for aggravating diseases or death rates (48). Both social isolation and loneliness were found to be predictive of CVD and type 2 diabetes, even after controlling for negative affect, but they were not predictive of COPD and cancer (49). Loneliness was comparatively common among people with chronic headaches (50). Obesity increased the risk of CVD, diabetes (especially in combination with high BMI), cancer, and migraine (51-53) and had negative effects on respiratory function (54). Dyslipidemia also had negative effects on respiratory function (54). Additionally, dyslipidemia increased the risk of CVD and diabetes (51, 55) and has been linked to specific types of cancer (56, 57). Also hypertension was associated with cancer (57). Hypertension was furthermore a risk factor for diabetes and exacerbated CVD (55), and was, according to some studies, associated with migraine (58). Elevated (esp. high fastening) blood glucose is a known risk factor for cardiovascular events (59). Lastly, smoking and physical inactivity have been linked to CVD, chronic respiratory disease, diabetes, cancer, and migraine (43, 60). Thus, empirical investigations that intend to contribute to a better understanding of the relationship between depression and major illnesses also need to consider these relevant - and potentially confounding - factors.

In fact, the association of depression and chronic diseases has been examined in a variety of cross-sectional and prospective studies using both population-based and patient samples, indicating that prevention and/or treatment of depressive symptoms might have beneficial effects for physical health, too. The aim of the present paper was to expand on this important public health issue. As the relation of depressive symptoms and chronic illness has been most extensively studied in CVD and to a lesser extent in other chronic diseases, we investigated five common conditions within the same population sample. While the morbidity of chronic somatic and mental diseases differs considerably between men and women, sex differences in the association of mental and somatic diseases have hardly been systematically explored. Therefore, we used sex-specific analyses. We also controlled for relevant sociodemographic,

somatic, and lifestyle risk factors of the respective diseases that could constitute confounding variables.

In summary, the purposes of this prospective study are:

(I) To predict incident chronic disease based on depressive symptoms regarding five major diseases (CVD, chronic obstructive lung disease, diabetes mellitus, cancer, and migraine) in the German population from baseline to 5-year follow-up.
(II) To examine whether the effects of depressive symptoms at baseline on the onset of chronic disease 5 years later differ between women and men.

4.2 Methods

4.2.1 Procedure and study sample

The GHS a population-based, prospective, observational single-center cohort study in the Rhine-Main-Region, Germany (61-63). Its aim is to improve the individual risk prediction for diseases. The project focuses on several diseases, such as CVD, metabolic diseases, diseases of the immune system, eye diseases, and mental disorders. The study protocol and documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate and the local data safety commissioner. All study investigations have been conducted in line with the Declaration of Helsinki and principles outlined in recommendations for Good Clinical Practice and Good Epidemiological Practice. Research was performed in accordance with all regulations. Participants were included after giving informed consent. Exclusion took place in case of inability to participate due to psychological and physical impairments or insufficient knowledge of the German language. The sample was drawn randomly from the local population registry in the city of Mainz and the district of Mainz-Bingen, stratified 1:1 for sex and residence and in equal strata for decades of age (the included age range was 35 to 74 years). The response, defined as the recruitment efficacy proportion, was 60.3%. At Baseline (2007-2012), a total of *N*=15,010 participants were included. Of these participants, *N* = 12,422 (82.8%) participated in the follow-up study (2012-2017).

For this study, only participants who participated in the Baseline and Follow-Up assessment were included. Furthermore, participants with missing values in the baseline depression assessment were excluded. This led to a sample of *N* = 12,285 with a mean age of 54.4 (±10.9) at baseline; including 6,005 women (48.9%) and 6,280 men (51.1%). In order to study disease incidence, we created subsamples for each chronic disease by excluding participants who already had the respective disease at baseline. They were, however, included in the analyses statistically predicting the onset of the other diseases. The subsamples consisted of more than 10,000 participants each: CVD: *N* = 11,049; chronic obstructive lung disease: *N* = 11,681; diabetes: *N* = 11,333; cancer: *N* = 11,228 and migraine: *N* = 11,452.

4.2.2 Materials and assessment

The 5-hour baseline examination in the study center comprised an evaluation of classical cardiovascular risk factors and clinical variables, a computer-assisted personal interview, laboratory examinations from a venous blood sample, blood pressure and anthropometric measurements. All examinations were performed according to standard operating procedures by certified medical technical assistants.

4.2.3 Measures

4.2.3.1 *Chronic diseases*

CVD included coronary artery disease, myocardial infarction, peripheral arterial disease, stroke, and congestive heart failure. Presence of these diseases were assessed by inquiring whether participants had previously been diagnosed with the respective disease by a physician. A confirmative answer for at least one of the diseases indicated presence of CVD. The question was similar in the baseline and follow-up assessment: At baseline, it referred to the complete medical history, whereas at follow-up, it referred to the period since the baseline examination. Cancer was assessed in the same way. Chronic obstructive lung disease was assessed by inquiring about medicated asthma or medicated chronic bronchitis. Diabetes mellitus was defined as self-reported history of diabetes, corresponding medical therapy, or fasting blood glucose ≥126 mg/dL or non-fasting blood glucose ≥200 mg/dL. Migraine was assessed with the question 'Did you have migraine in the last 12 months?'. Migraine was defined as regular attacks over a period of at least one year.

4.2.3.2 Depressive symptoms

Depressive symptoms were measured with the depression module of the Patient Health Questionnaire-9 (PHQ-9). It assesses the frequency of the nine diagnostic criteria of major depression according to DSM-V (64). Using a Likert scale ranging from 0=not at all to 3=nearly every day, participants are asked to indicate how often they were bothered by the respective symptom over the course of the last two weeks. The sum score ranges from 0 to 27. Clinically relevant symptom burden was defined as a sum score ≥10. Löwe et al. (65) found a sensitivity of 81% and a specificity of 82% for depressive disorders determined by this cut-off. Additionally, the PHQ-9 was confirmed as a reliable and unidimensional measure for depression (66). Within the present sample, its internal consistency was good (Cronbach's α = 0.80).

4.2.3.3 Sociodemographic factors

Sociodemographic variables were assessed via self-report. These included: participants' sex, age in years, SES, living with partner (no/yes) and living alone. SES was defined as an index ranging from 3 (lowest SES) to 21 (highest SES) based on education, profession, and income following Lampert, Kroll, Müters, and Stolzenberg (67).

4.2.3.4 Psychological factors

Loneliness was assessed by a single item 'I am frequently alone/have few contacts' rated as 0 = no, does not apply; 1 = yes it applies, but I do not suffer from it; 2 = yes, it applies, and I suffer slightly; 3 = yes, it applies, and I suffer moderately; 4 = yes, it applies, and I suffer strongly (68).

4.2.3.5 Metabolic factors

This study included the metabolic factors BMI, dyslipidemia, obesity, blood glucose, and hypertension. BMI was calculated by dividing weight (kg) through height (in m^2). Obesity was defined as a body-mass index ≥30 kg/m^2. A diagnosis of dyslipidemia was based on the current intake of lipid-modifying drugs or a low-density lipoprotein / high-density lipoprotein ratio >3.5. Blood glucose was measured by HbA1C. Hypertension was assessed by mean systolic blood pressure (≥140 mm Hg) or mean diastolic blood pressure (≥90 mm Hg) or use of antihypertensive medications.

4.2.3.6 Lifestyle factors

As lifestyle factors, smoking and physical activity were included. Smoking was dichotomized into non-smokers (combining never smokers and ex-smokers) and smokers (>=1

cigarette/day). Physical activity was inquired with the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH; (69). Participants were asked to report about their regular physical activity during an average week over the past year. The SQUASH captures four common domains of physical activity: commuting, household (domestic) work, leisure-time, and work activities. Physical activity was measured based on its frequency (days per week), duration (average time per day), and effort (light/moderate/intense). Sleeping, lying, sitting, and standing was classified as inactivity. Each domain of physical activity was assigned a MET value (70). Furthermore, an intensity score (ranging from 1 to 9) (71) and the total minutes of activity per week were calculated. This information was used to create an activity score, reported as total minutes of activity per week x intensity score. For interpretability reasons, this value was divided by 1000, i.e., regression coefficients for physical activity represent a 1000-units increase in activity score.

4.2.4 Statistical analyses

Descriptive statistics were performed as absolute and relative proportions for categorical data, means, and standard deviations for continuous variables and median with interquartile range (if not fulfilling normal distribution). Inference tests between depression and no depression were calculated with t-tests or $\chi 2$-tests. We performed multivariate logistic regressions in order to ascertain whether depressive symptoms predicted the incidence of chronic diseases. The investigated chronic diseases were modeled as dichotomous dependent variables. For each disease, two models were tested: In model a, we entered depression (depressive symptoms based on the PHQ-9 sum score), sex, interaction of depression with sex, sociodemographic characteristics (age, SES, living with partner, living alone) and the psychological characteristic loneliness. Model b additionally included metabolic factors (BMI, dyslipidemia, obesity, blood glucose, hypertension) and lifestyle factors (physical activity, smoking).

4.3 Results

4.3.1 Participant characteristics

Descriptive statistics, stratified for the presence of depression at baseline, are displayed in Table IV-1. Of the total sample of 12,285 participants, 873 were depressed (i.e., they surpassed the PHQ-9≥10 cut-off). With regard to sociodemographic factors, depressed participants were more likely to be women, younger, not living with a partner, living alone, had a lower SES. More of them also indicated feeling lonely. Concerning metabolic factors, depressed individuals had a higher BMI and more of them had dyslipidemia and obesity. No differences were found with respect to blood glucose levels and hypertension. Additionally, depressed participants were more likely to be smokers than non-depressed participants, but there were no differences concerning physical activity.

Table IV.1. Characteristics of participants at baseline.

	Total sample	No depression (PHQ-9<10)	Depression (PHQ-9≥10)	*p*-value
Sociodemographic				
Sex (women)	6,005 (48.9%)	5,487 (48.1%)	518 (59.3%)	<.001
Age	54.4±10.9	54.6±10.9	52.4±9.9	<.001
Living with partner	10,114 (82.3%)	9,511 (83.4%)	603 (69.1%)	<.001
Living alone	1,637 (13.5%)	1,435 (12.7%)	202 (24.0%)	<.001
SES	13.3±4.4	13.4±4.4	12.4±4.2	<.001
Psychological				
Loneliness	1,188 (9.7%)	866 (7.6%)	322 (37.4%)	<.001
Metabolic				
BMI	26.4 (23.8-29.7)	26.3 (23.8-29.6)	27.4 (24.3-30.9)	<.001
Dyslipidemia	4,060 (33.1%)	3,722 (32.7%)	338 (38.7%)	<.001
Obesity	2,875 (23.4%)	2,607 (22.8%)	268 (30.8%)	<.001
Blood glucose	5.5 (5.2-5.8)	5.50 (5.2-5.8)	5.50 (5.2-5.8)	.150
Hypertension	5,869 (47.8%)	5,468 (47.9%)	401 (46.1%)	.310
Behavioral				
Smoking	2,199 (17.9%)	1,978 (17.4%)	221 (25.3%)	<.001
Physical activity	7.2 (5.2-9.4)	7.2 (5.1-9.4)	7.4 (5.5-9.7)	.063

Note: Descriptive statistics were performed as absolute and relative proportions for categorical data, means, and standard deviations for continuous variables and median with interquartile range if not fulfilling normal distribution.

4.3.2 New onset of diseases

The number of cases for new onset of disease was *N* = 444 for CVD, *N* = 308 for chronic obstructive lung disease, *N* = 447 for diabetes mellitus, *N* = 569 for cancer and *N* = 353 for migraine. The incidence proportions at 5-year follow-up were 4.0% for CVD, 2.6% for chronic obstructive lung disease, 3.9% for diabetes mellitus, 5.1% for cancer, and 3.1% for migraine.

4.3.3 Main analyses

We perform several multiple logistic regression analyses in order to examine the effect of depressive symptoms on new onset of CVD, chronic obstructive lung disease, diabetes mellitus, cancer and migraine. Table 2 reports coefficients of the predictor depressive symptoms at baseline. Based on the respective model a (adjusted for socioeconomic factors and loneliness), baseline depressive symptoms predicted incidence of CVD, chronic obstructive lung disease, diabetes mellitus, and migraine at follow-up in the total sample and in the subsamples of women and men. In the respective model b (additionally adjusted for metabolic and lifestyle factors), depressive symptoms were still predictive of chronic obstructive lung disease and migraine in the total sample and in women and men. A one-unit increase in depressive symptoms at baseline increased the risk for the onset of the respective disease by 5 to 8%[1]. Associations with CVD in men (p = .065) and with diabetes mellitus in women (p = .077) only reached trend level, not statistical significance.

Full models are displayed in the Supplement. Supplementary Table S-IV.1 displays the full model for the complete sample, Supplementary Tables S-IV.2 and S-IV.3 display the full model separately for women and men. Male sex was an important predictor of CVD and diabetes

[1]The relatively low incidence proportions allow approximation of risk by the odds ratios.

mellitus; and female sex of migraine. Interactions between depressive symptoms and sex were not statistically significant. Higher age was a predictor of CVD and cancer, whereas lower age was a predictor of migraine. For men, lower age additionally predicted diabetes mellitus. Lower SES was a predictor of diabetes and migraine in the whole sample. Sex-specific models revealed an effect of SES on chronic diseases (CVD and migraine) only in women. Higher BMI predicted CVD, chronic obstructive lung disease and diabetes. However, for men, there was no effect of BMI on chronic obstructive lung disease. Dyslipidemia was a significant predictor of diabetes mellitus, but in sex-specific analyses, this only applied to men. Blood glucose levels and hypertension were significant predictors of diabetes mellitus and migraine. Sex-specific models, however, revealed an effect of blood glucose on migraine only for men and an effect of hypertension on migraine only for women. Smoking was a significant predictor for CVD and chronic obstructive lung disease, although in sex-specific analyses, the effect of smoking on chronic obstructive lung disease was not significant in men. Lastly, physical activity predicted diabetes mellitus only in men.

Table IV.2. Results of multiple logistic regression models of new onset of CVD, chronic obstructive lung disease, diabetes mellitus, cancer, and migraine on depressive symptoms at baseline.

	CVD				Chronic obstructive lung disease				Diabetes mellitus				Cancer				Migraine			
	OR	CI	*p*	Nag. R^2	OR	CI	*p*	Nag. R^2	OR	CI	*p*	Nag. R^2	OR	CI	*p*	Nag. R^2	OR	CI	*p*	Nag. R^2
Total																				
Model a	**1.06**	1.02-1.10	.003	.110	**1.08**	1.04-1.13	<.001	.062	**1.05**	1.02-1.09	.005	.074	1.02	0.98-1.05	.390	.082	**1.07**	1.03-1.13	.003	.100
Model b	1.04	1.00-1.09	.053	.360	**1.08**	1.03-1.13	.001	.310	1.03	0.98-1.07	.220	.500	1.02	0.98-1.06	.270	.310	**1.08**	1.03-1.14	.001	.280
Women																				
Model a	**1.05**	1.01-1.10	.019	.120	**1.08**	1.03-1.12	<.001	.073	**1.06**	1.02-1.10	.007	.088	1.02	0.98-1.06	.260	.050	**1.05**	1.02-1.09	.004	.096
Model b	1.03	0.98-1.09	.240	.430	**1.06**	1.01-1.12	.017	.380	1.05	0.99-1.10	.077	.540	1.01	0.97-1.06	.610	.320	**1.05**	1.01-1.09	.019	.290
Men																				
Model a	**1.06**	1.02-1.10	.002	.099	**1.08**	1.03-1.13	.002	.052	**1.05**	1.01-1.09	.006	.059	1.02	0.98-1.06	.260	.050	**1.06**	1.01-1.12	.017	.061
Model b	1.04	1.00-1.09	.065	.320	**1.07**	1.02-1.12	.008	.220	1.03	0.99-1.08	.170	.470	1.03	0.99-1.08	.110	.310	**1.07**	1.02-1.13	.010	.230

Note: OR=odds ratio; CI=confidence interval (2,5%-97,5%); Nag. R^2=Nagelkerke R^2. For statistically significant predictors, the OR is printed in bold.

Model a: adjusted for sex and interaction of depression with sex (only total sample), sociodemographic characteristics (age, social economic status, living with partner, living alone) and loneliness (psychological factor).

Model b: adjusted for sex and interaction of depression with sex (only total sample), sociodemographic characteristics (age, social economic status, living with partner, living alone), loneliness (psychological factor), metabolic factors (BMI, dyslipidemia, obesity, blood glucose, hypertension) and lifestyle factors (physical activity, smoking).

4.4 Discussion

In this study, we examined the associations of depressive symptoms and new onset of the major chronic somatic diseases, CVD, chronic obstructive lung disease, diabetes mellitus, cancer, and migraine over a course of five years within a representative adult community cohort including participants aged 35 to 74 years. The statistical models included tests of sex-specific effects and the most relevant confounding variables (from different domains of life) of the associations of interest.

When adjusted for demographic data and loneliness, in men and women, baseline depression was predictive of CVD, chronic obstructive lung disease, diabetes mellitus, and migraine, but not of cancer. When we additionally adjusted for metabolic and lifestyle baseline risk factors, there was an 8% increase of chronic obstructive lung disease and migraine per point of depressive symptoms. The association with CVD showed only a trend, and no associations were found with diabetes mellitus and cancer. There were no statistically significant interactions of depressive symptoms and sex in the prediction of disease. However, when women and men were analyzed separately, in addition to the predictive value of depressive symptoms on chronic obstructive lung disease and migraine, a trend for the prediction of CVD was found in men only, and a trend for the prediction of diabetes was found in women only.

The present findings extend the existing prospective research on the association between depression and chronic somatic disease from CVD to other important chronic diseases, which are also associated with diminished quality of life. The statistically significant effects on chronic obstructive lung disease, CVD, and the negative findings regarding diabetes and cancer are in line with previous reports from the ELSA study (4), a population-based British study of healthy adults aged 50 and over. The strength of the observed associations was similar, too. Additionally, our results are consistent with investigations of a national Danish registry study including almost 6 million patients which indicated increased circularly, endocrine, pulmonary conditions, but not cancer in up to 15 years following the diagnosis of depression (6). We extended previous research by carefully conducting sex-specific analyses, both in the form of interaction terms and sex-specific analyses.

Comorbid medical and mental conditions may be influenced by pre-existing adverse factors, such as shared environmental risk factors, socioeconomic disadvantage, substance use, childhood maltreatment, or shared genetic factors. At the baseline assessment, depression was associated with female sex, lower age, sociodemographic disadvantage, living without a partner, living alone, and a considerably higher rate of loneliness. Additionally, depressed individuals were more likely to be smokers. In the following, the observed associations *over time* corroborate previous research which found that effects of mental disorders on medical illness are likely to be mediated by SES and lifestyle factors (6). They were also relevant predictors for CVD, chronic obstructive lung disease, and diabetes in this study. However, there were no significant effects of loneliness, living without a partner, or living alone on the new onset of any of the chronic diseases. This finding contrasts a Danish study with a similar age range that reported longitudinal associations of loneliness and social isolation with CVD and diabetes (49). However, the differential results could be explained by commonalities shared by depression and loneliness, and the predictive value of loneliness for depression itself (72, 73). Furthermore, depressed individuals had more metabolic (BMI, obesity, dyslipidemia) risk factors at baseline, which is in line with previous studies. Associations between obesity and new onset of chronic diseases were not found, which contradicts previous findings (51). Whereas current research found dyslipidemia to be a risk factor for diabetes and

CVD (55), we only found an effect of diabetes in men. While their interaction is not fully understood, these risk factors are plausible links to new onset of somatic disease. Discussed pathways include e.g., via stress (74) and sympatho-adrenergic activation (social factors), metabolic or inflammatory pathways (75) which played a role in linking depression and CVD (9), or direct toxic effects (such as smoking). Our study also indicated differential associations between depressive symptoms and major illnesses; and it suggested that lifestyle factors were of varying relevance: In the models of CVD and diabetes, the effects of depressive symptoms were diminished once physical activity and smoking were included in the analyses (in addition to the metabolic factors). Interestingly, the effects of depressive symptoms on chronic obstructive lung disease remained statistically significant after including smoking. Smoking was previously highlighted as a strong risk factor for the onset of asthma in several reviews and meta-analyses (76) and chronic bronchitis (77, 78). Thus, besides prevention and intervention efforts directly aimed at promoting mental health, support of smoking cessation could be an important measure to counteract the development of chronic physical illnesses in the community, especially in individuals with mental illness.

Screening for depressive symptoms has been established in medical treatment guidelines for chronic diseases to various degrees (e.g., for CVD (79) or oncological disorders (29, 80)). The present findings also suggest the need to implement screening for chronic obstructive lung disease, diabetes, and migraine. At the same time, depressed patients should be screened for modifiable risk factors such as metabolic and lifestyle factors, and for somatic diseases. Within the context of primary care or counselling/psychotherapy, depressed individuals who seek support could also be offered lifestyle interventions, especially supporting smoking cessation.

4.4.1 Strengths and limitations

The strengths of our study are the large size of a population-based sample and the statistical control of important confounding variables, including demographic, metabolic, and lifestyle factors. This analytic approach must be considered conservative as it also included potential mediators between depressive symptoms and somatic disease, reducing the associations of interest.

While we expect self-reported diagnoses to be reliable (4), it is a limitation that incident somatic diagnoses were mainly based on self-report. Additionally, the assessment of migraine was imprecise. While chronic migraine should be measured according to the number of times a typical migraine headache occurs within a month, we only assessed whether someone suffered from migraine in the previous twelve months. Information about depressive symptoms was also gathered via self-report (instead of, e.g., operationalized as a formal diagnosis). Research has found strong, statistically significant correlations between clinician-rated instruments and self-report assessments for depression exist (81). Comparing the PHQ-9 with semi-structured diagnostic interviews, studies found that sensitivity for major depression was similar, especially for slightly older adult populations (82). The present study assessed depression at baseline, when participants' age ranged between 35 and 74 years. Mental disorders most frequently start in young adulthood (when individuals are in their twenties or thirties), and we do not know depressed participants' age at onset of depression in the present sample, or who experienced a chronic course of depression. As previous research showed that the cumulative incidences of diagnosis of medical conditions within 15 years were higher among persons diagnosed with a mental disorder at a younger age (6), the present operationalization may have underestimated the association of depression with subsequent

somatic illness. Any interpretation of the findings also needs to consider that we investigated the new onset of somatic disease, and we excluded one third of participants who already suffered from chronic disease at baseline. Furthermore, comorbidity exists between the diseases examined in this study, for example between chronic obstructive lung disease (e.g., COPD) and CVD (83, 84), and diabetes (84). Besides, there are also individuals who do have one of the studied chronic diseases, but have not yet received a formal diagnosis. Furthermore, unlike Poole & Steptoe (4) who used data of a ten-year follow-up and Momen et al. (6) who investigated up to 15-year follow-up data, we were limited to a five-year follow-up.

Supplementary Table S-IV.1. Results of multiple logistic regression models of new onset of CVD, chronic obstructive lung disease, diabetes mellitus, cancer, and migraine on depressive symptoms at baseline.

	CVD			Chronic obstructive lung disease			Diabetes mellitus			Cancer			Migraine		
	OR	CI	*P*	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*
Depressive symptoms	1.04	1.00-1.09	.053	**1.08**	1.03-1.13	.001	1.03	0.98-1.07	.220	1.02	0.98-1.06	.270	**1.08**	1.03-1.14	.001
Sex (women)	**0.57**	0.39-0.82	.003	1.25	0.82-1.91	.300	**0.54**	0.37-0.81	.002	0.91	0.67-1.24	.550	**2.79**	1.88-4.14	<.001
Depressive symptoms*sex	0.99	0.93-1.06	.770	0.98	0.91-1.04	.440	1.03	0.97-1.10	.370	1.00	0.95-1.06	.980	0.96	0.90-1.02	.200
Sociodemographic															
Age	**1.08**	1.06-1.09	<.001	1.01	1.00-1.03	.100	0.99	0.97-1.00	.072	**1.05**	1.04-1.07	<.001	**0.95**	0.94-0.97	<.001
SES	0.99	0.96-1.02	.370	0.99	0.95-1.02	.410	**0.97**	0.94-1.00	.045	1.01	0.99-1.04	.220	**0.96**	0.93-0.99	.008
Living with partner	0.87	0.47-1.60	.650	1.04	0.52-2.09	.900	0.79	0.44-1.44	.450	1.49	0.76-2.94	.250	1.05	0.63-1.75	.840
Living alone	0.75	0.38-1.45	.390	1.18	0.56-2.48	.660	0.79	0.41-1.50	.470	1.57	0.77-3.20	.220	0.90	0.50-1.61	.720
Psychological															
Loneliness	1.10	0.73-1.67	.650	0.98	0.63-1.54	.940	1.21	0.80-1.83	.370	0.95	0.65-1.38	.790	1.12	0.76-1.63	.570
Metabolic															
BMI	**1.08**	1.05-1.12	<.001	**1.05**	1.01-1.09	.021	**1.07**	1.04-1.11	<.001	1.01	0.98-1.05	.450	1.04	1.00-1.08	.064
Dyslipidemia	1.25	0.99-1.57	.063	1.26	0.95-1.69	.110	**1.43**	1.12-1.83	.004	1.12	0.91-1.38	.290	0.94	0.70-1.28	.700
Obesity	0.78	0.54-1.14	.200	0.97	0.62-1.53	.900	1.27	0.88-1.84	.200	1.00	0.71-1.41	.990	0.66	0.41-1.05	.081
Blood glucose	1.06	0.90-1.26	.480	0.89	0.70-1.13	.330	**51.41**	34.13-77.43	<.001	1.00	0.85-1.17	.960	**0.73**	0.56-0.94	.014
Hypertension	1.21	0.93-1.56	.150	1.11	0.82-1.50	.490	**1.76**	1.33-2.33	<.001	1.13	0.91-1.41	.280	**0.72**	0.53-0.96	.027
Lifestyle															
Physical activity	1.02	0.99-1.05	.240	1.01	0.97-1.04	.690	0.98	0.95-1.01	.140	0.98	0.96-1.01	.240	0.98	0.95-1.02	.350
Smoking	**2.04**	1.55-2.70	<.001	**1.71**	1.25-2.35	<.001	1.17	0.87-1.58	.300	0.88	0.66-1.17	.370	0.96	0.71-1.29	.790
	Nagelkerke R^2=.360			Nagelkerke R^2=.310			Nagelkerke R^2=.500			Nagelkerke R^2=.310			Nagelkerke R^2=.280		

Note: OR=odds ratio; CI=confidence interval (2,5%-97,5%). For statistically significant predictors, the OR is printed in bold.

Supplementary Table S-IV.2. Results of multiple logistic regression models of new onset of CVD, chronic obstructive lung disease, diabetes mellitus, cancer, and migraine on depressive symptoms at baseline for women.

	CVD			Chronic obstructive lung disease			Diabetes mellitus			Cancer			Migraine		
	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*	OR	CI	*p*
Depressive symptoms	1.03	0.98-1.09	.240	**1.06**	1.01-1.12	.017	1.05	0.99-1.10	.077	1.01	0.97-1.06	.610	**1.05**	1.01-1.09	.019
Sociodemographic															
Age	**1.07**	1.04-1.09	<.001	1.01	0.98-1.03	.570	1.00	0.98-1.03	.880	**1.02**	1.00-1.04	.016	**0.95**	0.93-0.96	<.001
SES	**0.94**	0.89-1.00	.037	0.99	0.94-1.05	.770	0.98	0.93-1.04	.550	0.99	0.96-1.03	.770	**0.94**	0.91-0.98	.006
Living with partner	1.07	0.42-2.76	.880	0.87	0.39-1.94	.740	1.10	0.46-2.58	.830	1.36	0.62-2.97	.440	1.15	0.64-2.06	.640
Living alone	0.86	0.31-2.39	.770	1.05	0.43-2.55	.910	1.03	0.41-2.62	.950	1.25	0.54-2.92	.600	0.80	0.40-1.61	.540
Psychological															
Loneliness	0.90	0.47-1.73	.750	0.60	0.30-1.20	.150	1.54	0.88-2.72	.130	1.06	0.65-1.74	.810	0.95	0.59-1.51	.820
Metabolic															
BMI	**1.07**	1.02-1.13	.012	**1.06**	1.00-1.11	.037	**1.09**	1.04-1.14	<.001	1.01	0.97-1.06	.610	1.03	0.98-1.07	.240
Dyslipidemia	1.35	0.89-2.05	.160	1.08	0.69-1.71	.730	1.43	0.96-2.13	.080	1.23	0.87-1.74	.240	1.00	0.66-1.50	.990
Obesity	0.74	0.38-1.45	.380	1.09	0.56-2.11	.800	1.15	0.63-2.12	.650	0.99	0.56-1.72	.960	0.67	0.36-1.23	.200
Blood glucose	0.91	0.63-1.30	.600	0.93	0.65-1.34	.700	**43.18**	22.31-83.54	<.001	1.07	0.83-1.39	.600	0.88	0.64-1.20	.410
Hypertension	**1.80**	1.14-2.83	.011	1.07	0.69-1.67	.760	**1.78**	1.13-2.80	.013	1.08	0.77-1.53	.640	**0.64**	0.44-0.94	.023
Lifestyle															
Physical activity	1.04	0.98-1.09	.200	0.99	0.93-1.05	.720	1.01	0.96-1.07	.660	0.97	0.93-1.02	.260	0.97	0.93-1.01	.180
Smoking	**2.54**	1.60-4.03	<.001	**1.92**	1.22-3.00	.005	1.41	0.87-2.26	.160	0.89	0.58-1.36	.590	0.85	0.59-1.24	.410
	Nagelkerke R^2=.430			Nagelkerke R^2=.380			Nagelkerke R^2=.540			Nagelkerke R^2=.320			Nagelkerke R^2=.290		

Note: OR=odds ratio; CI=confidence interval (2,5%-97,5%). For statistically significant predictors, the OR is printed in bold.

Supplementary Table S-IV.3. Results of multiple logistic regression models of new onset of CVD, chronic obstructive lung disease, diabetes mellitus, cancer, and migraine on depressive symptoms at baseline for men.

	CVD			Chronic obstructive lung disease			Diabetes mellitus			Cancer			Migraine		
	OR	CI	p	OR	CI	p	OR	CI	p	OR	CI	p	OR	CI	p
Depressive symptoms	1.04	1.00-1.09	.065	**1.07**	1.02-1.12	.008	1.03	0.99-1.08	.170	1.03	0.99-1.08	.110	**1.07**	1.02-1.13	.010
Sociodemographic															
Age	**1.08**	1.06-1.10	<.001	1.02	1.00-1.04	.070	**0.98**	0.96-1.00	.021	**1.08**	1.06-1.10	<.001	**0.96**	0.94-0.98	.001
SES	1.00	0.97-1.04	.850	0.98	0.94-1.02	.360	0.97	0.93-1.00	.051	1.02	0.99-1.06	.130	0.98	0.93-1.03	.400
Living with partner	0.73	0.33-1.62	.440	1.57	0.38-6.51	.540	0.55	0.24-1.25	.150	2.40	0.58-9.84	.230	0.74	0.26-2.09	.560
Living alone	0.68	0.28-1.65	.390	1.64	0.37-7.26	.520	0.57	0.23-1.42	.230	3.35	0.78-14.32	.100	0.89	0.29-2.75	.840
Psychological															
Loneliness	1.25	0.73-2.15	.410	1.59	0.87-2.92	.130	0.95	0.51-1.77	.880	0.78	0.44-1.40	.400	1.48	0.77-2.86	.240
Metabolic															
BMI	**1.09**	1.04-1.14	<.001	1.02	0.96-1.10	.490	**1.06**	1.01-1.11	.024	1.02	0.97-1.07	.500	1.07	0.99-1.15	.095
Dyslipidemia	1.21	0.92-1.61	.180	1.46	1.00-2.14	.053	**1.41**	1.03-1.92	.032	1.11	0.85-1.45	.450	0.88	0.56-1.39	.580
Obesity	0.80	0.50-1.27	.340	0.96	0.51-1.82	.900	1.39	0.86-2.25	.170	0.97	0.62-1.53	.910	0.58	0.27-1.26	.170
Blood glucose	1.13	0.93-1.37	.220	0.87	0.64-1.19	.390	**57.28**	33.83-96.99	<.001	0.96	0.79-1.17	.700	**0.52**	0.34-0.80	.003
Hypertension	0.98	0.72-1.34	.890	1.17	0.77-1.77	.470	**1.75**	1.22-2.51	.002	1.20	0.89-1.62	.220	0.84	0.52-1.34	.460
Lifestyle															
Physical activity	1.01	0.98-1.05	.530	1.02	0.98-1.07	.350	**0.96**	0.92-1.00	.031	1.00	0.96-1.04	.980	1.00	0.95-1.06	.890
Smoking	**1.79**	1.26-2.53	.001	1.52	0.97-2.37	.067	1.05	0.72-1.55	.790	0.86	0.58-1.28	.460	1.17	0.72-1.92	.520
	Nagelkerke R^2=.320			Nagelkerke R^2=.220			Nagelkerke R^2=.470			Nagelkerke R^2=.310			Nagelkerke R^2=.230		

Note: OR=odds ratio; CI=confidence interval (2,5%-97,5%). For statistically significant predictors, the OR is printed in bold.

5 Study 3: Does social support prevent suicidal ideation in women and men? Gender-sensitive analyses of an important protective factor within prospective community cohorts

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5.1 Introduction

Suicidal ideation and behavior are important public mental health issues. Worldwide, close to 800,000 deaths per year are estimated to occur as a result of suicide (1). Overall lifetime prevalence rates are approximately 9.2% for suicidal ideation and 2.7% for suicide attempts (2). Suicidal ideation and behavior are increasingly viewed as a distinct clinical entity with complex biopsychosocial etiology (3). Together, these terms cover a continuum which ranges from passive death wishes to dangerous attempts and deaths by suicide (4). Since non-fatal suicide attempts also have serious consequences and any expression of suicidal ideation indicates great emotional distress, all of these suicide outcomes should be taken seriously. According to the WHO, empirical research on risk factors is of paramount importance to identify particularly vulnerable individuals (5). However, risk assessment is still a difficult task (6, 7), partly because large-scale investigations that analyze factors from different areas of life in combination (such as genetic-biological, sociodemographic, psychological, and environmental variables) are scarce.

The role of a person's gender in shaping (mental) health has come to the fore of public health research in recent years (8). Health-related differences between women and men are not only influenced by genetics and biology, but also by socialization. Gender (in terms of both identity as well as self-concept, i.e. masculinity and femininity (9)) correlates with suicide outcomes: While men are much more likely to die by suicide (10), a systematic review on suicidal behavior in Europe and America has concluded that suicidal ideation and behavior are more common among women (11). Women are generally more likely to report mental distress (i.e., in the form of internalizing disorders such as depression (12, 13)). This included suicidal ideation, e.g., in investigations of the German general population and the state Rhineland-Palatinate (14, 15). In addition, many risk factors for suicidal ideation and behavior that are common in the community differ considerably between women and men (16, 17), such as depressive disorders, anxiety disorders, PTSD, drug and alcohol abuse, levels of education and SES, and experiences of child maltreatment and sexual abuse.

Gender aspects are also of particular importance in social relationships (18) and women and men have shown differences regarding the needs for and the use of social ties and coping strategies (19-21). This is relevant with respect to the emergence of suicidal ideation as the most influential etiological theories have highlighted social connectedness and community as central protective factors, for instance the Interpersonal Psychological Theory of Suicide (22). In fact, research has indicated that the effects of social risk and protective factors are modified by gender (23, 24). Within an Australian community study, women and men differed with regard to the implications of perceived burdensomeness and thwarted belongingness (25), two constructs indicating difficulties relating to others which aggravate individual suicide risk according to the Interpersonal Psychological Theory of Suicide (22). Higher levels of thwarted belongingness increased suicidal ideation only in women. Furthermore, marriage per se appeared to be a protective factor for men, whereas this did not apply to married women the same way (for them, having a young child was found to be protective) (26, 27). Recent evidence has also suggested that men were at higher risk for suicide once a relationship ended (28). Male suicide attempters were prevented from seeking help by internalized hegemonic masculinity role expectations (29).

Besides gender differences, research has also highlighted substantial regional disparities. In Germany the former existence of the German Democratic Republic (Eastern states) and Federal Republic of Germany (Western States) caused differences in socialization within the

population which is reflected in individual health and health behaviors (30), e.g., suicide rates were higher in the eastern federal states than in the western federal states (31). Suicide rates were higher among men compared to women (32). However, suicide attempts were most prevalent among young women, closely followed by young men (33).

5.1.1 Objective of this study

The present study operationalized the interplay of sociodemographic, social, and environmental factors in a common statistical model: In order to better understand the potentially different mechanisms underlying suicidal ideation in women and men, this study explored the interaction of social support and gender within a longitudinal study design. We tested whether gender modified the association of social support and suicidal ideation while taking previously established risk factors into account and testing for potential socialization effects in Germany within a large population sample of pooled cohorts from two different German regions.

5.2 Methods

5.2.1 Study design and sample

The present investigation included data drawn from two studies of the GESA consortium (34) whose main aims comprise identifying gender differences in prevalence rates of mental health outcomes and determining gender differences and similarities in risk- and protective factors for mental health in different regional cohorts. The two included studies were GHS representing midwest Germany (35, 36) and SHIP representing northeast Germany (37) which includes an area of the former German Democratic Republic. For our baseline sample, we included data from the GHS S-1 wave (2007-2012) (age range 35-74) and the SHIP FF-1 (2008-2012) and Legend (2007-2010) waves (age range 31-93), which complement each other. For our follow-up sample, we included data from the GHS F-1 wave and the SHIP FFF-1 wave, including data from the years 2012-2017 and 2014-2016. We only included respondents who participated in the baseline and follow-up study. Data are comparable regarding the timing of the baseline collection and duration of follow-up assessments. Respondents with missing values on the social support scale and suicidal ideation were excluded (GHS: *N* = 517 (4.2%); SHIP: *N* = 46 (3.2%)), which led to a final sample of *N* = 13,290 (*N* = 6,568 women and *N* = 6,722 men). For an overview of the included studies, see Supplementary Figure S-V.1.

5.2.2 Measures

5.2.2.1 Social support

Within the GHS, social support was measured using the Brief Social Support Scale which includes both emotional-informational and tangible social support (38). For example, items assessed the availability of a person who understands one's problems or who could offer support when being sick. Respondents indicated on a four-point scale how often such a person was available for them. The response options were "always" (1), "mostly" (2), "sometimes" (3), and "never" (4). Internal consistency of the total scale was satisfactory (Cronbach's α = .86) (38). Within SHIP, social support was measured using the Social Support Questionnaire (F-SozU). Fourteen items assessed general perceived social support, e.g., availability of a person

who offers emotional or practical support, social integration, and social strain. Respondents could answer on a five-point scale. Response categories were “does not apply at all” (1), “does rather not apply” (2), “partially applies” (3), “applies” (4), and “applies exactly” (5). The questionnaire was shown to have a high internal consistency (Cronbach’s α = .94) (39). In order to allow for a comparison of these scales, a sum score for each was calculated. For the GHS, the items were first inversed. After this transformation, a higher score on an item indicated higher social support, as was already the case for SHIP. In order to derive a categorical variable from these sum scores with a comparable interpretation in both cohorts, the sum scores of both social support scales were divided into three equal parts (33% quantile and 66% quantile). They indicated low (1), medium (2), and high social support (3) with reference to the respective underlying population. In the present analyses, we compared people with medium or high social support with people with low social support.

5.2.2.2 Suicidal ideation

Suicidal ideation was measured using the ninth item of the PHQ-9 depression module: “Over the last two weeks, how often have you been bothered by thoughts that you would be better off dead or hurting yourself in some way?”. Response options for this item were the same as for all PHQ-9 items: 0 = ”not at all”, 1 = ”several days”, 2 = ”more than half the days”, and 3 = ”nearly every day”. We applied the standard coding for suicidal ideation as assessed by the PHQ-9 (see e.g., 40): participants who reported to not have these thoughts at all were categorized as reporting no suicidal ideation (0) and participants who reported to be bothered by these thoughts at least on several days were coded as reporting suicidal ideation (1).

5.2.2.3 Sociodemographic variables

The sociodemographic variables gender, age, level of education, household income, and employment status at baseline were included as covariates in the analyses. Gender was measured as self-report (participants reported whether they were women or men). Sex and gender are important modifiers of (mental) health and illness within the population (8). Sex (biological aspects) and gender (social aspects) are related constructs; however, the present paper focuses social and interpersonal ramifications, which is why we use the term gender. Age was derived from birthday and study entry date. Education (in years) was derived from educational and work degrees. Years of education were assigned to the different educational, vocational and professional levels, with all respondents receiving a score ranging from 7 to 18 years. Household income was included as a continuous variable, based on mean values of the respective income categories of the monthly household income variables used in the two cohorts. Current employment status was categorized as “no employment” (including unemployed people, homemakers, retirees, etc.) or “employment” (including full-time, part-time and marginal employment).

5.2.2.4 Living situation and family

This study included several variables representing living situation and family status. Marital status was recoded into two categories: married and not married (including singles, divorced people, and widowers and widows). For the GHS cohort, the categories “registered partnership” and “married but living separately” and for the SHIP cohort, the category “married, but living separately” were added to the category “married”. The categories “single”, “divorced” and “widowed” were combined in the category “not married”. The number of persons in a household was a continuous variable based on self-reported household members (including participant and spouse, children etc.). Living alone was included as a dichotomous variable. Having children and number of children were self-reported. In the GHS, these questions

specifically focused on biological children, whereas in the SHIP study, adopted and foster children were included as well.

5.2.2.5 Region

In order to control for regional effects in analyses of the pooled sample, we included a variable for the GHS cohort (representing midwest Germany) and a variable for the SHIP cohort (representing Eastern Germany).

5.2.3 Data analysis

Analyses were performed in DataSHIELD version 4.1 (41-43), a system for privacy-preserving analyses where individual-level data of different cohorts do not have to be pooled for joint analyses. DataSHIELD allows for analyses via several R packages, based on R-version 3.5.2 (44).

First, we performed descriptive analyses in DataSHIELD in order to provide information on the overall sample and the separate cohorts. Descriptive analyses were stratified by social support and we have used statistical tests to compare respondents who received low social support to respondents receiving middle or high social support. Additionally, we calculated Cohen's d to determine the magnitude of the observed effects.

Secondly, we calculated simultaneous multiple logistic regression models of suicidal ideation within the pooled sample and within each cohort including interaction terms to investigate gender as a potential effect modifier. Applying a longitudinal study design, we attempted to examine the effects of social support on suicidal ideation five to seven years later. In the first model, we tested the direct effect of social support on suicidal ideation. In the second model, we added gender as a covariate. Model 3 additionally comprised interaction terms of social support and gender. In the final model, model 4, all potentially confounding variables such as sociodemographic covariates, living situation and family status, and cohort were added.

5.3 Results

5.3.1 Sample characteristics

In total, the present analyses included 13,290 participants. Their mean age was 54.42 (SD = 11.02) years and almost half of them were women.

5.3.2 Prevalence of suicidal ideation

Of the 13,290 participants, 7.4% (*N* = 982) reported suicidal ideation. In general, more women (8.6%, *N* = 565) than men (6.2%, *N* = 417) reported suicidal ideation. The gender-specific distribution of suicidal ideation, disaggregated into social support categories, is shown in Figure V.1.

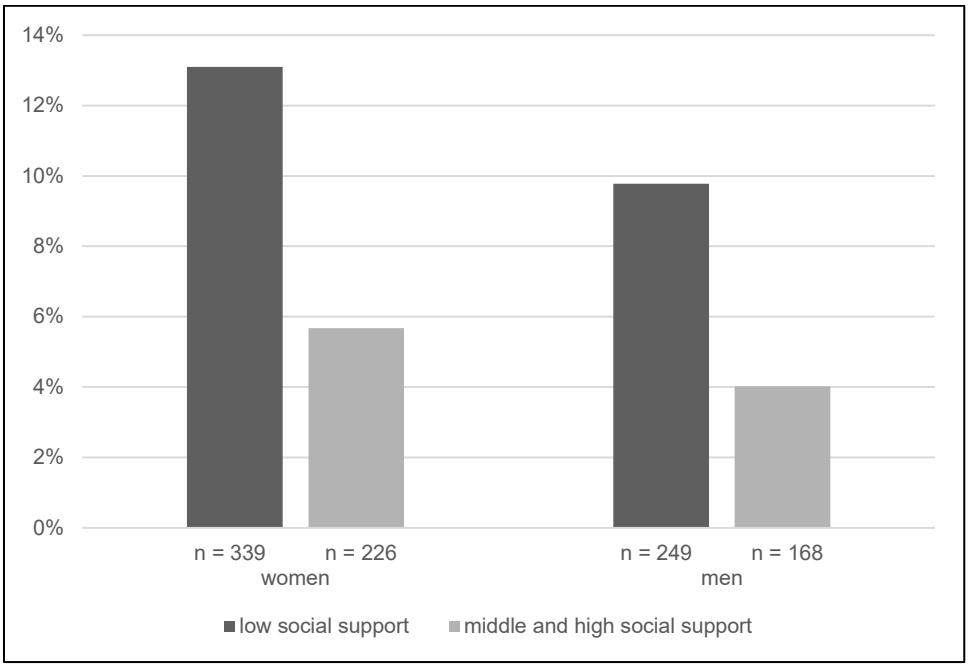


Figure V.1. Suicidal ideation for women and men, subdivided into social support categories.

5.3.3 Associations between measures of interest

There was a strong, statistically significant association between low social support and suicidal ideation both within the pooled sample (see Table V.1) and the individual cohorts (Supplementary Table S-V.1). This association applied to both women and men (Supplementary Table S-V.2).

Within the pooled sample, higher levels of social support were associated with more years of education and a higher household income, however, effect sizes were small. Further, being married, living with a partner, living in a larger household and having children were significantly associated with middle-high social support (rather than low social support) with small to medium effect sizes. These associations were found within the pooled sample, within both cohorts, and in women and men. However, the association between having children and middle-high social support was stronger for men ($p < 0.001$) compared to women ($p = 0.043$).In the pooled sample, social support was not associated with gender, age, or employment status.

Within the individual cohorts, we observed statistically significant effects of gender, although in different directions, and effect sizes were small: Within the GHS cohort, men were more likely to indicate receiving middle and high social support, whereas in the SHIP cohort, women were more likely to receive middle and high social support. In both cohorts, years of education and household income were significantly associated with social support with small to medium effect sizes. Being married was (compared to being single, divorced or widowed), only associated with social support within the GHS cohort. Furthermore, having children was associated with middle and high social support, yet within SHIP, only a trend was found.

Table V.1. Sample characteristics of the overall population, stratified by the level of social support.

	All (*N* = 13,290)	Low social support (*N* = 5,135; 38.6%)	Middle/ high social support (*N* = *8,155;* 61.4%)	*p*	*d*
Sociodemographic					
Gender				.071	0.03
women (%)	6,568 (49.4)	2,589 (50.4)	3,979 (48.8)		
men (%)	6,722 (50.6)	2,546 (49.6)	4,176 (51.2)		
Age (M±SD)	54.42±11.02	54.35±10.81	54.47±11.15	.564	0.01
Educational years (M±SD)	13.98±2.87	13.86±2.84	14.05±2.88	<.001	0.07
Household income (M±SD)	3457±2445	3107±2132	3676±2591	<.001	0.23
Employment status				.123	0.03
no employment (%)	4,854 (36.6)	1,917 (37.4)	2,937 (36.1)		
employment (%)	8,402 (63.4)	3,203 (62.6)	5,199 (63.9)		
Living situation/ family					
Marital status				<.001	0.29
married (%)	10,154 (76.4)	3,525 (68.7)	6,629 (81.3)		
not married (%)	3,133 (23.6)	1,607 (31.3)	1,526 (18.7)		
Living with partner				<.001	0.38
no (%)	2,370 (17.8)	1,379 (26.9)	991 (12.1)		
yes (%)	10,917 (82.2)	3,753 (73.1)	7164 (87.9)		
Number of persons in household (M±SD)	2.49±1.10	2.37±1.15	2.56±1.06	<.001	0.17
Children				<.001	0.14
no (%)	1,774 (14.4)	823 (17.4)	951 (12.5)		
yes (%)	10,543 (85.6)	3,899 (82.6)	6,644 (87.5)		
Mental distress					
Suicidal ideation				<.001	0.25
no (%)	12,308 (92.6)	4,547 (88.5)	7,761 (95.2)		
yes (%)	982 (7.4)	588 (11.5)	394 (4.8)		

Note: Not married includes singles, divorced people and widowers and widows. Employment includes fulltime, part-time and marginal employment; no employment includes unemployed people, homemakers, retirees etc.

5.3.4 Main analyses

We observed a strong association of social support and suicidal ideation within the pooled longitudinal cohorts: After controlling for sociodemographic factors, living situation and cohort effects, middle or high social support was associated with a significantly lower probability to report suicidal ideation five years later (final model 4: OR = 0.42, CI = 0.34-0.52). This effect was highly significant in all models. There was no statistically significant interaction of gender and social support (final model 4: ratio of ORs = 1.00, 95%-CI = 0.73-1.35).

Furthermore, male gender was negatively related to suicidal ideation in all models in which it was included as a covariate. With regard to sociodemographic factors, age, employment status and household income were significantly associated with suicidal ideation: Higher age, being employed, and having a higher household income reduced the probability to report suicidal ideation. There was also a cohort effect in the sense that living in northeast Germany was associated with a higher likelihood of reporting suicidal ideation compared to living in midwest Germany. For details, see Table V-2.

Table V.2. Results of multiple logistic regression models of suicidal ideation on social support.

	Model 1			Model 2			Model 3			Model 4		
	OR	95% CI (L; U)	*p*	OR	95% CI (L; U)	*p*	OR	95% CI (L; U)	*p*	OR	95% CI (L; U)	*p*
Social support												
low (ref)												
middle and high	**0.393**	0.344; 0.449	<.001	**0.394**	0.345; 0.450	<.001	**0.400***	0.335; 0.477	<.001	**0.418***	0.336; 0.520	<.001
Gender												
women (ref)												
men				**0.710**	0.622; 0.810	<.001	**0.719**	0.605; 0.856	<.001	**0.760**	0.618; 0.934	.009
Interactions												
Social support*gender												
Ratio: middle/high vs. low in men vs. women							0.967	0.740; 1.265	.809	0.997	0.734; 1.354	.985
Sociodemographic												
Age										**0.985**	0.975; 0.995	.004
Educational years										1.003	0.974; 1.033	.851
Household income										**0.928**	0.881; 0.975	.003
Employment status												
no employment (ref)												
Employment										**0.742**	0.607; 0.908	.004
Living situation and family												
Marital status												
married (ref)												
not married										0.910	0.694; 1.194	.494
Living with partner												
no (ref)												
yes										0.757	0.559; 1.025	.072
Number of persons in household										0.957	0.864; 1.061	.407
Children												
no (ref)												
yes										0.846	0.666; 1.075	.170
Region												
Cohort												
GHS (ref)												
SHIP										**0.554**	0.417; 0.735	<.001
Deviance model (R^2)	6835.581			6784.692			6784.633			5209.350		

Note: Not married includes singles, divorced people and widowers and widows. Employment includes fulltime, part-time and marginal employment; no employment includes unemployed people, homemakers, retirees etc. For interpretability reasons, household income was in the regression analyses divided by 1000, which means regression coefficients for household income represent a 1000 unit increase in household income. OR = Odds Ratio. 95% CI (L, U) = Lower and upper bounds of the Confidence Interval (95%). Statistically significant Odds Ratios are printed in bold.
* refers to Odds Ratio valid for women in models 3 and 4 which contain an interaction effect social support x gender

5.3.5 Gender-stratified analyses

In order to better understand the observed interaction effect, we conducted gender-stratified analyses. They revealed that negative associations of social support and suicidal ideation applied to both women (OR = 0.42, CI = 0.34-0.53) and men (OR = 0.41, CI = 0.33-0.51) and that they were slightly stronger in women (see Figure V.2). Furthermore, the effects of sociodemographic factors, living situation, and family factors differed between women and men: In women, higher age, higher household income, employment, and having children were associated with a lower probability to report suicidal ideation. In men, only a higher household income was associated with a decreased likelihood to report suicidal ideation. For details, see Supplementary Table S-V.3.

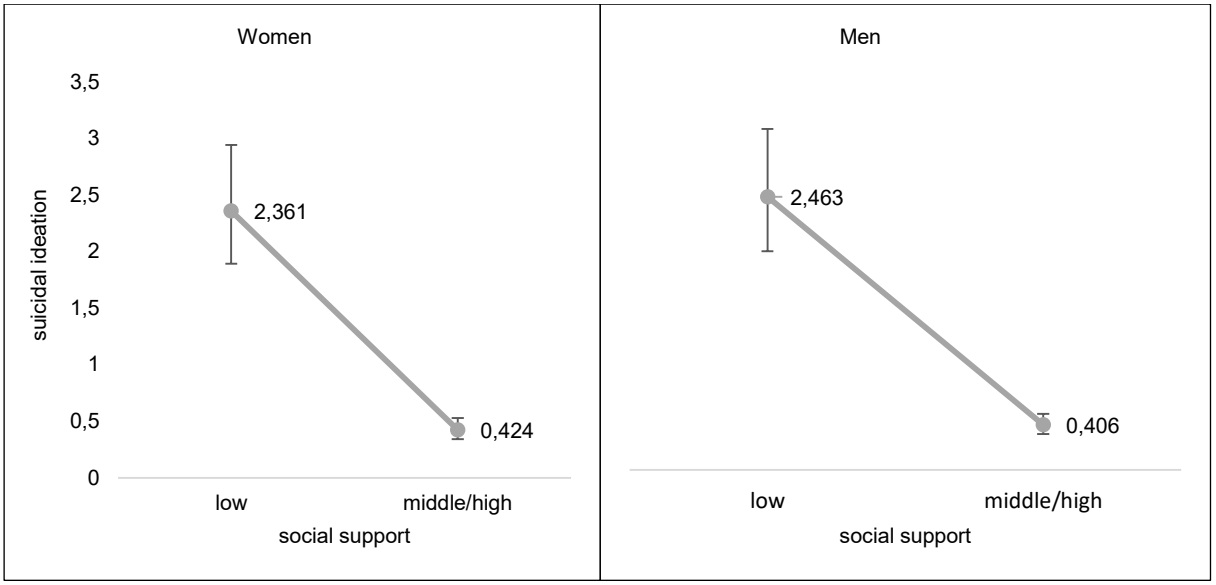


Figure V.2. Associations of social support and suicidal ideation for women and men.
Odds Ratios (incl. 95% CI) for the associations of low social support and medium and high social support with suicidal ideation by gender.

5.3.6 Cohort-specific analyses

When examining GHS and SHIP individually, the strong protective effect of middle or high social support was present in both cohorts. Higher age and being employed were negatively associated with suicidal ideation in both cohorts, but the negative effect of higher household income was only present in the GHS cohort. The protective effect of male gender was only present in the SHIP cohort. With respect to living situation and family status, in the GHS cohort, living with a partner was associated with a lower probability to report suicidal ideation. This was not the case in SHIP. Lastly, an interaction effect of social support with gender was found for SHIP. For details, see Table V.3.

Table V.3. Results of multiple logistic regression models of suicidal ideation on social support for GHS and SHIP.

	GHS				SHIP			
	OR	95% CI		*p*	OR	95% CI		*p*
		LB	UB			LB	UB	
Social support								
low (ref)								
middle and high	**0.467**	0.371	0.587	<0.001	**0.155**	0.076	0.319	<.001
Gender								
women (ref)								
men	0.816	0.657	1.012	0.064	**0.306**	0.137	0.682	.004
Sociodemographic								
Age	**0.987**	0.976	0.998	0.019	**0.967**	0.936	0.998	.040
Educational years	1.005	0.975	1.037	0.732	0.980	0.861	1.116	.763
Household income	**0.929**	0.881	0.976	0.003	0.742	0.338	1.146	.211
Employment status								
no employment (ref)								
employment	**0.786**	0.636	0.971	0.026	**0.471**	0.227	0.977	.043
Living situation and family								
Marital status								
married (ref)								
not married	0.857	0.642	1.144	0.296	1.464	0.651	3.294	.357
Living with partner								
no (ref)								
yes	**0.725**	0.527	0.999	0.050	1.439	0.530	3.910	.476
Number of persons in household	0.969	0.872	1.077	0.564	0.712	0.434	1.170	.180
Children								
no (ref)								
yes	0.811	0.634	1.039	0.097	1.706	0.598	4.870	.318
Interactions								
interactions social support*gender								
*low*women (ref)*								
*middle and high*men*	0.864	0.628	1.189	0.371	**4.770**	1.504	15.131	.008
Deviance model (R^2)	4755.452				431.781			

Note: Not married includes singles, divorced people and widowers and widows. Employment includes fulltime, part-time and marginal employment; no employment includes unemployed people, homemakers, retirees etc. For interpretability reasons, household income was in the regression analyses divided by 1000, which means regression coefficients for household income represent a 1000 unit increase in household income. OR = Odds Ratio. 95% CI (L, U) = Lower and upper bounds of the Confidence Interval (95%). Statistically significant Odds Ratios are printed in bold.

5.4 Discussion

The aim of the present study was to disentangle the effects of social, sociodemographic, and regional risk and protective factors shaping suicidal ideation in women and men. The grave mental distress which underlies all expressions of suicidal ideation and the high numbers of suicide deaths observed each year (45) make prevention an urgent mental health issue. Along these lines, this study deepened the knowledge about the interplay and relative importance of variables from different areas of life with respect to the statistical prediction of suicidal ideation years later by combining two cohorts from different regions.

In this pooled sample, a total of 7.4% of respondents reported suicidal ideation. Women reported suicidal ideation more often than men (respectively 8.6% versus 6.2%). The main analyses showed a strong association between social support and suicidal ideation: Middle or

high social support was associated with a lower probability to report suicidal ideation approximately five years later after controlling for sociodemographic factors, living situation and region (OR = 0.42, CI = 0.34-0.52). This effect was found in women and men. Yet, the mitigating effect of social support on suicidal ideation was slightly stronger for women (OR = 0.42, CI = 0.34-0.53) compared to men (OR = 0.41, CI = 0.33-0.51). Additionally, in both cohorts, middle and high social support was associated with a lower probability to report suicidal ideation. This effect was stronger in the GHS cohort (OR = 0.47, CI = 0.37-0.59) compared to the SHIP cohort (OR = 0.16, CI = 0.08-0.32).

The present results corroborate previous findings that social factors are important statistical predictors of suicidal ideation in the community. In particular, they show the protective impact of positive social connectedness (46, 47), supporting current, influential theories of suicidal ideation and behavior (22). Within the regression models, the effects of subjective reports of social support were comparatively stronger than those of more objective indicators of social integration, such as participants' living situation. This observation is in line with recent research which has highlighted that in the context of the COVID-19 pandemic, only the subjective experience of loneliness (and not physical distancing) was associated with suicidal ideation at a later time point (48). Previous studies showed that even after controlling for other mental disorders, the beneficial effects of social support and social integration remained strongly significant (49). Our investigation expands previous research by explicitly testing gender-dependent effects (using interaction terms) within large, prospective population cohorts. The results demonstrate the important protective effects of social support irrespective of an individual's living situation in both women and men. Likewise, a recent nationwide German study reported strong associations between loneliness and suicidal ideation in both genders (24).

With regard to regional differences, our results showed in both the overall sample and the gender-specific analyses that living in northeast Germany was associated with a lower probability to report suicidal ideation compared to living in midwest Germany. This is in line with a recent study which demonstrated higher rates of depression in West Germany (50), which was shown to be associated with suicidal ideation (14, 51).

Furthermore, the present results revealed similarities as well as slightly different patterns of other factors influencing the probability to report suicidal ideation in women and men. In accordance with other studies which showed an inverse association between income and psychological distress, especially for suicidal ideation and suicide attempts (52), higher household income was negatively associated with suicidal ideation. However, only for women, employment and children constituted protective factors. A previous study had shown that especially low job control and high job demands were associated with suicidal ideation (53). Work demand is positively associated with work satisfaction when the individual evaluation of job demands is positive (54) and is furthermore influenced by job control and social support: Presence of social support and job control foster well-being (54). Especially for women, job control was found to be beneficial to reduce stress levels and positively influence mental health (55). In general, women report higher job satisfaction than men (56, 57), which could explain why employment was a relevant protective factor against suicidal ideation only for them. The present finding that being a parent was a protective factor in women is in line with the results of previous studies (26, 27). However, other investigations showed that parenthood was more strongly associated with positive well-being for men than for women (58). An explanation for these diverging observations could be found in the different areas in which mothers and fathers experience parenthood-related stress (59): it has been suggested that women experience

more stress in the sub-areas of incompetence and role restriction, whereas fathers tend to suffer more from social isolation, a well-established risk factor for several suicide outcomes (60). We did not find associations of marital status or living alone with suicidal ideation, although previous evidence suggested that being married was a protective factor for men (26, 27), whereas ending a relationship was a risk factor for men (28). Future research should focus on further clarify the role of family in women and men's suicidal ideation.

5.4.1 Limitations

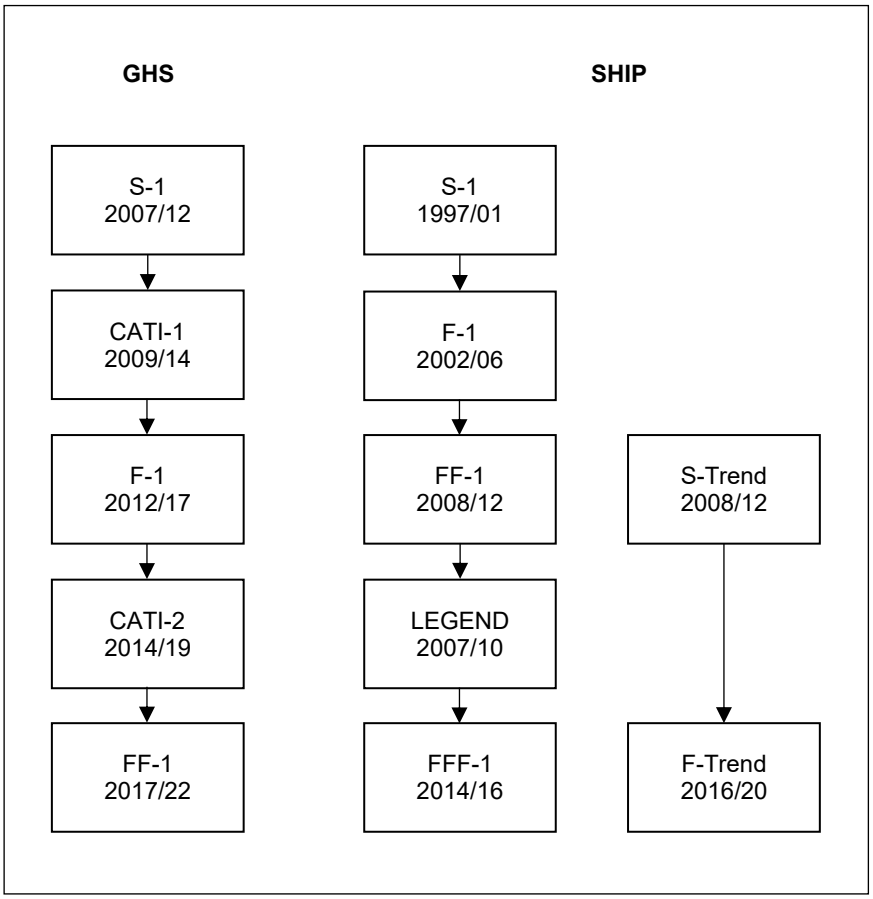
While a strength of our study refers to the large overall sample size and the combined investigation of cohorts from two different German regions that also differ with respect to social, cultural and economic factors, we need to point out that the number of people reporting suicidal ideation in the SHIP study was small, especially for men. A widespread difficulty in suicide research is that suicidal ideation and behavior are comparatively rare events in the population (with suicidal ideation still much more common than suicide attempts or deaths (10)), while some risk factors concern many citizens (e.g., male gender) (61). In the current study, we also observed low numbers of individuals reporting suicidal ideation. Since the sample drawn from the SHIP cohort in particular was rather small, the importance of the diverging gender-specific findings within the regions should not be overstated. Due to this limitation, we refrain from drawing further conclusions on these observations.

Another limitation of this study is the way suicidal ideation was assessed. Suicidal ideation was measured using a single item at one measurement point. Therefore, the present investigation cannot give insight into the temporal dynamics of suicidal ideation (62). Further, as the evaluated measurement points were years apart, the study yields no information about temporally closer (i.e., same-day) links of social support and suicidal ideation. These aspects restrict the interpretation of the present results, also because previous research has suggested that individuals who show greater variability in their reports of suicidal ideation might be particularly vulnerable (63). A potential solution for future research could lie in a combination of the strengths of large-scale longitudinal cohort studies with ambulatory assessment designs (see e.g., 64). While structured, in-depth clinical interviews are the gold standard for assessing suicidal ideation, this was not a feasible procedure within the present cohort studies. However, suicidal ideation measured using the PHQ-9 item, has shown relevant relations to subsequent suicide mortality in previous studies (65). Social support was measured by two different, standardized self-report scales in the two cohorts. In order to be able to compare predictors for suicidal ideation we stratified social support for each scale separately into terciles increasing the generalizability of our findings across measures and cohorts from different regions. Additionally, this study considers suicidal ideation separately from other depressive symptoms, although suicidal ideation is often conceptualized as a part of depressive disorders. However, there is a growing recognition that depressive disorders in particular or mental illness in general are neither prerequisites nor sufficient causes for suicidal crises (66). Furthermore, this study only assessed risk factors for suicidal ideation. While suicidal ideation is a risk factor for suicidal behavior, there are important further, specific risk factors distinguishing the two (as conceptualized by e.g., the ideation-to-action framework (4, 67)). Exposure to suicidal behavior in the social environment was not found to moderate the relation between lifetime suicidal ideation and suicide attempt (68). Thus, the present study does not give insight into gender-dependent risk constellations underlying suicide attempts and suicide deaths. There is a need for gender-sensitive research regarding specific risk factors for suicidal behavior, such as the

role of acquired capability for suicide (including fearlessness of pain and death) which differed between women and men (e.g., 69).

5.4.2 Conclusion

Based on two prospective community samples with more than 13,000 participants spanning over five years, social support was a highly significant protective factor preventing suicidal ideation in both women and men. This effect was observed in statistical models that controlled for sociodemographic factors, living situation, and family status, highlighting the importance of the subjective perception of social connectedness. Future research could further clarify potential gender-dependent ramifications of family variables. There is also a need to expand respective gender-sensitive approaches to the empirical study of suicidal behavior.



Supplementary Figure S-V.1. Overview of cohort samples from which data was drawn to conduct the present investigation.

GHS: Gutenberg Health Study. SHIP: Study of Health in Pomerania. S: Sample, F: Follow-up, CATI: Computer Assisted Telephone Interview. Adapted from: Burghardt et al., 2020.

Supplementary Table S-V.1. Cohort-specific sample characteristics of the participants, stratified by the level of social support.

	GHS					SHIP				
	All (*N* = 11,906)	Low social support (*N* = 4,716; 39.6%)	Middle/ high social support (*N* = *7,190;* 60.4%)	*p*	*d*	All (*N* = 1,384)	Low social support (*N* = 419; 30.3%)	Middle/ high social support (*N* = *965;* 69.7%)	*p*	*d*
Sociodemographic										
Gender				.002	0.057				.003	0.16
women (%)	5,820 (48.9)	2,388 (50.6)	3,432 (47.7)			748 (54.0)	201 (48.0)	547 (56.7)		
men (%)	6,086 (51.1)	2,328 (49.4)	3,758 (52.3)			636 (46.0)	218 (52.0)	418 (43.3)		
Age (M±SD)	54.26±10.82	54.18±10.68	54.31±10.91	.521	0.012	55.82±12.59	56.28±12.22	55.62±12.75	.368	0.05
Educational years (M±SD)	14.16±2.92	14.02±2.88	14.25±2.93	<.001	0.079	12.50±2.44	12.14±2.32	12.66±2.47	<.001	0.21
Household income (M±SD)	3632±2569	3231±2214	3893±2744	<.001	0.260	2034±956	1805±890	2134±967	<.001	0.35
Employment status				.129	0.028				.107	0.09
no employment (%)	4,227 (35.6)	1,713 (36.4)	2,514 (35.0)			627 (45.4)	204 (48.8)	423 (43.9)		
employment (%)	7,648 (64.4)	2,989 (63.6)	4,659 (65.0)			754 (54.6)	214 (51.2)	540 (56.1)		
Living situation/ family										
Marital status				<.001	0.327				.284	0.06
married (%)	9,172 (77.0)	3,237 (68.7)	5,935 (82.5)			982 (71.0)	288 (68.9)	694 (71.0)		
not married (%)	2,732 (23.0)	1,477 (31.3)	1,255 (17.5)			401 (29.0)	130 (31.1)	271 (29.0)		
Living with partner				<.001	0.403				<.001	0.22
no (%)	2,098 (17.6)	1,269 (26.9)	829 (11.5)			272 (19.7)	110 (26.3)	162 (16.8)		
yes (%)	9,806 (82.4)	3,445 (73.1)	6361 (88.5)			1,111 (80.3)	308 (73.7)	803 (83.2)		
Number of persons in household (M±SD)	2.51±1.12	2.39±1.17	2.60±1.08	<.001	0.188	2.26±0.91	2.14±0.88	2.31±0.91	.001	0.19
Children				<.001	0.132				.053	0.10
no (%)	1,645 (15.0)	774 (18.0)	871 (13.1)			129 (9.3)	49 (11.8)	80 (8.3)		
yes (%)	9,292 (85.0)	3,532 (82.0)	5,760 (86.9)			1,251 (90.7)	367 (88.2)	884 (91.7)		
Mental distress										
Suicidal ideation				<.001	0.242				<.001	0.26

no (%)	10,985 (92.3)	4,164 (88.3)	6,821 (94.9)	1,323 (95.6)	383 (91.4)	940 (97.4)
yes (%)	921 (7.7)	552 (11.7)	369 (5.1)	61 (4.4)	36 (8.6)	25 (2.6)

Note: Not married includes singles, divorced people and widowers and widows. Employment includes fulltime, part-time and marginal employment; no employment includes unemployed people, homemakers, retirees etc.

Supplementary Table S-V.2. Gender-specific sample characteristics of the participants, stratified by the level of social support.

	women					men				
	All (*N* = 6,568)	Low social support (*N* = 2,589; 39.4%)	Middle/ high social support (*N* = 3,979; 60.6%)	*p*	*d*	All (*N* = 6,722)	Low social support (*N* = 2,546; 37.9%)	Middle/ high social support (*N* = 4,176; 62.1%)	*p*	*d*
Sociodemographic										
Age (M±SD)	54.06±10.96	54.20±10.85	53.98±11.02	.416	0.020	54.77±11.06	54.51±10.77	54.93±11.23	.126	0.04
Educational years (M±SD)	13.64±2.76	13.62±2.76	13.65±2.75	.688	0.011	14.30±2.93	14.09±2.89	14.42±2.95	<.001	0.11
Household income (M±SD)	3207±2170	2933±2020	3382±2236	<.001	0.209	3695±2661	3277±2223	3948±2862	<.001	0.01
Employment status				.132	0.037				.640	0.01
no employment (%)	2620 (40.0)	1061 (41.1)	1559 (39.2)			2234 (33.3)	856 (33.7)	1378 (33.1)		
employment (%)	3932 (60.0)	1518 (58.9)	2414 (60.8)			4470 (66.7)	1685 (66.3)	2785 (66.9)		
Living situation/ family										
Marital status				<.001	0.213				<.001	0.37
married (%)	4834 (73.6)	1755 (67.8)	3079 (77.4)			5320 (79.2)	1770 (69.6)	3550 (85.0)		
not married (%)	1733 (26.4)	833 (32.2)	900 (22.6)			1400 (20.8)	774 (30.4)	626 (15.0)		
Living with partner				<.001	0.318				<.001	0.45
no (%)	1406 (21.4)	761 (29.4)	645 (16.2)			964 (14.3)	618 (24.3)	346 (8.3)		
yes (%)	5160 (78.6)	1826 (70.6)	3334 (83.8)			5757 (85.7)	1927 (75.7)	3830 (91.7)		
Number of persons in household (M±SD)	2.44±1.10	2.36±1.17	2.49±1.05	<.001	0.118	2.53±1.09	2.38±1.13	2.63±1.05	<.001	0.23
Children				.043	0.054				<.001	0.20
no (%)	274 (4.9)	123 (5.6)	151 (4.4)			1500 (22.3)	700 (27.5)	800 (19.2)		
yes (%)	5329 (95.1)	2056 (94.4)	3273 (95.6)			5214 (77.7)	1843 (72.5)	3371 (80.8)		
Mental distress										
Suicidal ideation				<.001	0.260				<.001	0.23
no (%)	6003 (91.4)	2250 (86.9)	3753 (94.3)			6305 (93.8)	2297 (90.2)	4008 (96.0)		
yes (%)	565 (8.6)	339 (13.1)	226 (5.7)			417 (6.2)	249 (9.8)	168 (4.0)		

Note: Not married includes singles, divorced people and widowers and widows. Employment includes fulltime, part-time and marginal employment; no employment includes unemployed people, homemakers, retirees etc.

Supplementary Table S-V.3. Gender-specific multiple logistic regression models of suicidal ideation on social support.

	Women				Men			
	OR	95% CI		p	OR	95% CI		p
		LB	UB			LB	UB	
Social support								
low (ref)								
middle and high	**0.424**	0.340	0.528	<.001	**0.406**	0.325	0.507	<.001
Sociodemographic								
Age	**0.980**	0.965	0.995	.010	0.987	0.973	1.001	.073
Educational years	0.996	0.953	1.041	.857	1.010	0.970	1.051	.635
Household income	**0.913**	0.838	0.988	.022	**0.936**	0.876	0.997	.039
Employment status								
no employment (ref)								
employment	**0.686**	0.525	0.897	.006	0.782	0.570	1.073	.128
Living situation and family								
Marital status								
married (ref)								
not married	0.930	0.624	1.386	.722	0.882	0.607	1.284	.513
Living with partner								
no (ref)								
yes	0.776	0.501	1.202	.256	0.742	0.484	1.138	.171
Number of persons in household	0.905	0.776	1.056	.206	1.000	0.869	1.152	.989
Children								
no (ref)								
yes	**0.613**	0.402	0.936	.023	0.920	0.687	1.232	.576
Region								
Cohort								
GHS (ref)								
SHIP	**0.583**	0.407	0.836	.003	**0.472**	0.294	0.756	.002
Deviance model (R^2)	2512.320				2688.159			

Note: Not married includes singles, divorced people and widowers and widows. Employment includes fulltime, part-time and marginal employment; no employment includes unemployed people, homemakers, retirees etc. For interpretability reasons, household income was in the regression analyses divided by 1000, which means regression coefficients for household income represent a 1000 unit increase in household income. OR = Odds Ratio. 95% CI (L, U) = Lower and upper bounds of the Confidence Interval (95%). Statistically significant Odds Ratios are printed in bold.

6 Study 4: Gender differences in the prevalence of mental distress in East and West Germany over time: A hierarchical age-period-cohort analysis

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6.1 Introduction

Mental health, a state of wellbeing that allows the individual to cope with stressors of everyday life and function productively (1), is characterized to a large part by the absence of mental distress and mental disorders. Both mental distress and mental disorders have become a major public health concern affecting quality of life, work productivity, physical illnesses, and life expectancy of a large proportion of the general population (2). While mental distress refers to distress in response to an external stressor and can be characterized by e.g., (symptoms of) anxiety or depression (3), psychological disorders consist of a pattern of persistent behavioral or psychological symptoms that influence several areas of life.

Mental health is subject to different temporal trends: it may vary depending on age, time period, and birth cohort. Moreover, mental health differences are frequently found between women and men, and between regions. When analyzing temporal trends, it is important to note that age, period, and cohort effects are highly related to one another. Age effects refer to developmental or age-specific transformation, the general pattern of individual transformation from childhood through adulthood and old age that are consistently noted in all birth cohorts and across all time-periods (4). Period effects, on the other hand, describe differences among individuals due to historical events that leave unique imprints, no matter the age. Finally, cohort effects refer to differences among individuals categorized by their time of birth, they share critical formative moments and similar socialization experiences with their respective birth cohort (4). Ideally, age, period, and cohort effects are examined simultaneously. However, due to the exact multicollinearity and conceptual relationship between age, period, and cohort, it is difficult to correctly estimate these effects. Studies apply different methodical frameworks based on specific theory-based assumptions in order to disentangle these effects (5). Thus, comparisons between studies are feasible only to a limited extent.

With regard to age effects, a Dutch study revealed self-reported prevalence of mental illnesses to be lower and general mental health to be better for the elderly (6). Similar results are found in a study in the USA; using the CIDI, lifetime and recent major depressive episodes are less prevalent among respondents of 65 years and older (7). However, a longitudinal survey study covering a 15-year period found a U-shape for depressive symptoms with highest symptoms burden for the age group 25-35 years and from 75 years onwards after controlling for cohort effects (8). A study including 27 European countries assessed self-reported depressive symptoms and also found the highest prevalence of current depressive disorder among persons of 75 years and older (9). A hierarchical age-period-cohort (HAPC) analysis on the life course trajectory of mental health from the UK partly confirmed this finding, as it revealed mental health to increase throughout life-course, but slowing during middle-age and worsening again slightly in older age (10). In Germany, the prevalence of current depressive symptoms (self-reported) was highest among 18-29-year-olds and decreased with age, whereas the lifetime prevalence of diagnosed depression was highest among 60-69-year-olds (11). Among the German elderly (53-80 years), a U-shape for the prevalence of depressive symptoms was found (12).

Period and cohort effects are also found in mental health studies. In a study applying HAPC models, recent birth cohorts in the UK generally reported worse mental health (10). A study from 1993 examining age and cohort effects for the occurrence of depression in a US sample reported that the birth cohort 1950-1959 had the lowest age of a first episode of depression (13). An age-period-cohort (APC) analysis in Canada and USA revealed highest levels of psychological distress in the oldest (born before 1939) and more recent (born 1989-1992) birth

cohorts (14). With regard to period effects, a systematic review and meta-analysis addressing the period 1980-2013 reported the highest prevalence estimates of common mental disorders worldwide in studies undertaken in the 1990's (15). In Canada and the USA, levels of mental distress were highest around 2000 (14). In the USA, reported depressive symptoms were highest between 2000 and 2010 (16). A German study applying HAPC models to examine APC trends in depressive symptoms found a U-shaped cohort effect where cohorts born around 1930 until 1950 exhibited less depressive symptoms compared to earlier and later born cohorts (17) .

Within Germany, differences in mental health are found between the former eastern and western federal states. Founded after World War II , the two German States existed from 1949 to 1990. They evolved with contrary and antagonistic political and economic systems. The federal republic of Germany followed the (capitalist) system of the Western European countries, whereas the German Democratic Republic (GDR) followed the example of the Russian-Soviet (socialist) system. The socialization processes and living conditions were therefore extremely different between the former East and West Germany, leading to different risk and protective factors regarding mental health. While many people suffered from political persecution and repression, leading to increased somatic symptoms, anxiety and depression later in life (18), other system-related factors like a low official unemployment rate and increased social mobility could be regarded as protective factors for mental health. The re-unification was accompanied by drastic changes in almost all aspects of life; while average income has been increasing in East Germany since 1990, they remain lower compared to West Germany (19, 20), and the unemployment rate 20 years after re-unification was still twice as high in East compared to West Germany (21). Regarding demographic characteristics, the East German population was reduced by 16% since re-unification (19), especially young people and women left East Germany. Even though the inner German migration has aligned now, the East still consists of an older population strata (19) and has a lower life expectancy than West Germany. These sociodemographic and socioeconomic differences are reflected in birth cohorts.

With regard to mental health, evidence shows that results for East and West Germany strongly differ between survey year and mental health outcome. A study examining psychological distress and mental disorders in former East and West Berlin one year after the fall of the Berlin wall did not find differences in ICD-10 diagnoses (22). However, a large nationally representative survey reported higher prevalence rates of mental disorders (assessed with CIDI) in the Western compared to the Eastern states in 1998/1999 (23) concerning depression, somatoform disorder, substance abuse, eating disorders, and social anxiety. Studies comparing mental health between East and West Germany 10 years after reunification found no differences in mental health between participants residing in East and West Germany (24), whereas life satisfaction was higher among West Germans compared to East Germans (25). Perceived stress did not differ between formerly East and West Germany 20 years after reunification (26), whereas prevalence of depression diagnosis was found to be lower in East compared to West Germany (27). Another study, however, did not confirm these differences for adolescents (28). Evidence for mental health differences between East and West Germany is thus inconclusive. An analysis covering a longer time frame and using representative data of Germany is thus needed to shed further light on the temporal trends in these two regions.

Differences in mental health exist between women and men. For most internalizing disorders (e.g., major depression (29) and anxiety disorders), women are more frequently affected than men (30, 31), whereas for externalizing disorders (e.g., substance abuse) men are more

frequently affected (32). Representative German studies have shown that approximately one in three women and one in four or five men had a diagnosis of a mental disorder in the previous 12 months (33). Sex differences in mental health can be explained by hormones (34, 35) and dysregulations in the HPA axis (34, 36), especially for stress-related mental disorders. Gender differences in mental health can be explained by e.g., gender-based violence (37), low self-esteem (34), and differences in risk behavior and identification of disease symptoms (38). Hence, sex and gender interact in the development of diseases (39, 40). Myocardial infarction and depression are gender stereotypical diseases (41). Myocardial infarction is known as typical disease for men and is therefore often overlooked for women (40), while depressive disorders are considered a typical disease for women and underdiagnosed for men (41).

Age effects in mental distress differ for women and men. Results from an Australian study reveal a consistent decrease in mental distress for women, whereas for men, the decrease only starts in late adulthood (42). In the USA, women in all age groups report depression more often than men and this gender gap increases in adulthood (43). Regarding period effects, a Swedish study showed that the prevalence of self-reported anxiety increased between 1980/81 and 2004/5 for women and men in most age groups, except for men aged 64-71 and women aged 56-63 (44). Additionally, cohort effects were found; for men, anxiety increased from birth cohort 1942-40 onwards, while for women, this increase was already observed from birth cohort 1926-33 and stagnated with birth cohort 1974-81 (44). With regard to period trends, a British study shows increased mental distress especially for women between the years of 1991 and 2008 (45). Moreover, an Australian study revealed increased mental distress between 2001 and 2017 for both women and men (46). The prevalence of diagnosed depression increased in Germany between 2009 and 2017, especially in young men (47). Once again, none of these studies estimated age, period, and cohort effects simultaneously with regard to differences between men and women.

6.1.1 Objective of this study

In order to gain more insight into temporal trends of self-reported psychological distress in East and West Germany and between women and men, we will apply HAPC analyses. In these analyses, cohort and period are modelled as random effects and age, gender, region, and control variables are modelled as fixed effects. The present work aims to disentangle effects on mental distress caused by different political system. The following two main research questions are studied:

(I) Are age, period, or cohort associated with mental distress in the years from 2006 until 2021?
(II) What role do gender and German region play as main predictor variables within these associations?

6.2 Methods

6.2.1 Sample

Data of ten German representative studies with the same recruitment procedure conducted in the years 2006, 2010, 2014, 2017, 2018, 2019, 2020, 2021 were analyzed. Sample sizes ranged from 2503 participants in 2020 to 5036 participants in 2006 (Supplementary Table S-VI.1). Data was collected by an independent agency (USUMA, Berlin) in nation-wide surveys.

Samples were representative in terms of age, gender and education. Applied eligibility criteria were an age of at least 14 years and a sufficient understanding of the German language. Participants were chosen via a random-route procedure. Individuals in multi-person households were randomly selected using a Kish Selection Grid. The target person participated in a face-to-face interview conducted by a trained interviewer and additionally independently filled out several questionnaires. See Supplementary Table S-VI.1 for further information for each survey.

Before interviews started, all potential participants were informed of the aims of the respective survey that included aspects of general and mental health as well as political attitudes and beliefs, method of data collection, and handling of data including data privacy and anonymity in responses. They then provided informed consent. Minors gave informed assent and informed consent was given by their parents or legal guardians. The study and procedure, including the consent procedure, were approved by the institutional ethics review board of the University of Leipzig (s. ethic approval numbers in Supplementary Table S-VI.1).

For this study, we excluded participants who did not fully complete the mental distress questionnaire, e.g. participants with missing values on at least one of the items (*n*=290, 1.05%). Since these missings did not exceed 5%, they were deleted listwise (48). Furthermore, we excluded people with gender ‘divers’ (*n* = 5), since it was not possible to compute analyses on this very small group. Lastly, we selected participants of 16 years and older, yielding a final sample of 27033 individuals. The sample consisted of 14560 (53.9%) women and 12473 (46.1%) men with 5445 persons living in East Germany (20.1%) and 21588 in West Germany (79.9%). Women were overrepresented in both East and West Germany (52.3% versus 47.7% in East Germany; 54.2% versus 45.8% in West Germany). Respondents showed an age range of 16 to 99 years (*M* = 49.2; SD = 17.7). For a sample description per included study year, see Table VI-1.

Table VI.1. Description of complete sample (*N* = 27,033) stratified by gender and German region.

Survey year	*N*	Gender		Region		Age	Birth cohort					Partner		Net household income		
		men	women	West Germans	East Germans		<1946	1946-1959	1960-1969	1970-1980	>1980	Not living together	Living together	<1250	1250-2500	from 2500 onwards
Total	27033	12473 (46.1%)	14560 (53.9%)	21588 (79.9%)	5445 (20.1%)	49.20± 17.70	4491 (16.6%)	6188 (22.9%)	5388 (19.9%)	4580 (16.9%)	6386 (23.6%)	14217 (52.6%)	12761 (47.2%)	4802 (17.8%)	11770 (43.5%)	9646 (35.7%)
2006	4916	2266 (46.1%)	2650 (53.9%)	3927 (79.9%)	989 (20.1%)	48.90± 17.55	1513 (30.8%)	1163 (23.7%)	962 (19.6%)	778 (15.8%)	500 (10.2%)	2235 (45.5%)	2681 (54.5%)	1058 (21.5%)	2564 (52.2%)	1045 (21.3%)
2010	2458	1133 (46.1%)	1325 (53.9%)	1962 (79.8%)	496 (20.2%)	51.16± 18.09	690 (28.1%)	576 (23.4%)	439 (17.9%)	388 (15.8%)	365 (14.8%)	1184 (48.2%)	1274 (51.8%)	508 (20.7%)	1276 (51.9%)	602 (24.5%)
2013	2441	1139 (46.7%)	1302 (53.3%)	1946 (79.7%)	495 (20.3%)	50.08± 17.90	473 (19.4%)	610 (25.0%)	447 (18.3%)	398 (16.3%)	513 (21.0%)	1344 (55.1%)	1097 (44.9%)	506 (20.7%)	1118 (45.8%)	744 (30.5%)
2014	2459	1133 (46.1%)	1326 (53.9%)	1965 (79.8%)	494 (20.1%)	50.01± 17.36	403 (16.4%)	630 (25.6%)	478 (19.4%)	428 (17.4%)	520 (21.1%)	1304 (53.0%)	1155 (47.0%)	454 (18.5%)	1054 (42.9%)	888 (36.1%)
2016	2406	1089 (45.3%)	1317 (54.7%)	1915 (79.6%)	491 (20.4%)	49.47± 17.69	323 (13.4%)	556 (23.1%)	503 (20.9%)	403 (16.7%)	621 (25.8%)	1095 (45.5%)	1280 (53.2%)	444 (18.5 %)	1013 (42.1)	876 (36.4%)
2017	2483	1111 (44.7%)	1372 (55.3%)	1994 (80.3%)	489 (19.7%)	49.08± 17.59	284 (11.4%)	575 (23.2%)	518 (20.9%)	410 (16.5%)	696 (28.0%)	1414 (56.9%)	1069 (43.1%)	380 (15.3%)	1027 (41.4%)	1005 (40.5%)
2018	2477	1125 (45.4%)	1352 (54.6%)	1980 (79.9%)	497 (20.1%)	48.33± 17.38	226 (9.1%)	545 (22.0%)	522 (21.1%)	469 (18.9%)	715 28.9%)	1404 (56.7%)	1067 (43.1%)	414 (16.7%)	1020 (41.2%)	1043 (42.1%)
2019	2448	1143 (46.7%)	1305 (53.3%)	1959 (80.0%)	489 (20.0%)	48.97± 17.48	215 (8.8%)	556 (22.7%)	493 (20.1%)	454 (18.5%)	730 (29.8%)	1351 (55.2%)	1089 (44.5%)	328 (13.4%)	976 (39.9%)	1098 (44.9%)
2020	2442	1146 (46.9%)	1296 (53.1%)	1951 (79.9%)	491 (20.1%)	46.37± 17.51	144 (5.9%)	446 (18.3%)	525 (21.5%)	415 (17.0%)	912 (37.3%)	1459 (59.7%)	975 (39.9%)	331 (13.6%)	754 (30.9%)	1189 (48.7%)
2021	2503	1188 (47.5%)	1315 (52.5%)	1989 (79.5%)	514 (20.5%)	50.26± 18.03	220 (8.8%)	531 (21.2%)	501 (20.0%)	437 (17.5%)	814 (32.5%)	1427 (57.0%)	1074 (43.0%)	379 (15.1%)	968 (38.7%)	1156 (46.2%)

Note: For the year 2017, sample recruitment took place between November 2017 and January 2018. The vast majority was recruited in 2017 (80%). For the year 2021, sample recruitment took place between December 2020 and January 2021.The vast majority was recruited in 2021 (85%). Descriptive statistics were performed as absolute and relative proportions for categorical data and means and standard deviations (M±SD) for continuous variables.

6.2.2 Measures

The Patient Health Questionnaire-4 (PHQ-4) is an ultra-brief reliable and valid screener for depression and anxiety (49). An update of normative data from the German general population reports acceptable reliability for PHQ-4 based on McDonald's omega (ω = 0.85; 95% CI: 0.84 to 0.86) (50). Depression consist of two items of the screening instrument PHQ-9 (51), namely: "little interest or pleasure in doing things" and "feeling down, depressed, or hopeless". Anxiety includes the two screening items of the Generalized Anxiety Disorder-7 (GAD-7) questionnaire (52): "Feeling nervous, anxious or on edge" and "not being able to stop or control worrying". The frequency of occurrence in the past two weeks was rated from 0 = "not at all", 1 = "several days", 2 = "over half the days", and 3 = "nearly every day" for all items. The sum score of the four items was calculated as measure for mental distress (range 0-12). A higher score indicated more mental distress. For the analyses, a single factor solution was used as a measure of distress.

Definitions of generations differ between East and West Germany. For East Germany the grouping of Ahbe and Gries (53) is often applied, whereas for West Germany the division of Klimczuk (54) is more suitable. In order to create cohorts that represent both East and West German, these two definitions were combined and birth cohorts were divided into five groups. The first group existed of respondents born before 1946 and was labelled as pre- World War II / World War II generation. The second group included the birth years 1946 until 1959 and represented the post-war generation experiencing the formation of the two separate German states, the beginning of the cold war, and the economic growth in the west. Birth cohorts in the third group from 1960 to 1969 were labelled the cold war area generation. The fourth group included birth cohorts from 1970 until 1980 representing respondents being children at time of the existence of the former Democratic Republic, but experiencing the unified Germany as adults. The fifth and last group included respondents born after 1980. This group had little to no experience with the separate states, but did experience the transformation in the east. In conclusion, each of five cohort groups (born: <1946, 1946-1959, 1960-1969, 1970-1980, >1980) contained an approximately equal number of participants.

Age and survey year were included as continuous variables. Gender (1 = men, 2 = women) and region (1 = West Germany, 2 = East Germany) were included as main predictor variables. Living with partner (0 = no, 1 = yes) and categorical net household income (<1250, 1250-2500 and from 2500 onwards) were included as confounders.

6.2.3 Statistical analyses

All analyses were performed in R version 3.6.3. First, descriptive analyses were computed in order to provide information on differences in prevalence of mental distress between gender and region.

Afterwards, multi-group confirmatory factor analysis (MGCFA) was applied for age groups, birth cohorts and survey year to test measurement invariance (MI) of the PHQ-4. In these MGCFA's, three models were tested sequentially, with each level introducing an additional restriction to the model. The configural, metric, and scalar model test invariance for the factor structure, factor loadings, and intercept values between groups. MI testing included a series of model comparisons by applying adjusted χ^2-difference tests (55). A non-significant χ^2-difference ($p \geq .010$) indicates MI among the tested models. As the χ^2-statistic is sensitive to sample size, we further focused on the differences ΔCFI; values ≤ .01 indicate the invariance

of the models (56, 57). Besides ΔCFI, we examined the standardized root mean square (SRMR), which is an absolute measure of fit. A value less than .08 is considered as a good model fit (58). The root mean square error of approximation (RMSEA) is often used as goodness-of-model fit. However, the RMSEA often falsely indicates a poor fitting model when models with small degrees of freedom are tested (59), and was therefore not reported.

In order to test whether age, birth cohort and time period affect mental distress, HAPC analyses were conducted. APC analyses are impeded by the perfect multicollinearity between age, period, and birth cohort: any two of the three dimensions, age, period, and cohort, fix the third. Yang and Land (60) offer a solution to this problem using multilevel modelling on repeated cross-sectional sample survey data: age and age^2 are included as fixed effects, whereas cohort and period are included as random effects. The APC models were fitted using the *lmer* function within the *lme4* package in *R*. In our first model (M1), age, age^2, cohort, and period were tested. In the second model (M2), the main predictor variables gender and German region were added to the model. The third model (M3) additionally included control variables and in the last model (M4), an interaction term for gender with German region was implemented. For all models, marginal and conditional R^2 for explained variance was reported. To assess significance of period and cohort effects, the fit of models without each of these terms (i.e., models A + C and A + P) were compared with the fit of the complete model (A + P + C) (61, 62).

In order to allow for a simultaneous estimation of the APC effects, strong assumptions about the nature of the data have to be made that cannot be tested directly (5). We therefore performed several robustness tests. Firstly, estimates from the HAPC models with unequal intervals for age, year, and cohort may depend on the width chosen for these intervals (63). We thus tested our first model (M1) using different grouping variables of birth cohorts and compared them. Secondly, the HAPC method could be biased, i.e. results may be a consequence of data structure (64), especially when it comes to near linear trends in the random part of the model. In our case, this means linear trends in cohort and period effects would be underestimated or ignored. We thus compared our first model (M1) with other model variants. In order to test for linear effects of cohort or period, we subsequently moved one of them from the random part of the model into the fixed part of the model while the other one remained a random factor. We then compared the new models with M1. Furthermore, in order to examine both a linear and non-linear effect of cohort and period, we compared our main model (M1) with models including cohort or period in both the fixed and random part of the model respectively. We compared Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), logLikelihood, and Deviance to determine which model fit the data better.

6.3 **Results**

6.3.1 Descriptive analyses

The prevalence of mental distress fluctuates over time. The highest levels of mental distress were reported in 2020 (*M* = 2.18, SD = 2.31) and the lowest in 2016 (*M* = 1.42, SD = 2.18) and 2021 (*M* = 1.41, SD = 2.10), see Supplementary Table S-VI.2a. Moreover, prevalence rates of mental distress differ across age groups. The highest levels of mental distress were found for the oldest age group, namely 75 years and older (*M* = 2.24, SD = 2.47). Lowest levels of mental distress were reported by respondents in the age groups 25 to 34 (*M* = 1.58, SD = 2.12) and 35 to 44 (*M* = 1.55, SD = 2.14), see Supplementary Table S-VI.2b. Lastly, prevalence of mental

distress differs across cohorts with the oldest cohort, born before 1946, reporting the highest levels of mental distress (*M* = 1.99, SD = 2.33), see Supplementary Table S-VI.2c.

When comparing women and men as well as East and West Germany, results reveal that throughout the years, average levels of mental distress have always been higher for women compared to men. However, the pattern of levels of distress over time was similar for women and men. Differences in levels of mental distress between East and West Germany were found in 2006 and 2010 with higher levels of mental distress for East Germans (s. Supplementary Table S-VI.2a). Hereafter, alternating higher levels of distress were found in East and West Germany. In the last year, levels of mental distress were higher for West Germans. The course of mental distress for women and men in East and West Germany over time is displayed in Figure 1. With regard to age groups, women in all age groups reported higher mental distress compared to men, but the course was similar for women and men. The same applies to gender differences in mental distress across cohorts. Women reported more mental distress than men within each cohort, however the patterns of levels of distress were similar. No significant differences between East and West Germany across age groups and cohorts was found (s. Supplementary Tables S-VI.2b and S-VI.2c).

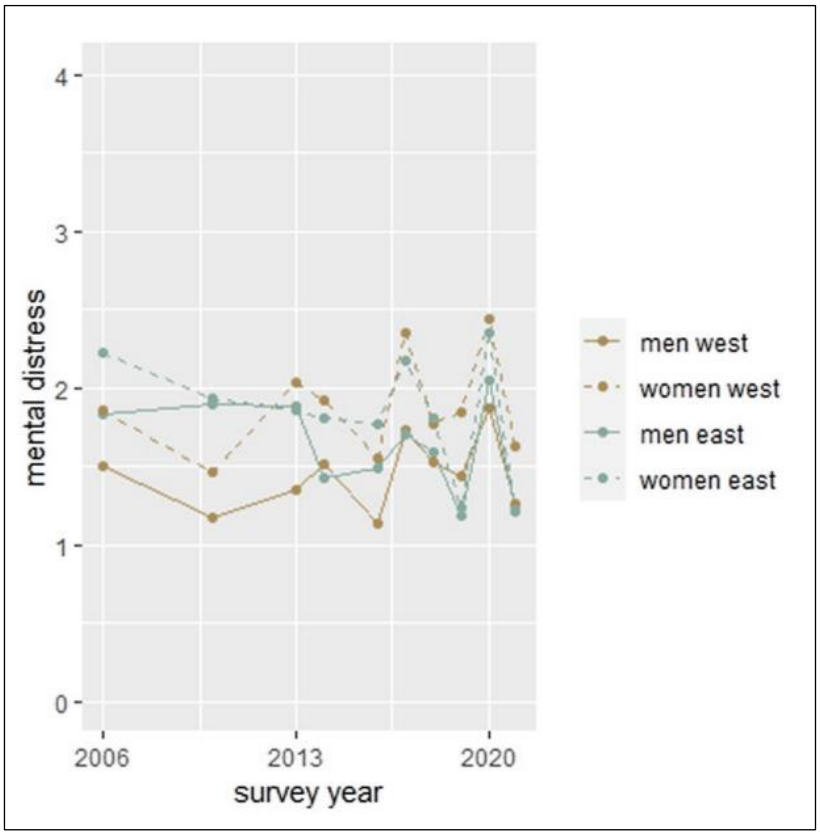


Figure VI.1. Mental distress over time by gender and German region.
Mean values of mental distress are reported.

6.3.2 MI PHQ-4 for age groups, birth cohorts and survey year

In order to ensure that mean values of PHQ-4 can indeed be compared between survey years, birth cohorts and age groups, we performed MGCFA to test MI. The results are shown in Supplementary Table S-VI.3. For the MGCFA including survey year, the configural model had

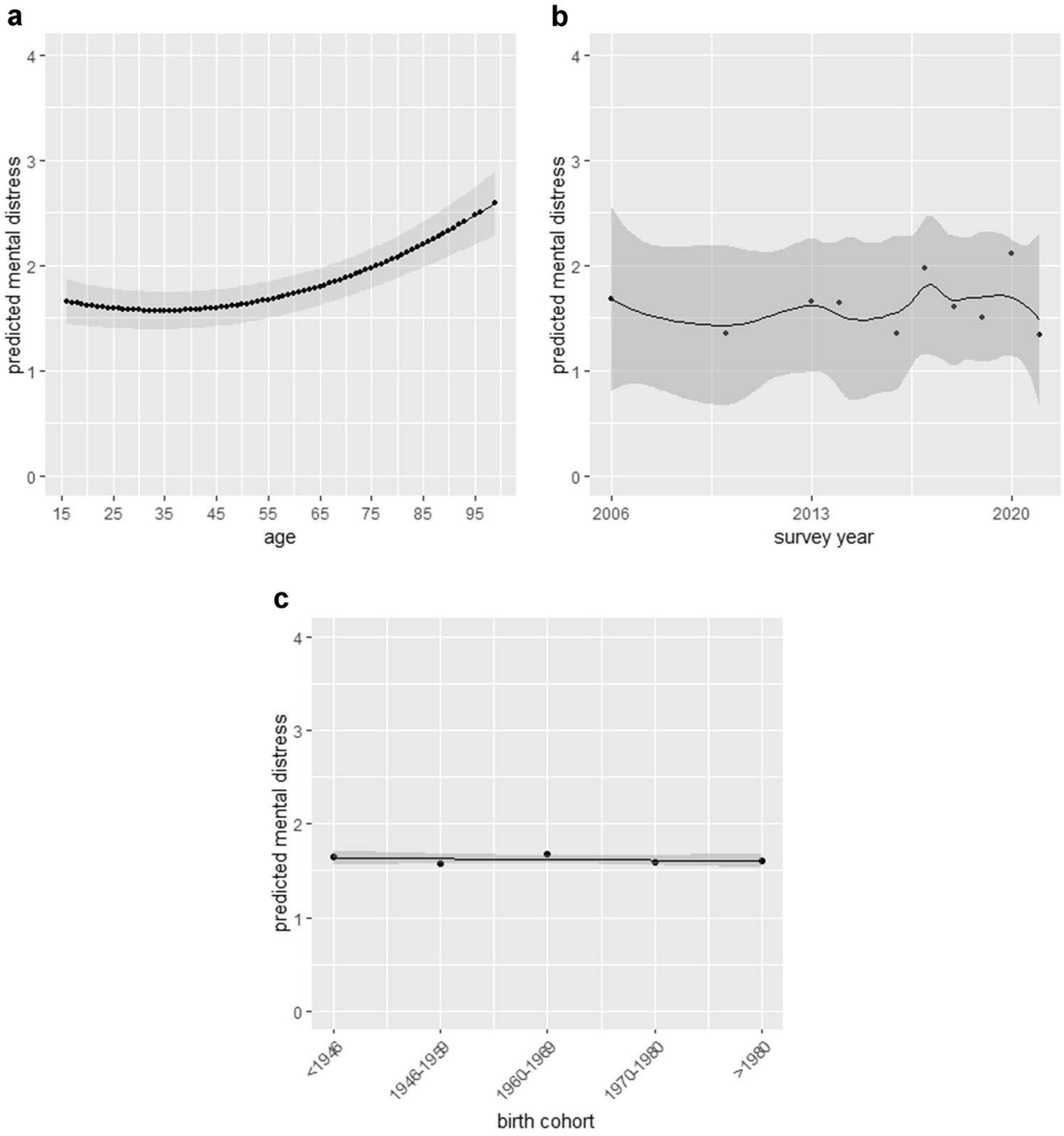
a good model fit (CFI = 0.98, SRMR = 0.02). The changes in CFI in the metric compared to the configural model and the scalar compared to the metric model were all smaller than 0.01. The value of SRMR remained far below 0.08. This indicated that factor structures, factor loadings and intercept values are similar across survey years and mean values and regressions coefficients for PHQ-4 can be compared across survey years. The MGCFAs including birth cohort and age groups also revealed measurement invariance for PHQ-4 across the respective groups.

6.3.3 APC analyses

Model 1 of the HAPC analyses included only age, age^2, period and cohort effects. Age had a significant negative effect on mental distress (-0.017; 95% CI: -0.03, -0.01), which suggested that after period and cohort effects were taken into consideration, the level of mental distress decreased by 1.7% with every one year increase in age. Figure VI-2a displays the combined effect of age and age^2.

Predicted mental distress also varied by period and cohort, when controlling for the remaining two. The random effects variance components from Model 1 indicated smaller differences in mental distress outcomes by cohort than by period. The period effects showed strong fluctuations, especially in the last years. Predicted mental distress slightly decreased between 2006 and 2010, followed by a rebound in 2013-2014, but declining again thereafter. In 2017 and 2020, peak values of predicted mental distress were found. For details, see Figure VI-2b. As to the cohort effect, predicted values of mental distress were highest in the oldest cohort, born before 1946. After that, mental distress decreases and remained constant over the cohorts, see Figure VI.2c. These results are also displayed in Table VI.2 (s. Model 1). The explained variance for this model was 1.9%.

In order to address possible biases of our results due to the widths of the cohort categories, we compared our results to results from alternative models in which cohort was divided in several other categories. These alternative models did not significantly change the data fit and did not change the significance of the age and period effect. Only the cohort effect disappeared in one of the alternative models, but remained significant in all other model variants. In order to test for linear effects of cohort and period, we compared our results to results from models in which cohort or period were modelled as solely fixed or both fixed and random effects. We observed a slightly better fit only for the model with a linear period effect and with cohort modelled as a random effect. However, additional tests did not indicate a significantly better fit to the data.



Figures VI.2a, VI.2b, and VI.2c. Predicted age, age^2, period, and cohort effects on mental distress without confounding variables. (**a**) Age and age^2 effect, (**b**) period effect, (**c**) cohort effect.

Period and cohort effects are based on random effects estimated from models, age effects are based on fixed-effects coefficients in models. The grey shade area represents the 90% confidence interval. In figures 2b and 2c, the points represent the predicted values per year and birth cohort respectively, the trend line represents the total effect over years and birth cohorts.

Table VI.2. Regression results of mental distress on gender, German region, and other control variables from hierarchical age-period-cohort models: Representative German Survey, 2006-2021.

Fixed effects	Model 1 Coef. (95% CI)	Model 2 Coef. (95% CI)	Model 3 Coef. (95% CI)	Model 4 Coef. (95% CI)
Intercept	1.698 (1.53; 1.87)***	1.480 (1.31; 1.65)***	2.268 (2.07; 2.47)***	1.617 (1.28; 1.95)***
Age	-0.017 (-0.03; -0.01)**	-0.016 (-0.03; -0.01)**	0.006 (-0.01; 0.02)	0.006 (-0.01; 0.02)
Age^2	0.248 (0.14; 0.35)***	0.234 (0.13; 0.34)***	0.002 (-0.11; 0.11)	-0.003 (-0.11; 0.11)
Living area (ref. = west)				
east		0.059 (-0.01; 0.12)	-0.035 (-0.10; 0.03)	0.280 (0.07; 0.49)**
Gender (ref. = men)				
women		0.381 (0.33; 0.43)***	0.303 (0.25; 0.36)***	0.552 (0.39; 0.72)***
Living with Partner (ref. = yes)				
no			0.149 (0.09; 0.21)***	0.151 (0.09; 0.21)***
Household income (ref. = less than €1250)				
1250-2500			-0.834 (-0.91: -0.76)***	-0.833 (-0.91: -0.76)***
from 2500 onwards			-1.151 (-1.24: -1.07)***	-1.149 (-1.23: -1.06)***
Gender*Living area (ref. = men*east Germany)				
women*west Germany				-0.207 (-0.34; -0.08)**
Random Effects	Variance component	Variance component	Variance component	Variance component
Period effect (year)	0.069***	0.069***	0.074***	0.075***
Cohort effect (birth cohort)	0.003*	0.002*	0.003*	0.004*
marginal R^2 / conditional R^2	0.005 / 0.019	0.012 / 0.027	0.049 / 0.065	0.050 / 0.066

Notes: 1) *p<.05, **p<.01, ***p<.001, two-tailed test; 2) marginal R^2 describes the proportion of variance explained by the fixed factors alone, conditional R^2 describes the proportion of variance explained by both the fixed and random effects; 3) significance of random period and cohort effects was tested by comparing the fit of models without these terms (i.e., models with A+C and A+P) with the fit of the complete model (A+P+C), p-values were obtained using the chi-squared distribution test; 4) continuous predictors were centered around the grand mean, reported estimates are standardized.

Models 2 through 4 investigated the effects of gender and German region on mental distress when controlling for age, age^2, period, and cohort (s. Table VI.2). Age and age^2 became insignificant when sociodemographic and socioeconomic control variables were included. The negative effect of age on mental distress thus disappeared. Furthermore, period and cohort differences slightly increased, indicating that gender, German region and other control variables did not explain the period and cohort effects.

In Model 2, significant differences for gender were found. Women reported 38.1% higher mental distress than men. However, no significant effect was found for German region; no differences in reported mental distress were found between individuals living in East and West Germany. These findings remained when including socioeconomic and sociodemographic control variables (living with partner and household income), as reported in Model 3. Respondents not living with a partner reported higher mental distress compared to respondents living with a partner. In addition, higher household income was associated with a decrease in mental distress. In the last model (Model 4), the included interaction term for gender and German region was found to be significant, indicating that women in West Germany reported significantly higher mental distress compared to women in East Germany. For men it is the other way around, men in East Germany report slightly higher levels of mental distress compared to men in West Germany. Women reported the highest values in both East and West Germany. This interaction is displayed in Figure VI.3. The explained variance in this last model was 6.6%.

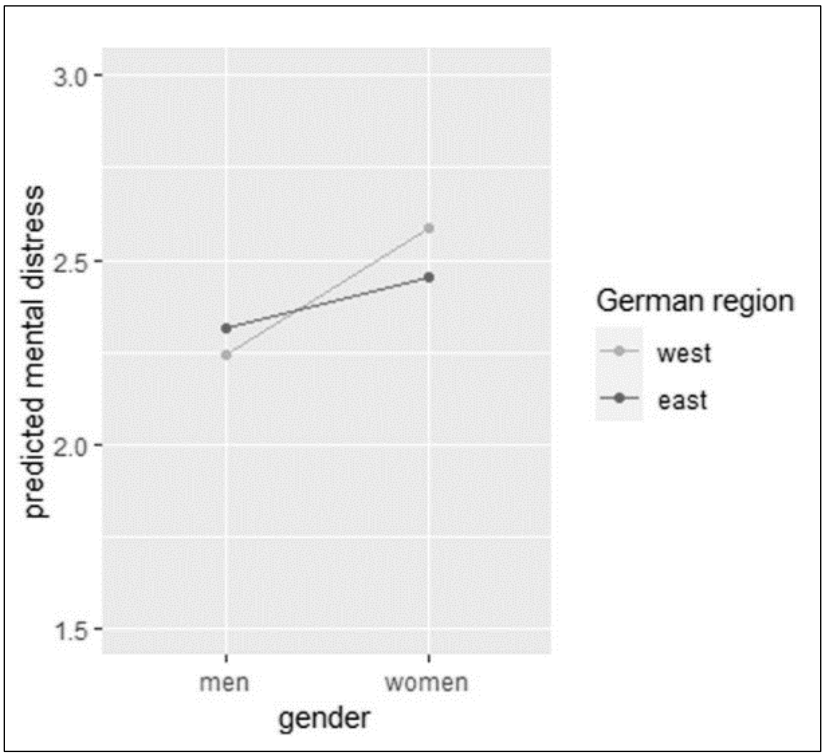


Figure VI.3. Interaction plot for gender and German region based on Model 4 of the HAPC analyses.

6.4 Discussion

Findings on the mental health of residents from former Eastern and Western Germany have been contradictory. Analyzing repeated cross-sectional data from representative German surveys spanning 15 years, this study used HAPC models to disentangle age, time period and birth cohort effects on mental distress while testing for gender and regional effects (i.e. former Eastern and Western German states).

Findings revealed significant period effects. Research has shown that global public health is closely linked to political, economic, and social determinants (65). In this study, peak values for mental distress were found in the years 2017 and 2020 for both women and men and East and West Germany. Important political events can affect mental health in general and serve as an explanation for these peaks.

For the increased level of mental distress in 2017, one explanation can be found in several political and demographic upheavals taking place in the previous years. In a referendum in 2016, the United Kingdom decided to leave European Union. Furthermore, in November 2016 Donald Trump was elected president of the United States of America. These two events exemplify a wave of right-wing anti-globalization politics, which has risen in much of the Western world (65). Shortly thereafter, in 2017, elections in three west European countries (France, the Netherlands, and Germany) took place and one of the main campaign issues was the alliance with the European Union. The discussions about this topic destabilized democratic cohesion, with antagonistic groups in society forming around this issue, further paving the way for right-wing parties such as the German *Alternative für Deutschland* (66). These political movements were partly set in motion through the so called “refugee crisis” in 2015 und 2016. In those years, large numbers of refugees from countries such as Syria, Iraq, Afghanistan, and Somalia applied for asylum in European countries which was shown to destabilize democracies in Europe (67) and which strongly contributed to the success of the radical right and right-wing populist parties (68). This could have caused an increase in mental distress, since countries with a liberal democratic political system report on average more positive results on population’s physical and mental health indicators (69). Furthermore, due to the perceived threat associated with the “refugee crisis” and democratic instability, quarrels and protests increased. A systematic review from 2020 revealed the compelling evidence that protests, also nonviolent, can be associated with adverse mental health outcomes, especially major depression (70).

The second peak in mental distress was found in 2020, which is likely to be caused by the COVID-19 pandemic and its first social lockdown restrictions. Literature has shown that this pandemic increased psychological health problems in Germany as in other countries. A systematic review and meta-analysis revealed that especially the prevalence of depression, anxiety, and distress increased during the pandemic (71). A meta-analysis examining longitudinal cohort studies showed a small but significant increase in mental health symptoms early in the pandemic (72). The survey included in this study took place at a similar time. However, effects for e.g. anxiety (but not depression) disappeared by mid-2020 and were comparable to pre-pandemic levels (72). Furthermore, a large British study examining anxiety and depression symptoms found a decrease in symptoms during the first 20 weeks following the initial lockdown (73) Findings of this study came from an online panel and therefore could be biased (74, 75). In German population surveys an increase in scores for depression and loneliness during the COVID-19 pandemic compared to scores in 2018 was found (76, 77),

even though certain parts of the population (e.g. women, young people, high-risk of poverty) were affected most strongly (77, 78).

In addition to a period effect, a significant cohort effect was found. Mental distress was highest in the oldest birth cohort, born before 1946. This cohort experienced World War II and the hardships of the post-war era. The elderly have experienced higher lifetime trauma exposure and PTSD prevalence than younger persons (79-81). Hence, this group may still suffer from mental health problems related to traumatic World War II experience 50 years after the end of the war (82). Traumatic events, especially war related, are highly connected to depressive symptoms (83, 84). Furthermore, people from the birth cohorts 1946-1959 and 1960-1969 showed lower mental distress compared to people from the oldest birth cohort. However, they reported higher mental distress compared to people from the youngest two cohorts. A possible explanation for this could be experiencing the negative consequences of the transformation of the system after Germany was re-united, i.e., unemployment (85), or other economic and social differences (19), this applies above all to the former East German population.

Age in itself did not affect mental distress when cohort- and period effects were considered. Age effects found in other studies could therefore be merely a result of cohort or period effects. Another explanation could be found in the measure for mental distress in this study. PHQ-4 measures mental distress based on core depressive and anxiety symptoms. Previous research revealed depression to be less prevalent among older adults (7). However, generalized anxiety disorder was shown to be higher among older age groups compared to younger age groups (86). Therefore, the insignificant effect of age in this study could be caused by the different directions of the effects within our outcome variable.

Women reported significant higher mental distress than men, which is in line with previous studies reporting more internalizing disorders (e.g., depression and anxiety) for women (87, 88). This was consistent over the survey years, also in times of crisis. Other studies also confirmed this, e.g., women reporting higher mental distress during the COVID-19 pandemic than men (89, 90). Unlike previous studies (27, 91), no significant difference between East- and West Germany in mental distress was found. Therefore, the period and cohort effect seem to play a role in the East- West differences. Interestingly, when combining gender and German region, a significant interaction effect was present, revealing women in West Germany to report more mental distress compared to women in East Germany, whereas it was the other way around for men.

6.4.1 Strength and Limitations

This study is the first in Germany to examine age, period, and cohort effects in mental distress for a time period of 15 years including gender and German region. By applying HAPC models, we identified and separated age, period, and cohort effects. Furthermore, it is the first study to combine HAPC models with the generally untested assumption of measurement invariance in age, period, and cohort studies.

Yet, several limitations need to be considered when interpreting these results. Although the HAPC model is currently often applied as an approach to examine age, period, and cohort effects simultaneously, the discussion regarding the appropriate way to analyze such effects remains vivid, as strong assumptions have to be made about the nature of the effects (5). Moreover, simulation studies revealed an underestimation of cohort effects when using the HAPC method (92). Robustness checks are one way of addressing these issues, but future

studies should consider other APC techniques in order to validate the results, e.g., the newly developed APC interaction model (93). Furthermore, the total time range covered in this study is still on the low end. Also, the number of years between the individual time points differ. In contrary to most APC studies, we used repeated cross-sectional sample survey data, which only simulates actual longitudinal data. Therefore, our findings do not provide insights in the possible causal effects for observed time trends. With regard to measurements, the classification of birth cohorts is partly theoretically and partly methodologically based, since a substantial amount of respondents is required in each cohort. We performed robustness tests using other cohort groups, which did not change our results. Lastly, we measured self-reported mental distress using the PHQ-4 scale. The PHQ-4 scale includes measured for symptoms of depression and anxiety, but results could differ from studies using solely depression or anxiety symptoms as outcome as well as from studies that are based on diagnosed psychological disorders.

6.4.2 Conclusion

The present work showed that the empirical analysis of factors associated with mental distress benefits from a multi-layered approach that differentiates risk and protective factors at different levels. Along these lines, the use of HAPC analyses yielded new insights: While results highlighted relevant period and cohort effects, no influence of age was found after sociodemographic and socioeconomic covariates were considered. Peak values for mental distress were found in the years 2017 and 2020. Further, mental distress was highest in the oldest birth cohort, born before 1946 and lowest in the youngest two birth cohorts. Lastly, results of an interaction term between gender and region revealed higher mental distress for men in East Germany compared to men in West Germany while women reported the highest values in both East and West Germany.

These findings indicate that major crises that affect society as a whole influence the mental health of a population. Thus, mental distress is not only shaped by fixed characteristics of a person, but also by structural societal factors. Therefore, effective prevention and intervention strategies must acknowledge structural differences. This could for example be done by investing into economic and political stability in order to reduce the hardships associated with major crises. Such an approach may be a beneficial extension of existing approaches for vulnerable groups within a society in addition to offering mental health support in the form of individual psychotherapy.

Supplementary Table S-VI.1. Response rate for all included surveys.

Survey year	Recruitment in/between	initially selected	response rate	final sample	ethics approval number
2006	July 2006	8106	62.1	5036	
2010	January 2010	4069	61.5	2520	
2013	June and July 2013	4360	57.5	2508	050/13-11032013
2014	February and March 2014	4607	54.8	2527	063-14-10032014
2016	January-March 2016	4830	52.3	2524	452-15-21122015
2017	November 2017-January 2018 *(80% in 2017)*	5160	49.1	2531	418/17-ek
2018	Mai-July 2018	5418	46.4	2516	132/18-ek
2019	Mai-July 2019	5393	46.9	2531	145/19-ek
2020	April-June 2020	5418	47.3	2503	043/20-ek
2021	December 2020-February 2021 *(85% in 2021)*	5902	40.0	2519	474/20-ek

Note: Random-Route-procedure to select participants (using Kish-Selection-Grid to select random household and target person). Addresses no one was home after multiple visits from interviewer, persons refusing to participate or persons unable to participate (illness, vacation and so on) or breaking off the interview lead to final sample.

Supplementary Table S-VI.2a. Mental distress over time for the overall sample and stratified by gender and region.

	Total	Gender			Region		
		men	women	*p*	west	east	*p*
2006	1.76±2.06	1.57±1.97	1.93±2.12	<.001	1.69±1.99	2.04±2.29	<.001
2010	1.45±2.15	1.32±2.12	1.56±2.17	<.01	1.33±2.05	1.91±2.46	<.001
2013	1.74±2.29	1.46±2.09	2.00±2.42	<.001	1.71±2.25	1.87±2.43	.200
2014	1.71±2.18	1.50±2.07	1.90±2.25	<.001	1.73±2.20	1.63±2.05	.333
2016	1.42±2.18	1.21±2.01	1.59±2.31	<.001	1.36±2.18	1.64±2.20	<.05
2017	2.05±2.42	1.73±2.19	2.31±2.57	<.001	2.08±2.40	1.95±2.51	.300
2018	1.67±2.21	1.54±2.19	1.77±2.22	<.05	1.66±2.22	1.70±2.19	.698
2019	1.57±2.13	1.38±2.02	1.73±2.20	<.001	1.66±2.17	1.21±1.92	<.001
2020	2.18±2.31	1.91±2.17	2.41±2.40	<.001	2.17±2.30	2.21±2.34	.721
2021	1.41±2.10	1.26±1.99	1.55±2.18	<.001	1.46±2.09	1.22±2.10	<.05

Note: Reported are the mean value with standard deviation (M±SD).

Supplementary Table S-VI.2b. Mental distress across age groups for the overall sample and stratified by gender and region.

	Total	Gender			Region		
		men	women	*p*	west	east	*p*
<25 years	1.62±2.16	1.32±1.94	1.90±2.32	<.001	1.62±2.18	1.59±2.08	.777
25-34 years	1.58±2.12	1.31±1.92	1.82±2.26	<.001	1.59±2.12	1.54±2.16	.565
35-44 years	1.55±2.14	1.36±1.98	1.71±2.25	<.001	1.54±2.11	1.64±2.27	.258
45-54 years	1.73±2.20	1.62±2.16	1.81±2.23	<.010	1.71±2.16	1.81±2.36	.240
55-64 years	1.78±2.28	1.66±2.25	1.88±2.29	<.010	1.75±2.25	1.87±2.36	.187
65-74 years	1.64±2.11	1.41±1.98	1.86±2.21	<.001	1.66±2.15	1.59±2.01	.357
>74 years	2.24±2.47	1.90±2.33	2.46±2.54	<.001	2.17±2.39	2.42±2.67	.055

Note: Reported are the mean value with standard deviation (M±SD).

Supplementary Table S-VI.2c. Mental distress across cohorts for the overall sample and stratified by gender and region.

	Total	Gender			Region		
		men	women	*p*	west	east	*p*
<1946	1.99±2.33	1.66±2.18	2.26±2.41	<.001	1.96±2.29	2.10±2.42	.078
1946-1959	1.70±2.18	1.59±2.12	1.81±2.22	<.001	1.68±2.17	1.78±2.21	.168
1960-1969	1.71±2.22	1.57±2.18	1.83±2.24	<.001	1.69±2.18	1.81±2.37	.140
1970-1980	1.54±2.10	1.37±1.95	1.69±2.21	<.001	1.54±2.08	1.54±2.20	.935
>1980	1.60±2.18	1.32±1.96	1.86±2.33	<.001	1.62±2.19	1.54±2.13	.241

Note: Reported are the mean value with standard deviation (M±SD).

Supplementary Table S-VI.3. Multi-group confirmatory factor analyses for survey year, cohort and age groups.

	χ^2	df	Δ χ 2	*p*	CFI	Δ CFI	SRMR
Survey year (period)							
Configural	982.742	20	---	<.001	0.981	---	0.020
Metric	1246.533	47	263.791	<.001	0.976	-0.005	0.036
Scalar	1592.580	74	346.047	<.001	0.970	-0.006	0.041
Generations (birth cohorts)							
Configural	911.343	10	---	<.001	0.982	---	0.020
Metric	956.291	22	44.948	<.001	0.981	-0.001	0.023
Scalar	992.348	34	36.057	<.001	0.981	0.000	0.024
Age groups							
Configural	886.670	14	---	<.001	0.982	---	0.019
Metric	923.605	32	36.935	<.001	0.982	0.000	0.022
Scalar	970.217	50	46.612	<.001	0.981	-0.001	0.023

Note: df = degrees of freedom; CFI = Comparative Fit Index; TLI =Tucker-Lewis Index, SRMR=Standardized Root Mean Square.

7 Discussion

The purpose of the current work was to broaden the perspective on women's and men's mental health by examining similarities and differences in risk and protective factors of mental health as well as investigating somatic and lifestyle effects in associations between mental and physical health. The main focus was on internalizing symptoms, comprising mental distress, depression, anxiety, and suicidal ideation. To this end, the work drew on high-quality, prospective community cohorts that provided data satisfying all aspects of the biopsychosocial model as well as large samples that enabled the investigation of comparatively rare outcomes as well as modeling of numerous risk/protective factors from several domains of life, including interaction terms and additional, stratified analyses.

The following section gives a brief overview of the main results. In section two, these findings are related back to the biopsychosocial model with a focus on differences and similarities between women and men. For the adequate evaluation of these findings, interpretations are informed by a gender perspective in the third section. The fourth section of this chapter summarizes the limitations of the conducted studies. Finally, future research ideas generated from the current findings are presented, with a focus on the relevance of differences between women and men and the inclusion of a gender perspective, are discussed in the fifth section and conclude with implications for clinical practice.

7.1 Summary of the main findings

In the first study, a systematic review of findings of three large, population-based German cohort studies on mental health for women and men was conducted. The goal was to examine sex-specific prevalence rates of mental disorders and to identify and integrate risk and protective factors for maintaining mental health across the lifespan. Published studies from KORA, SHIP, and GHS, representing the southern, north-eastern and mid-western parts of Germany, were identified through searches of the databases PubMed and Web of Science. A total of 52 articles were identified from the start of each cohort until summer 2019. Articles reporting prevalence rates of mental health [N = 22], explanatory factors for mental health [N = 25], or both [N = 5] were identified. Consistent across cohorts, women reported worse mental health than men. Higher prevalence rates of internalizing disorders were found for women (e.g., depression, depressed mood or depression symptoms, anxiety, suicidal ideation, and loneliness). This was independent of the different measurement scales applied in the studies. Risk and protective factors for mental health included social factors, lifestyle, physical health, BMI, diabetes, genetic and biological factors. In all areas, differences and similarities were found between women and men. The most evident were the sex-specific risk profiles for depression. For women, more internal risk factors were found (such as loneliness, social isolation, and low social support), but also specific biological factors (lower cholesterol levels and higher leptin levels) were important determinants for depression. For men, more external behavioral risk factors (e.g., physical inactivity and smoking), CVD (i.e., myocardial infarction and stroke), and markers for infection (higher interleukin-6 and hs-CRP levels; outcome depression combined with social isolation) were found as determinants for depression. Lastly, socioeconomic and family-related factors reflecting gender influenced mental health status (especially mental distress and suicidal ideation). This systematic review underlines the importance of focusing on sex-specific approaches in mental health research and the

development of prevention measures. Furthermore, it underscores the importance of considering the geographical region when examining mental health.

Literature has shown chronic diseases to influence (new onset of) depression, but depression, the most frequent and harmful mental disorder, has also been associated with specific somatic diseases as the leading cause of death. The influence of depression on chronic diseases is often still unclear. Therefore, the second study focused on the predictive effect of depressive symptoms on somatic diseases in women and men. In a representative German community sample of over 12,000 participants, baseline depressive symptoms (assessed using the PHQ-9) were tested as a predictor of new onset of CVD, chronic obstructive lung disease, diabetes, cancer, and migraine at five-year follow-up. To study disease incidence, subsamples for each chronic disease were created by excluding participants who already had the respective disease at baseline. Potential confounders were included in logistic regression models and sex-specific analyses were performed. Controlling for demographic characteristics and loneliness, in men and women, baseline depressive symptoms were predictive of CVD, chronic obstructive lung disease, diabetes, and migraine, but not of cancer. When we additionally adjusted for metabolic and lifestyle risk factors, there was an 8% increase in the risk of chronic obstructive lung disease and an 8% increase in the risk of migraine per point of depressive symptoms. The effect of depressive symptoms on CVD and diabetes was attenuated by metabolic and lifestyle factors and lost significance. Sex-sensitive analyses revealed significant effects of depressive symptoms on chronic obstructive lung disease and migraine for both women and men. Differences were found for CVD and diabetes; trends for the relevance of depressive symptoms for CVD in men (4%; p = .065), and for diabetes in women (5%; p = .077) were found. Lastly, sociodemographic factors (age and SES) influenced the new onset of chronic diseases. Lower SES predicted diabetes and migraine in the whole sample. However, sex-specific models revealed lower SES to be predictive of CVD and migraine in women and not predictive of any chronic disease in men. These findings underscore the need to implement screening for depression in the treatment of major somatic illnesses. At the same time, depressed patients should be screened for metabolic and lifestyle risk factors and somatic diseases and offered lifestyle interventions.

Since the systematic review also revealed differences in prevalence rates and risk factors for suicidal ideation between women and men, Study 3 focused on suicidal ideation. In this study, it was examined whether social support prevents suicidal ideation over time and whether this association differs for women and men. Data from the GHS (population-based representative community sample in mid-west Germany) and SHIP (population-based cohort study in northeast Germany) were used. Participants reporting low social support were compared to those receiving middle or high social support. Suicidal ideation was present in 7.4% (N = 982) of the pooled cohorts' 13,290 participants. More women (8.6%, N = 565) than men (6.2%, N = 417) reported suicidal ideation. Middle or high social support was associated with a lower probability of reporting suicidal ideation five years later after controlling for sociodemographic factors, living situation, and cohort (OR = 0.42, 95%-CI = 0.34–0.52). The effect was strongest among participants from the mid-west sample compared to the northeast sample. Men reported significantly lower suicidal ideation than women, but no statistically significant interaction of sex and social support was found (ratio of ORs = 1.00, 95%-CI = 0.73–1.35). Another important factor influencing suicidal ideation for both women and men was household income; it was negatively associated with suicidal ideation. For women, additional protective factors comprised employment and having children, which is why these can be considered gender-specific factors. When examining the two regions separately, middle or high social

support was found to be a protective factor against suicidal ideation five years later (after controlling for sociodemographic factors and living situation). However, only in the northeast sample, men were found to report less suicidal ideation than women did. In the sample for mid-west Germany, no difference between women and men was found. Overall, these findings pointed to a strong protective effect of social support for suicidal ideation.

Besides depression and suicidal ideation, anxiety impairs health and well-being and differs strongly in prevalence between women and men. The last study therefore focused on mental distress comprising depression and anxiety. Temporal trends in mental distress are complex and depend on numerous factors. Therefore, APC effects for mental distress over a 15-year time span were examined. In order to test whether these effects are sex- or region-dependent, both were tested as main predictors and an interaction term of sex with region was included in the model. Data on mental distress from ten repeated cross-sectional surveys of the general German population, covering the years from 2006 until 2021, was used. Mental distress was measured with the PHQ-4. Applying HAPC analyses, significant period and cohort effects were found, with peek values for mental distress in the years 2017 (M = 2.05, SD = 2.42) and 2020 (M = 2.18, SD = 2.31) and for the oldest birth cohort (born before 1946) (M = 1.99, SD = 2.33). Age was negatively associated with mental distress; mental distress decreased by 1.7% with every one-year increase in age, but became insignificant when sociodemographic and socioeconomic factors were considered alongside cohort- and period effects. Over the years, women reported consistently more mental distress than men; significant differences between women and men were found for all survey years. In the main analyses, an interaction effect for sex and region was found. Men in East Germany reported significantly higher mental distress compared to men in West Germany, while women reported the highest prevalence in both regions. Furthermore, mental distress was higher among respondents who reported not to be living together with a partner and respondents with a lower household income. Important political events as well as major crises can lead to an increase of mental distress in society. Furthermore, an association between birth cohort and mental distress could be linked to socialization effects of that certain time, causing trauma experiences or a specific coping style within this cohort group. Overall, the effects of age, period, and cohort did not influence differences in mental distress between women and men.

The findings of the three studies to are summarized in Figure VII.1.

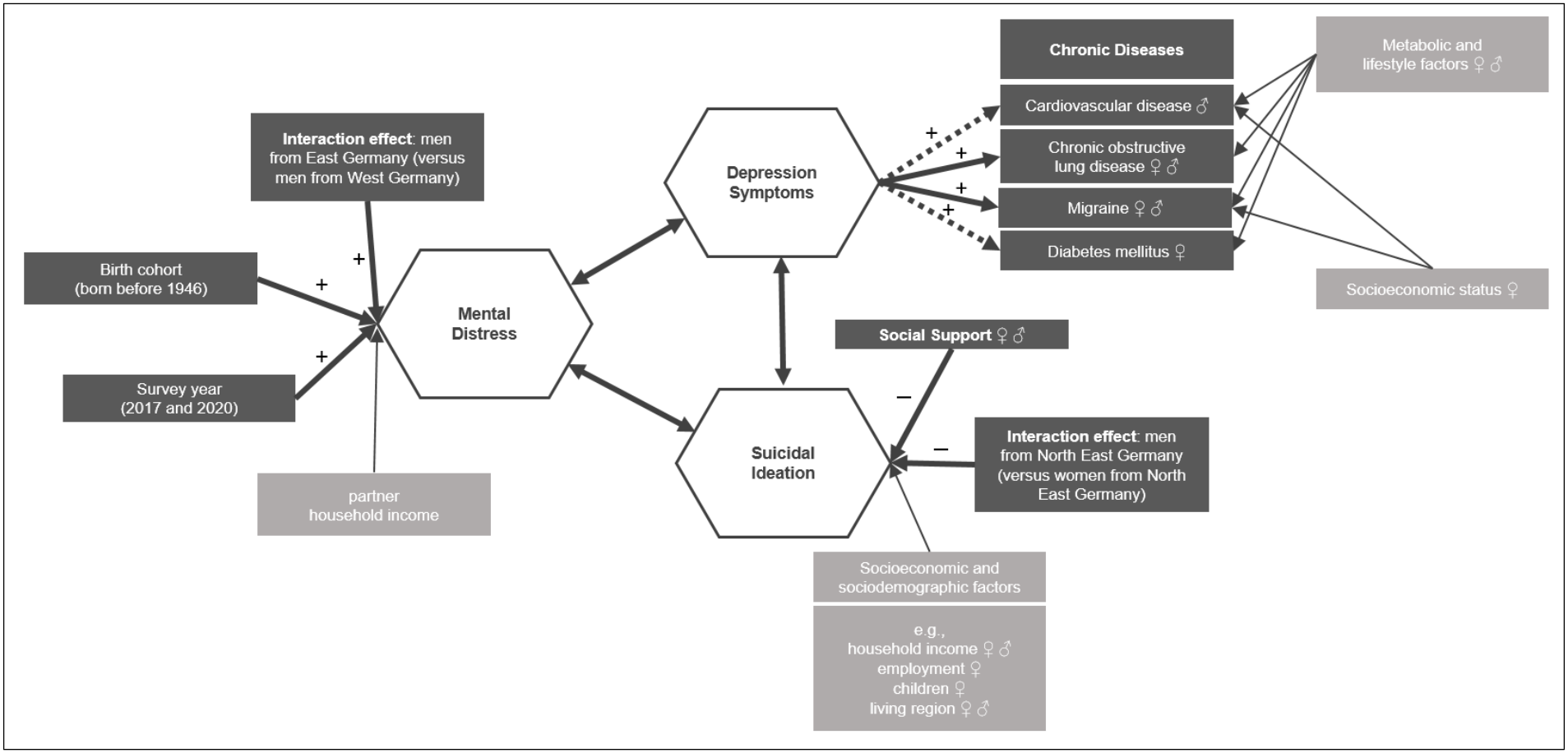


Figure VII. 1. Risk- and protective factors associated with depression symptoms, mental distress, and suicidal ideation for women and men.

7.2 Findings in the context of the Biopsychosocial Model

The multiple influences of biological, psychological, somatic and social and culture factors on mental health and associations between these factors are confirmed by the findings from the studies reported in this dissertation.

With regard to genetic and biological factors, we found glucose tolerance, the serotonin transporter gene, and cholesterol levels (for women), CRHR1 gene, insulin-like-growth factors and binding-proteins (for women and men), and interleukin-6, high-sensitivity C-reactive protein, the oxytocin receptor gene, and leptin levels (for men) to be relevant for mental health. Without further elaboration on all these factors and their associations with mental health, literature has shown that these genes do not necessarily cause mental health impairments or mental disorders, but merely pose a certain vulnerability for developing mental health symptoms or disorders. Hence, genetic and biological factors merely have an influence on mental health in combination with other factors. Although in the systematic review, an association between the oxytocin receptor and negative affect for men was found, other studies also revealed associations with depression and anxiety. However, these associations tend to depend on the quality of early environmental experiences (e.g., adverse childhood experiences) and ethnicity (1). Direct effects of the gene on psychopathological outcomes were not found in an earlier meta-analysis (2). Furthermore, high-sensitivity and C-reactive protein interleukin-6 were in the systematic review found to be associated with depression in men when they were also socially isolated. Interleukin-6 is known to play a key role in inflammation (3). Inflammation in turn is found to be strongly associated with physical (especially chronic inflammatory) diseases (3), which are known to be linked with social isolation and loneliness (4). Therefore, it is not surprising that inflammation is also strongly associated with mental disorders (5). The key question of "*What comes first?*" comes to mind and it is complicated to disentangle all these factors that play a role. Indicators of the metabolic syndrome / system such as cholesterol and leptin levels are also merely relevant for one's mental health in combination with other factors. Cholesterol levels were associated with depression only in women with high BMI / obesity. Leptin levels are only relevant for depression when a person also has sleep disturbances (women) or is socially isolated (men). Cholesterol and leptin levels in itself are not found to be associated with depressive disorder (6), but are associated with obesity (7, 8). BMI and obesity were in the systematic review found to be associated with mental health, especially somatic affective depressive symptoms (men), cognitive-affective depressive symptoms (women and men), and mental health-related quality of life (women), but also related to social indicators e.g., not living with a partner positively associated with BMI for men. A high BMI could indicate obesity which in turn is predictive of physical diseases, but also dependent on health behaviors such as physical inactivity and alcohol consumption, which in itself were found to be associated with impaired mental health. So, health behaviors also play an important direct and indirect role in mental health. These health behaviors are in turn influenced by socioeconomic factors. People with low SES are more likely to e.g. consume larger/risky amounts of alcohol or smoke. Low SES was found to be associated with higher levels of stress and inflammation and these are in turn associated with functional and structural adaptations in neural systems important for impulsive reward valuation and reflective self-control (9). Adverse health behaviors increase the likelihood of developing chronic diseases such as CVD and mental disorders, and they negatively impact their course. Especially for persons with a chronic disease, adverse health behaviors increase the risk of mental health symptoms. Smoking was associated with anxiety and depression in persons with CVD (10) and for people with multiple sclerosis alcohol consumption and smoking were associated with

depression and anxiety (11). The systematic review furthermore revealed direct associations between mental and physical health, such as associations between cancer and depression (in women), pulmonary disease and suicidal ideation (in women and men), and life-threatening diseases and PTSD (in women and men). It also revealed indirect associations between mental and physical health, for example, through somatic symptom reporting which was more often present for persons with metabolic syndrome, circulatory disease, bronchial diseases, cancer, and other diseases. Associations between mental and physical health are found for both women and men, it is however unclear which physical disease is associated with which mental disorder for women and for men, as well as whether a mental disorder is also in itself predictive of the new onset of physical illness.

In the second study reported in this dissertation, the focus lay on exactly those questions. As reported in Chapter 4, results strongly differed depending on what confounding factors were included in the analyses. When controlling for age, partnership, living situation, SES, and loneliness, in men and women, baseline depressive symptoms were predictive of CVD, chronic obstructive lung disease, diabetes, and migraine, but not of cancer. Interestingly, only age and SES were found to be directly associated with the new onset of chronic diseases, none of the other factors. When metabolic and lifestyle risk factors were included in the model as well, only an increased risk of depressive symptoms on new onset of chronic obstructive lung disease and migraine were found, with especially BMI and smoking being associated with chronic diseases (CVD and chronic obstructive lung disease), and for diabetes mellitus also dyslipidemia and blood glucose levels. Though these main effects remained similar when differentiating women and men, trends for the relevance of depressive symptoms for CVD in men and for diabetes in women were found. However, sex-specific models revealed lower SES to be predictive of CVD and migraine in women and not predictive of any chronic disease in men. Furthermore, the confounding factors differed between women and men. For CVD, for women age, SES, BMI, hypertension, and smoking were relevant predictors. For men, age, BMI, and smoking, but not SES and hypertension. The larger number of predictors of CVD for women might explain why no direct effect of depressive symptoms on increased risk for CVD was found in women. With regard to SES, these results are in contrast with a recent meta-analysis reporting an inversed association between SES and CVD for both women and men (12). Possibly, due to a higher prevalence of men smoking and the strong predictive effect of smoking on CVD. However, the effects of SES might be more profound in persons with multiple chronic diseases who were excluded from this study. With regard to chronic obstructive lung disease, for women BMI and smoking were relevant predictors, whereas for men none of the sociodemographic, psychological, metabolic, or lifestyle factors were found to be relevant. This might be explained by the role of bronchial hyper responsiveness, which is more common in women and may account for a faster decline of forced expiratory volume indicating smoking to be a more important risk factor of chronic obstructive lung disease for women (13). For diabetes mellitus, more risk factors were found for men than for women. For men age, BMI, dyslipidemia, blood glucose, hypertension, and physical activity were associated with diabetes mellitus, whereas for women, only BMI, blood glucose, and hypertension were associated with diabetes mellitus. The higher amount of factors associated with diabetes mellitus in men might explain the loss of the predictive effect of depressive symptoms on increased risk of diabetes mellitus in men. For migraine, besides depressive symptoms, age was predictive of an increased risk of migraine in women and men. For women, SES and hypertension were additionally relevant, whereas for men only blood glucose was a relevant predictor. This indicates a difference in pre-existing adverse factors influencing comorbid medical and mental conditions between women and men. For cancer no predictive effects of depressive symptoms

were found for either women or men and the only substantially associated factor was age. Possibly, predictive effects of depressive symptoms only exist for an increased risk of new onset of specific types of cancer. It could also imply, that cancer is predictive of (new onset of) depression, but not vice versa. This is for a large part confirmed by a large recent study examining the causality of genetically predicted depression and multiple types of cancer such as ovarian cancer, breast cancer, lung cancer, glioma, pancreatic cancer, lymphoma, colorectal cancer, thyroid cancer, bladder cancer, and kidney cancer revealing that revealed only a causal effect of depression on breast cancer (14).

Besides associations between mental and physical health, mental disorders are often comorbid. For example, depression and anxiety often co-occur and their symptoms are strongly correlated (15). In the review study, anxiety was found to be a risk factor for new onset of depression, but only in women. A recent meta-analysis including only longitudinal studies to examine the direction of effect between depression and anxiety revealed them to be bidirectional risk factors for one another (16). All types of anxiety disorders and symptoms predicted later depressive disorder and symptoms and vice versa. These effects did not significantly differ between women and men (16). Further, in our review, depression was associated with loneliness in both women and men, whereas loneliness was a risk factor for new onset of depression only for women. Related to loneliness, we found low social support to be associated with high mental distress in women and with new onset of depression in women and men, social isolation to be associated with depression in women, and living alone to be associated with suicidal ideation in men. However, there is a need to disentangle loneliness, social support and social isolation. Loneliness is defined as a subjectively negative perceived lack of social contact, belonging, or a sense of isolation (17). It refers to a discrepancy between social needs and actual social connections (18) either in quantity (referring to number of social contacts) and/or the quality (indicating the subjective experience of characteristics such as affection, intimacy, or conflict) (19). Loneliness and social isolation are thus distinct constructs, but also related. In contrast to loneliness, social isolation is an *objective* state of having a small network and infrequent interactions with others. Loneliness can exist even though a person is not socially isolated and vice versa (20). Many studies on loneliness have revealed associations with suicidal ideation and suicidal behavior. Loneliness is strongly associated with suicidal ideation, the prevalence of suicidal ideation rises with an increase in the level of loneliness (17). Social support can mitigate social isolation and loneliness. In our study (see Chapter 5) we examined the protective effect of social support on suicidal ideation. Since suicidal ideation is more present among women (21), whereas deaths by suicide are more prevalent among men (22), analyses included an interaction term between social support and birth sex. Furthermore, suicidal behavior is known to be strongly environment- and culture-dependent (e.g., more suicides in East- versus West Germany (23)). Therefore, the region of residence was included as a confounding variable and analyses were additionally stratified for region. As mentioned in Chapter 5, the results highlighted a protective effect of middle or high social support against suicidal ideation after controlling for confounders, which was significantly stronger for West Germany compared to East Germany. The interaction between sex and social support was not significant, in general women were more likely to report suicidal ideation than men. This finding is consistent with a study on loneliness and suicidal ideation in which associations between loneliness and suicidal ideation and suicidal behavior differed only minimally between women and men (17). Another important factor influencing suicidal ideation for both women and men was household income; it was negatively associated with suicidal ideation. This association was also confirmed in our systematic review and is also in line with previous review studies finding indebtedness (24)

and poverty (especially in low- and middle-income countries) (25) to be associated with suicidal ideation. Furthermore, poverty and deprivation were positively associated with suicide rates and higher socioeconomic areas related to smaller suicide rates, especially in studies on community levels (26). No gender differences were found in these associations. In our study, we did find gender differences with regard to employment. Employment was, for women, found to be a protective factor against suicidal ideation. This is in contrast to studies that found a protective effect of employment against suicidal behavior in both women and men (26) and to one of the studies in our review that found unemployment to be associated with suicidal ideation only in men. A review of life events and suicidality (as a general construct), suicidal ideation, suicide attempts (including intent, medical lethality, and number of attempts), and death by suicide reported the strongest association between life stressors and death by suicide, followed by suicide attempts and only to a limited amount by suicidal ideation (27). This might explain why we only found an effect of employment (regarding unemployment as a life event) for women. Furthermore, the group of persons committing suicide attempts strongly differs from the group with suicidal ideation (e.g., attempters only represent a relative minority of individuals with suicidal ideation (28)), which makes it difficult to compare findings of studies on suicide deaths and attempts with results regarding suicidal ideation. Lastly, as already mentioned, in Chapter 5, women might benefit more from their work (even though the double burden still mainly exists for women) than men. Overall, women report higher job satisfaction than men (29). Furthermore, for women having children was found to be a protective factor against suicidal ideation, indicating that the burden of children (perhaps even double the burden in combination with professional activity) does not weigh against the satisfaction and positive mental health outcomes children bring. Interestingly, in the region-stratified analyses, men were found to report less suicidal ideation than women in East Germany, whereas the number of suicides is highest in men in East Germany. This again underlines the difference in groups reporting suicidal ideation and actually engaging in suicidal behavior. Furthermore, the more deprived East Germany with incomes lying below the incomes achieved in West Germany might account for the reversed effect. However, due to the small number of men reporting suicidal ideation in East Germany in our study, it is difficult to further interpret these results. In this study, we did not include (aspects of) physical health, however, our review revealed links between social support and physical health e.g., low social support was associated with high physical distress for women and a predictive effect of lack of social support on increased somatic symptoms for women and men. Also, associations between genetic factors and health behavior were found in the review; social isolation was associated with the inflammation marker interleukin-6 in men and with physical inactivity in women and men. Such underlying health factors could mediate associations between social support and suicidal ideation and hence are overlooked in our study.

As already touched upon, sociodemographic and socioeconomic factors account for many differences in mental health between women and men and influence multiple factors associated with mental health. Sociodemographic and socioeconomic factors are embedded in a certain culture and society and certain regional characteristics therefore indirectly influence the mental health of persons living in this area. Such sociodemographic and socioeconomic differences of regions are often embedded in historical events and change over time. This is especially in Germany highly relevant, since socialization processes and living conditions in Germany strongly differed between the East and the West after being divided into two countries for almost three decades with opposite political systems (socialistic versus capitalistic system). These economic, social, and cultural differences that remained present after the German reunification. So, logically, being born in different times (and herewith belonging to different

birth cohorts) accounts for differences in mental health. Age effects by themselves are partly studied and a review study including studies with participants aged 65 and under revealed a general decrease in depression, anxiety, and mental distress over age groups (30). Furthermore, age of onset of mental disorders is mostly during childhood or adulthood (31). Studies focusing on older individuals found on the one hand anxiety disorders to be less common among older compared to younger adults, but at the same time, high comorbidities between depression and anxiety (32) and depression in the elderly was found to be a stronger risk factor of suicide than in younger adults (33). Another study confirmed suicidal ideation and suicidal behavior to be a serious problem among senior citizens and found social connectedness to be an extremely important protective factor against suicidal ideation and suicidal behavior in this age group (34). In our review, for older persons, higher education and higher income were associated with better mental health status, whereas having a large family (five children or more) was associated with lower mental health status. Studies examining age effects, however, have often pointed out that it is unclear whether certain effects are really age-dependent or whether they are cohort-dependent and thus subject to change over time, since each birth cohort is shaped by different (historical) events and living conditions. In the fourth article of this dissertation, the question of changes in mental distress over time and whether they can be explained by age, cohort, and/or period (time) effects was addressed with a focus on differences in trajectories for women and men and a comparison between East- and West Germany. Psychological distress, which is in this dissertation operationalized as a combination of depressive- and anxiety symptoms, peeked in 2017 and 2020 and in the oldest birth cohort (born before 1946). This cohort finding was also present in other studies that revealed a generation-specific differential course of disorders in East Germany after the reunification (35). Age effects were not found when including period and cohort as well as sociodemographic and socioeconomic factors. Over the years, women reported consistently and significantly more psychological distress than men. Furthermore, men in East Germany reported significantly higher mental distress compared to men in West Germany, while women had the highest prevalence of psychological distress in both regions. These findings are in line with a study revealing a stronger increase in lifetime depression symptoms in men compared to women in East Germany (36). Another study indicated a larger gender gap in satisfaction with mental and physical health in East Germany compared to West Germany (37), in particular with a decrease in satisfaction for men in East Germany. However, our finding that men in East Germany report lower suicidal ideation compared to men in West Germany is in contrast to these results, but can, as explained before, be caused by methodological limitations (small group of men with suicidal ideation in East Germany). In general, a health advantage for women is nowadays often found in East Germany. This is sometimes explained by women's better compensatory mechanisms to deal with psychosocial stress in East Germany. Interestingly, differences in mental distress between women and men were not explained by age, period, or cohort effects and therefore remain a general trend. Furthermore, mental distress was higher among respondents who reported not to be living together with a partner and respondents with a lower household income. This mirrors previous review reporting the importance of spouses for persons with depression (38) as well as other social relationships (especially with family or close friends) (39). Along the same lines, older studies already reported on the importance of *supportive* relationships for mental health; for both women and men supportive relationships are associated with low levels of psychological distress, while strained relationships were associated with high levels of mental distress (40). Also, the effects of low SES including low income on mental distress and disorders are well known (41) as well as the effects of economic problems of a region or country on the increased level of mental

distress and mental disorders of its inhabitants (42). Such effects are often explained by the general stress that arises from economic problems. Low SES or low income also affects one's health behavior; both are often associated with adverse health behaviors such as smoking, alcohol consumption, and reduced or lack of physical activity. These adverse health behaviors might be an additional explanatory pathway to an increase in mental distress and mental health symptoms or disorders. Adverse health behaviors increase physical health problems and diseases and physical health problems and diseases can in turn lead to mental disorders. In our review, we found, for example, men who were physically inactive to be less well socially integrated and more often affected by depression. Hence, once again, biological, psychological, somatic, and social factors can be seen to be interlocked in their associations with mental health, but the exact factors associated with one another, or pathways to health and illness, tend to differ for women and men.

7.3 Interpretation of the findings from a gender perspective

When examining risk factors for and consequences of mental health, differences between women and men seem to be more than sex differences. Society seems to play an important role in sex differences and strong interactions between birth sex, genes, environment, and sociocultural factors exist. This complex social system that structures the life experiences of all human beings is captured in the term *gender*.

7.3.1 Sex differences in health following *gendered* pathways

Sex refers to a person's biological status as male, female, or intersex. The indicators of biological sex are sex chromosomes, hormones, internal reproductive organs, and external genitalia (43). Gender refers to the culturally defined roles, responsibilities, attributes, and entitlements associated with being (or being seen as) a woman or man in a given setting, along with the power relations between and among women and men (43). The gendered system can be seen as a social system that defines women and men as different and this difference causes an unequal division of power, resources, and status between women and men.

As argued by Heise and colleagues (44) sex differences seem to be following *gendered* pathways. This process starts already at birth or moreover already prenatal. Gender roles (behavioral norms attributed to women and men in a given society) (45) shape the life prospects of an infant. This gender socialization starts with parents who adapt to certain behavior as soon as the sex of their baby is known and is further reinforced by e.g., family, teachers, peers, but also more broadly within the community (44). Social characteristics and behaviors are from birth (or prenatal) onwards differently distributed according to the binary birth sex. In this way, gender is an effect of sex on social-behavioral characteristics and described by Colineaux and colleagues (46) as gender pressure.

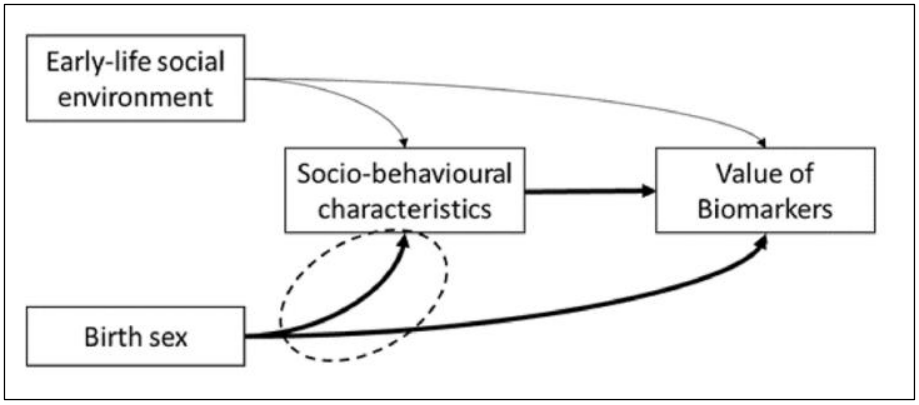


Figure VII.2. Model of *gender pressure*. Figure retrieved from publication *Explaining biological differences between women and men by gendered mechanisms* from Colineaux et al., 2023 (p. 4).

Of course, such specific gender norms and attribution to the gender system can also be contested. Mostly, however, boys are encouraged to adopt masculine gender roles or expressions (such as toughness and competitiveness), whereas women are encouraged to adapt feminine gender roles or expressions (such as being emotional, vulnerable, and in need of protection) shaping a person's gender identity (how people see themselves on the dimensions of femininity-masculinity) (45). Hirschfeld, a German physician, already argued at the beginning of the 19th century that people are located on a scale somewhere between the opposing poles of man and woman, neither of which is reached completely in one person, and that all people, to varying degrees, contain both feminine and masculine characteristics. These gender roles, norms, or expressions are also referred to as gender performance. In one of the models of Colineaux and colleagues (46) gender performance is described as the level at which the social characteristics and behaviors of an individual fit the stereotypes of masculinity (e.g., construction workers) and femininity (e.g., care activities such as childcare, nursing, taking care of older people) of a certain society. Gender is here described as an individually defined variable based on birth sex and early-life social environment.

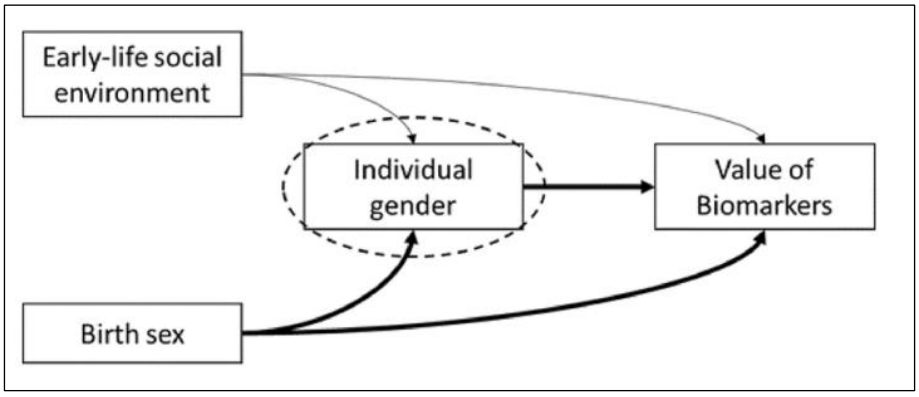


Figure VII.3. Model of *gender performance*. Figure retrieved from publication *Explaining biological differences between women and men by gendered mechanisms* from Colineaux et al., 2023 (p. 4).

These norms, roles, and performances are still strongly present in most boys and girls and women and men and influence gender relations (how individuals interact with or are treated by others based on ascribed or experienced gender) (45).

Lastly, institutions, structures and politics contribute to an institutionalized gender, which can explained by the distribution of power between women and men in institutions in society which shape social norms and justify different expectations and opportunities for women and men (45). Here, an interaction between birth sex and the social environment exists. Through socialization, processes of gender vary across societies or social groups. A given social environment does therefore not have the same effect on individuals solely depending on their sex attributed at birth (46). Associations between birth sex and certain behaviors differ between societies, e.g., in some societies, care work is strongly associated with female birth sex, whereas in others this association does not exist. Care activities are in this way an example of systematic gender mechanisms that are not directly caused or implied by actual birth sex.

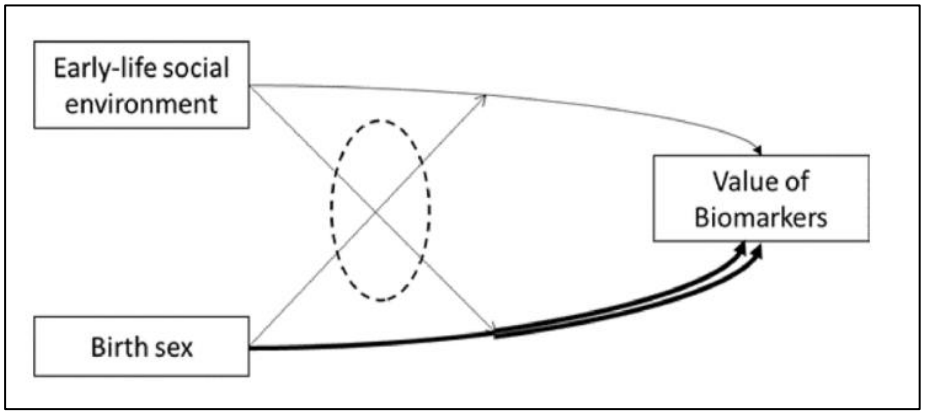


Figure VII.4. Model of *gender as the interaction between birth sex and early-life environment*. Figure retrieved from publication *Explaining biological differences between women and men by gendered mechanisms* from Colineaux et al., 2023 (p. 4).

Based on the neosexual revolution that revolved predominantly around gender difference, thrills, self-gratification, and prosthetic substitution (47) one would assume a reduced impact of the gender system over time. However, anti-gender movements have won in popularity in recent years. This international movement which opposes what it refers to as gender ideology, gender theory, or genderism (48) gained strength across Europe and attacked the rights of women and the LGBTIQ+ community (49). A current German population-based study revealed that sex differences regarding femininity increased from 2006 to 2018 (50). In 2018, femininity was higher in women and lower in men compared to 2006. Therefore, the social production of gender is still highly present and might even have increased over the last years, despite ideas, initiatives, and laws to move away from a stereotypical gender. This has direct and indirect consequences for an individual's health.

Sex-role theories suggest that the chronic stresses associated with traditional female roles lead to a higher prevalence of depression among women than men (51) (Mirowsky & Ross, 1989). In our study examining mental distress over time, no clear constant increase in mental distress between 2006 and 2020 was found for either women or men. There were clear peaks in mental distress for specific years. However, as discussed before, main crises such as the

refugee crisis and COVID-19 pandemic probably had a high impact on the levels of mental distress that overshadow other factors.

Differences between women and men that were caused by a combination of gender roles and expression and institutionalized gender are reflected in socioeconomic factors. Lower SES, an umbrella term for education, occupation, and income increased additionally to depressive symptoms the probability of new onset of CVD and migraine for women. This finding shows the possible far-reaching consequences of “the role” of women as caregivers and the discounting of the need for education as well as the gender payment gap. Furthermore, income itself (i.e., household income) predicted mental distress and suicidal ideation for women and men. Employment, however, predicted suicidal ideation only in women, which could be traced back to the double burden working moms have being employed and being the main caregiver for children or who are mainly responsible for unpaid domestic labor (52).

In East Germany, women have always received more support with regard to employment. The socialist regime propagated gender equality by promoting women’s participation in the labor force (53). State policies and organizational practices (such as daycare facilities) were designed to support women to combine their roles as mothers, housewives, and (paid) workers more easily (54, 55). As a consequence, female employment rates in East Germany (and also other post-socialist countries) were substantially higher compared to West Germany (and other Western countries) (56). The role of women in East Germany therefore also differed from the role of women in West Germany and paid labor and equal employment rights were more common and accepted in East Germany. Our findings that women in East Germany are less likely to suffer from mental distress and suicidal ideation than women in West Germany might be traced back to these differences in gender roles between East and West Germany which are less “traditional” in East Germany.

Biological or birth sex strongly interacts with gender, since human life courses, environments, experiences, and behaviors shape our biology (57). These exposures and experiences are distributed differently according to the sex assigned at birth and will therefore have different biological consequences in women and men.

7.3.2 Direct and indirect pathways to differential health outcomes in women and men

Biological or birth sex can in itself influence some specific health outcomes, e.g., diseases related to sex-linked hormones or sex-specific organs. The fact that women have two X chromosomes causes them to have a more aggressive immune system, which makes them (in combination with exposure and response to environmental triggers) more vulnerable to autoimmune diseases (58), whereas men with their one X chromosome are more vulnerable to chromosome abnormalities (59). This is also seen in the biomarkers that differ for women and men at birth. Cardiometabolic biomarkers (such as systolic blood pressure) are higher in men at birth, whereas inflammatory (such as C-reactive protein) and neuroendocrine (such as cortisol) biomarkers are higher in women at birth (46). In our study on depression leading to new onset of diseases, differences in the kind of diseases that occur could be due to these differences in vulnerabilities. As CVD are increasingly associated with genetic deviations (60) and type-I diabetes mellitus is known as an autoimmune disease (61), the findings in our study that depressive symptoms are associated with a trend of new onset of CVD in men and diabetes mellitus in women is supported by these differences in vulnerabilities. However, these patterns do not apply to chronic obstructive lung disease. Chronic obstructive lung disease is

also argued to have an autoimmune component (62, 63), but the new onset of chronic lung disease as a consequence of depression symptoms was, in our study, found for both women and men.

Many differences between women and men in health-related outcomes are additionally shaped by social determinants. An important social determinant is for example economic capital. Being born into a deprived rather than non-deprived family increased triglycerides, low-density lipoprotein, cholesterol, and C-reactive protein levels more strongly in women than in men (46). Further, the previously mentioned gender roles or expressions promote health differences in women and men while it causes them to be exposed to different risk factors. They cause, for example, gender segregation in employment which is related to differences in health risks (e.g., men are more involved in physically demanding jobs which confer higher risks of accidents and injuries, whereas women are more likely to work in care or service roles which have been linked to more musculoskeletal and mental health problems). For women, these burdens are underpinned by their higher domestic and care responsibilities (for example for children, but also for sick family members). Additionally, one's gender identity causes differences in health behaviors. Many studies have shown men to engage in more risky behaviors (e.g., aggression/violence, reckless driving, unhealthy nutrition, risk-taking sexual behaviors) which can in turn diminish their health, whereas women experience health disadvantages caused by body dissatisfaction. Also, one's gender identity causes differences in access to health care. Gender roles/expressions and relations cause men to visit a health general practitioner or health specialist less quickly when having complaints than women. Masculine gender roles might not only prevent men from seeking help when experiencing mental health problems, it might even prevent them from admitting having any psychological problems to themselves. This might also explain the higher rates of suicidal ideation in women versus the higher suicide attempts in men. Lastly, institutionalized gender causes a bias in the healthcare systems. Besides the differences in symptoms between women and men (which are currently still for a large part unknown due to the male focus in research) that pose a disadvantage for women, women's health-related complaints are more often attributed to psychosomatic than physical causes, due to the stereotype of women being more fragile and overemotional. Furthermore, women frequently receive inferior care compared to men (e.g., less aggressive treatment and less follow-up care). These differences are reinforced by an overrepresentation of men as leaders of medical institutions and men in certain specialist care (e.g., surgeons). Lastly, as already briefly mentioned, differences between women and men can be attributed to biased health research, which already starts with differences in funding of research, data collection, and inclusion of participants in studies. This is one of the main aspects of institutionalized gender. As the pharmaceutical research industry still has a focus on men causing insufficient tests of medication for women (by for example including fewer women than men in trials), a gender bias in research expands much further. Due to unspoken assumptions, specific associations are only tested for women or men. Furthermore, in most studies, women and men are not examined separately and no interaction terms as formal tests of differences are included, obscuring and overseeing any possible differences between women and men and further ignoring differences in pathways towards adverse health outcomes in women and men. This is, among other reasons, caused by an underrepresentation of women in leadership positions in research (e.g., invited for talks, secure grant funding).

Therefore, gender inequality and restrictive gender norms in any form have far-reaching implications for a person's health. They impact health through differential exposures, health-

related behaviors and access to care. Furthermore, gender-biased health research and health-care systems reinforce and reproduce gender inequalities with serious implications for health. This process was illustrated by Heise and colleagues (44).

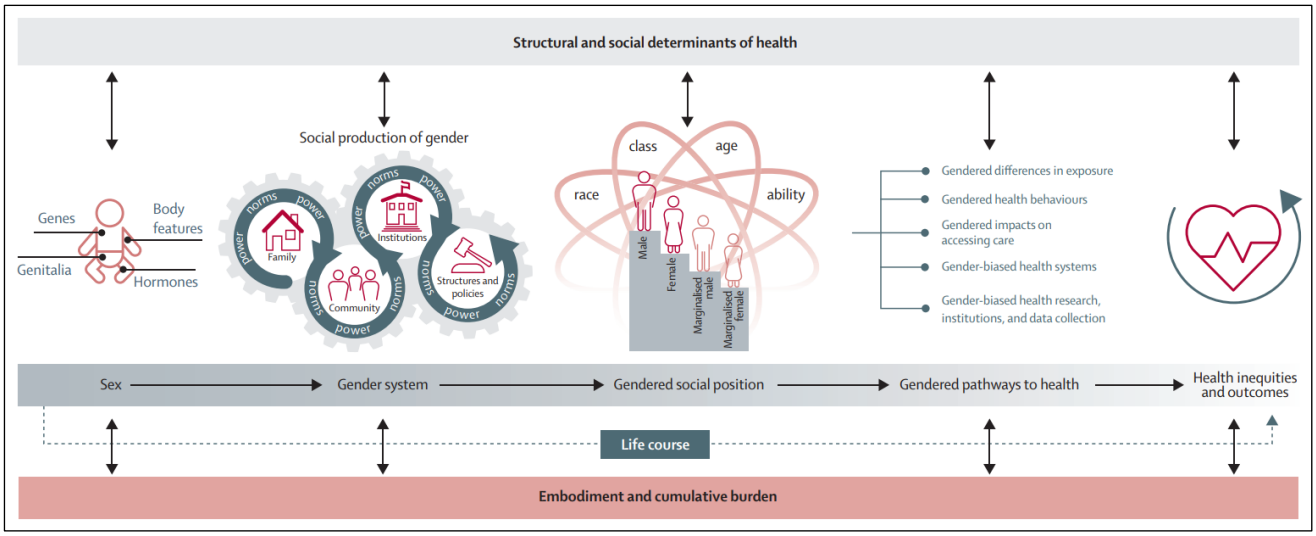


Figure VII.5. Model displaying structural and social determinants of health. Figure retrieved from publication *Gender inequality and restrictive gender norms: framing the challenges to health* from Heise et al., 2019 (p. 4).

7.3.3 Gender equality in health

Gender equality in health implies that women and men are on equal footing to fully exercise their rights and potential to be healthy, contribute to health development, and benefit from health-related outcomes. To achieve such equality, gender equity (a fair distribution of benefits, power, resources, and responsibilities between women and men) is necessary. This does not mean women and men should be treated in the exact same way when it comes to health. Sex-specific differences in health vulnerabilities should be kept in mind as well as differences of symptoms for women and men and different responses to treatment. Thus, recognizing that there are differences between women and men in terms of health needs, access to and control over resources, these differences need to be addressed in order to correct imbalances between women and men in order to diminish unfair, unnecessary, and preventable inequalities that exist between women and men.

In order to address the bias in health research, the differences in the manifestations of illnesses, diverging treatments offered to women and men, and the inferior care of women compared to men, the empowerment of women is still an important issue. Empowerment of women is a process by which women gain power and control over their own lives and acquire the ability to make strategic choices. It exists of women's sense of self-worth, their right to have and to determine choices, their right to have access to opportunities and resources, their right to have the power to control their own lives, and their ability to influence the direction of social change to create a more just social and economic order, nationally and internationally. Especially this last aspect can be achieved by the equalization of institutionalized gender. An equal division of women and men in powerful positions. Further, the government and

institutions can support empowerment processes by first raising awareness of the persisting differences between women and men and addressing these issues in policies.

With regard to mental health, an equalization of genders might contribute to the better mental health of both women and men alike. Stigma and shame still play an important role in mental health. The stigma of mental illness can be defined as the negative attitude (based on prejudice and misinformation) that is triggered by a marker of illness, e.g., off behaviors (64). Stigma can lead to discrimination, which in turn could decrease self-esteem and self-confidence and limit treatment effects or even trigger a relapse for those in remission.

Stigma and shame with regard to mental disorders are more present among men than women. This is due to the masculinity stereotype in which men are less supported to show their weaknesses, admit having problems, and supported to seek help (so-called toxic masculinity). Activities that can prevent the occurrence or reoccurrence of mental health problems such as talking about one's intimate thoughts with family and friends as social support, and practicing exercises that connect body and mind such as yoga or meditation are also more taken up by women than men. By normalizing mental illness and displaying mental disorders to be treatable diseases that are caused by actual chemical changes in the brain, people could feel more comfortable seeking the treatment they need. Further, the difference in manifestations of mental disorders between women and men (e.g., being sad and lethargic as depression symptoms in women versus angry and irritable depression symptoms in men, possibly combined with more physiological side effects such as heart racing) can favor mis- or underdiagnoses. Potentially, men do indeed seek help for depression, anxiety, and suicidal ideation, but their mental condition is not recognized as such and therefore, they do not receive the adequate and needed treatment. An increased awareness of gender differences in mental disorders and symptoms as well as training for therapists can thus advance gender equalization in mental health.

7.4 Limitations

Several limitations of the current work have to be considered when interpreting the results. A brief overview summarizes the main limitations that apply to all studies and several limitations specific to the individual studies. These have already been presented in the discussion section of each study.

First of all, one of the main limitations refers to the self-report of individuals' mental health in all studies. Most studies included in the systematic review as well as all three own studies measured mental health (i.e., depression, suicidal ideation, and mental distress) with questionnaires instead of operationalizing them as formal diagnoses. The instruments used have, however, been shown to be valid and reliable in psychometric studies and they had also been constructed oriented towards the diagnostic criteria for the respective mental disorders (65, 66). Furthermore, statistically strong correlations between clinician-rated instruments and self-report assessments of depression (67), suicidal ideation (68), and mental distress (69) were found. Due to the large size of the population-based community samples and the high-quality sampling procedure of the different cohort studies, it was possible to include and statistically control for relevant other factors (including potential confounders), and the results of these studies can be generalized to the general German adult population.

The main limitation of the first study examining the relation between depression and new onset of chronic diseases are possible similar causes underlying both depression and the diseases of interest. An important factor underlying depression and chronic diseases is for example chronic stress. The central nervous system, which involves the processing of sensory information, integration with previous experiences, neural and neuroendocrine adjustments, and planning of behavioral responses facilitates the functions of adaptive neural pathways that respond adequately to stressors (e.g., increases in heart rate and blood pressure) (70). At the same time, the hyper-responsiveness of the HPA axis following a stressful event could cause changes in brain structure and function, which in turn could influence new onset of depression (71). A preliminary stage of a chronic disease could activate a hyper-responsive reaction of the HPA axis, which in turn leads to depression symptoms. In this case, the body reacts to the (early stage) of a disease by causing depression symptoms. Therefore, not including undiagnosed chronic diseases could have biased the results, especially while for several of the included chronic diseases underdiagnosis is a known issue. For example, chronic lung disease was assessed as medicated asthma or medicated chronic bronchitis. Lung diseases (e.g., COPD, asthma, and chronic bronchitis) are often underdiagnosed (72-74). Since participants of the GHS did not undergo spirometry (a test to objectively test airflow and especially airflow obstruction), these non-diagnosed or preliminary stages of disease could not be included in the study. Underdiagnosis of chronic bronchitis was stronger marked in men than in women (73), therefore, especially for men results should be interpreted with caution. Also, ischemic heart disease (also called coronary heart disease or coronary artery disease) especially myocardial infarction, diabetes mellitus, and migraine are often underdiagnosed (75). Further, as mentioned before, a limitation in this study is the inclusion of confounder variables that might mediate between depressive symptoms and somatic diseases.

With regard to the second study examining the relation between social support and suicidal ideation, one should keep in mind that social support can be seen as an important resilience factor, but coping strategies of individuals as a response to a specific (stressful) event may play an equally important role (76). Adaptive and maladaptive emotion regulation strategies have a strong influence on mental health and health behaviors and these strategies were not considered in this study. Furthermore, tangible and emotional social support was measured by both instruments, but the nature of the social contacts which might influence its effects on one's mental health status was not considered. The protective effects of social ties on mental health are not uniform across groups in society, e.g., for women with low resources social connections might increase mental health problems, especially if these connections entail role strain associated with obligations to provide social support to others (77). Further, suicidal ideation was measured with one item at one time point. The potentially substantial temporal dynamics in suicidal ideation (78) could therefore not be considered. A recent study, however, revealed satisfying reliability between self-reported suicidal ideation and suicidal ideation measured with ecological momentary assessments (repeated sampling of subjects' current behaviors and experiences in real-time, in participants' natural environments). Also, in this study, alcohol consumption was not controlled for in the analyses, although it was found to be associated with suicidal ideation and is especially dangerous in combination with low social support (79). Lastly, suicidal ideation was also in this study only reported by a small number of individuals, especially by men in East Germany, therefore results for this group should be interpreted with caution. When comparing East and West Germany, the use of different measurements for social support should be kept in mind.

With regard to the last study examining mental distress over time for women and men and between East and West Germany, one important limitation is the still relatively short total time span, which forces rough grouping of cohorts, and the different number of years between the individual time points differ. Since the study included multiple repeated cross-sections, no causal effects for the observed time differences could be given. Furthermore, the methodology applied in this study is still often discussed, since it forces one to make strong assumptions on the nature of the age, period, and cohort effect and they might partly be underestimated. Lastly, since mental distress refers to depression and anxiety and these both are internalized disorders that are more often reported by women than men and only in recent years slightly increasingly reported by men, comparisons over time for men might be biased.

7.5 Future research and practical implications

The current study provides a groundwork for future research into the complex relationships of mental health vulnerabilities for women and men. It reveals the importance of focusing on women and men separately in research as well as including biological and social aspects.

Future research should address the health bias in women and men, since there are multiple factors contributing to the gender gap in mental health (80). First of all, it is important to examine whether women and men report similar or different symptoms for specific mental disorders. This perspective should be included in standardized assessments of mental disorders. Further, sampling women and men from different sociodemographic- and socioeconomic background is important in order to at least partly include gender aspects from the societal and cultural perspective and to address intersections of different risk- and protective factors as well. Third, in examining mental health, it is extremely important to look at the overall group and to examine women and men separately to see if effects for women and men differ or have different effect sizes or to test interaction terms with birth sex. This offers the possibility to determine 1) what risk- and protective factors are more important for whom, 2) what risk factors are more often present among either women or men (e.g., with regard to risk factors for STBs, sexual abuse more common among women, whereas military service is more common among men), and 3) what risk factors concern only women or men (e.g., for women hormonal changes during pregnancy or menopause).

8 Abstract

Health differences between women and men are rooted in anatomy, physiology, genetics, and hormones. These differences have for a long time been neglected in medical research due to a male default in medicine. For a long time, women were not included or underrepresented in clinical studies causing increased negative health outcomes in women compared to men. Genetic and hormonal differences as well as symptom differences between women and men cause differences in prevalence rates of diseases and outcomes between women and men, which are reinforced by differences in health behaviors. Overall, these factors cause a *gender gap* in mortality.

The purpose of the current work including four studies was to broaden the perspective on women's and men's mental health by examining similarities and differences in risk and protective factors of mental health as well as investigating somatic and lifestyle effects in associations between mental and physical health. The main focus lay on internalizing symptoms (mental health symptoms linked to negative emotionality), comprising mental distress, depression, anxiety, and suicidal ideation. To this end, the work drew on high-quality, prospective community cohorts that provided data satisfying all aspects of the biopsychosocial model as well as large samples that enabled the investigation of comparatively rare outcomes as well as modelling of numerous risk/protective factors from several domains of life, including interaction terms and additional, stratified analyses.

The biopsychosocial model, presuming there is always an interaction between the mind and the body, was used as a starting point for this dissertation. It includes the words *bio* referring to biological factors or physiological pathology (genetic determinants), *psycho* referring to psychological factors such as thoughts, emotions, and behaviors, and *social* referring to socio-economical, socio-environmental, and cultural factors. Biological factors causing differences in internalizing disorders between women and men can be found in the regulation of the HPA axis (which is in stressful situations more rapidly activated in women), differences in sex hormones, and differences in inflammation and immune responses. Psychological factors underlying differences in internalizing disorders between women and men are early stress experiences such as childhood adversity or differences in emotion regulation strategies. Social and environmental factors affecting women's and men's mental health differently can be seen in family-related aspects (relationships and relationship quality) and economic aspects (e.g., SES), which in combination can also have different outcomes (e.g., double burden for women combining child rearing and employment).

A systematic review of findings of three large, population-based German cohort studies (representing different parts of Germany) on mental health for women and men was conducted. Results revealed higher prevalence rates of internalizing disorders for women (e.g., depression, depressed mood or depression symptoms, anxiety, suicidal ideation, and loneliness). Risk and protective factors for mental health included social factors, lifestyle (e.g., BMI), somatic health (including physical diseases such as diabetes mellitus), and genetic and biological factors. The most evident were the sex-specific risk profiles for depression. For women, more internal risk factors were found (such as loneliness, social isolation, and low social support), but also specific biological factors (lower cholesterol levels and higher leptin levels) were important determinants for depression. For men, more external behavioral risk factors (e.g., physical inactivity and smoking), CVD (i.e., myocardial infarction and stroke), and markers for infection (higher interleukin-6 and hs-CRP levels) were found as determinants for depression. Lastly, socioeconomic and family-related factors influenced mental health status

(especially mental distress and suicidal ideation). These findings underline the importance of focusing on sex-specific approaches in mental health research and the development of prevention measures.

In the second study, the focus lay on the association between mental and physical health. This study examined the predictive effect of depression symptoms on the new onset of (chronic) physical diseases (CVD, chronic obstructive lung disease, diabetes, cancer, and migraine) in women and men. Controlling for demographic characteristics and loneliness, in men and women, baseline depressive symptoms were predictive of CVD, chronic obstructive lung disease, diabetes, and migraine, but not of cancer five years later. Additionally adjusting for metabolic and lifestyle risk factors, there was an 8% increase in the risk of chronic obstructive lung disease and an 8% increase in the risk of migraine per point of depressive symptoms. The effect of depressive symptoms on CVD and diabetes was attenuated by metabolic and lifestyle factors and lost significance. Sex-sensitive analyses revealed significant effects of depressive symptoms on chronic obstructive lung disease and migraine for both women and men. Differences were found for CVD and diabetes; trends for the relevance of depressive symptoms for CVD in men (4%; p = .065), and for diabetes in women (5%; p = .077) were found. These findings underscore the need to implement screening for depression in the treatment of major somatic illnesses. At the same time, depressed patients should be screened for metabolic and lifestyle risk factors and somatic diseases and offered lifestyle interventions.

In the third study, the focus lay on protective factors. It was examined whether social support prevents suicidal ideation over time, whether this association differs for women and men, and whether this association differs for East- and West Germany. More women (8.6%, N = 565) than men (6.2%, N = 417) reported suicidal ideation. In East Germany men were found to report less suicidal ideation than women, no difference between women and men in West Germany was found. Middle or high social support was associated with a lower probability of reporting suicidal ideation five years later after controlling for sociodemographic factors, living situation, and region. The effect was strongest among West compared to East Germans. Men reported significantly lower suicidal ideation than women, but no statistically significant interaction of sex and social support was found (ratio of ORs = 1.00, 95%-CI = 0.73–1.35). Overall, these findings pointed to a strong protective effect of social support for suicidal ideation.

Besides depression and suicidal ideation, anxiety impairs health and well-being and differs strongly in prevalence between women and men. The last study therefore focused on mental distress comprising depression and anxiety and examined temporal trends over a 15-year time span in East- and West Germany. Applying HAPC analyses, significant period and cohort effects were found, with peek values for mental distress in the years 2017 (M = 2.05, SD = 2.42) and 2020 (M = 2.18, SD = 2.31) and for the oldest birth cohort (born before 1946) (M = 1.99, SD = 2.33). Age was negatively associated with mental distress; mental distress decreased by 1.7% with every one-year increase in age, but became insignificant when sociodemographic and socioeconomic factors were considered alongside cohort- and period effects. Over the years, women reported consistently more mental distress than men; significant differences between women and men were found for all survey years. In the main analyses, an interaction effect for sex and region was found. Men in East Germany reported significantly higher mental distress compared to men in West Germany, while women reported the highest prevalence in both regions. Overall, the effects of age, period, and cohort did not influence differences in mental distress between women and men.

The multiple influences of biological, psychological, somatic, and social and culture factors on mental health and associations between these factors are confirmed by the findings from the studies reported in this dissertation. Biological and genetic factors do not necessarily cause mental health impairments or disorders, but pose a certain vulnerability for developing mental health symptoms or disorders. Strong associations between mental and physical health exist, but differ between women and men. Depression symptoms are predictive of new onset of physical illness, but metabolic and life style factors play an important role in these associations. With regard to resilience, social support poses a protective effect against suicidal ideation for both women and men. Social and regional factors play an important role in mental health within a society, mental distress increases with crises in society. Regardless of this, mental distress is more strongly present in women than men. Hence, biological, psychological, somatic, and social factors can be seen to be interlocked in their associations with mental health, but the exact factors associated with one another, or pathways to health and illness, tend to differ for women and men and seem to be more than solely sex differences.

The existing sex differences seem to be following gendered pathways, they are strongly influenced by gender roles and expression (behavioral norms attributed to women and men in a given society and acting according to these roles) as well as institutionalized gender (distribution of power between women and men in institutions in society which shape social norms and justify different expectations and opportunities for women and men). These gender aspects are reflected in social determinants and promote health differences in women and men by 1) exposing them to different health risks, 2) causing differences in health behaviors, 3) causing differences in access to health care, 4) an existing bias in healthcare systems. Gender equality would be beneficial for better mental health in both women and men. Future studies should therefore address the health bias in women and men by 1) examining whether women and men report similar of different symptoms for specific mental disorders, 2) sampling women and men from different sociodemographic- and socioeconomic backgrounds to at least partly include gender aspects from the societal and cultural perspective, 3) examining the overall group as well as women and men separately to see if effects for women and men differ or have different effect sizes or to test interaction terms with birth sex. This last point helps to determine 1) what risk- and protective factors are more important for whom, 2) what risk factors are more often present among either women or men, and 3) what risk factors concern only women or only men.

9 Deutschsprachige Zusammenfassung

Auf die Gesundheit bezogene Geschlechterunterschiede sind verwurzelt in Anatomie, Physiologie, Genetik und Hormonen. Diese Disparitäten wurden aufgrund eines in der Medizin vorherrschenden männliches Standards in der empirischen Forschung und Praxis jedoch lange Zeit vernachlässigt. Eine Implikation dieses Standards bestand auch darin, dass Frauen lange Zeit in (klinischen) Studien nicht einbezogen wurden oder unterrepräsentiert waren, was negative Gesundheitsfolgen bei Frauen mit bedingte. Genetische und hormonelle Verschiedenheiten sowie Abweichungen in der Symptomatik führen zu divergierenden Prävalenzraten und Auswirkungen von Krankheiten bei Frauen und Männern. Durch zusätzliche Unterschiede im Gesundheitsverhalten entsteht ein sogenannten *gender gap* in der Mortalität.

Das Ziel der vorliegenden Arbeit, die insgesamt vier Studien umfasst, bestand darin, die Perspektive auf die psychische Gesundheit von Frauen und Männer zu erweitern. Dazu wurden sowohl Übereinstimmungen als auch Unterschiede bezogen auf Risiko- und Schutzfaktoren der psychischen Gesundheit sowie somatische und lebensstilbedingte Effekte hinsichtlich der Zusammenhänge psychischer und körperlicher Gesundheit untersucht. Der Schwerpunkt dieser Arbeit lag auf internalisierenden Symptomen (psychische Beschwerden, die mit negativer Emotionalität verbunden sind) und umfasste psychischen Distress, Depression, Angst und Suizidgedanken. Die Daten stammten aus prospektiven Kohortenstudien mit hohen methodischen Standards, die Daten zu allen Aspekten des biopsychosozialen Models umfassten. Außerdem ermöglichten diese großen Stichproben die Untersuchungen relativ seltener Manifestationen von Krankheit bzw. Gesundheit (wie Suizidalität) sowie die Modellierung zahlreicher Risiko- und Schutzfaktoren aus verschiedenen Lebensbereichen einschließlich Interaktionstermen und zusätzlicher, stratifizierter Analysen.

Das Biopsychosoziale Modell, das grundsätzlich von einer Interaktion zwischen Psyche und Körper ausgeht, diente als Ausgangspunkt für diese Dissertation. Es umfasst das Wort *bio*, das sich auf biologische oder physiologische Einflüsse (genetische Determinanten) bezieht, das Wort *psycho*, das sich auf psychologische Faktoren wie Gedanken, Emotionen und Verhaltensweisen bezieht und das Wort *sozial*, das auf sozioökonomische, sozial-umweltbedingte und kulturelle Faktoren Bezug nimmt. Biologische Faktoren, die zu den Unterschieden bezogen auf die Manifestation internalisierender Störungen bei Frauen und Männern beitragen können, sind zum Beispiel die Regulation der Hypothalamus-Hypophysen-Nebennierenrinden-Achse (die in stressigen Situationen bei Frauen schneller aktiviert wird), Unterschiede bezüglich Geschlechtshormonen und der Entzündungs- sowie Immunreaktionen. Möglicherweise relevante psychologische Faktoren umfassen das Erleben stressvoller Ereignisse in der Kindheit, inklusive Traumata, sowie Unterschiede in der Emotionsregulation. Soziale und umweltbezogene Faktoren, die sich unterschiedlich auf die psychische Gesundheit von Frauen und Männern auswirken können, sind familienbezogene (z.B. Beziehungen und deren Qualität) sowie ökonomische Aspekte (z.B. sozioökonomischer Status). Deren Effekte können auch durch ihre Kombination modifiziert werden (z.B. die doppelte Belastung für Frauen, die aus der Gleichzeitigkeit von Kindererziehung und Berufstätigkeit entsteht).

In einer systematischen Übersichtsarbeit, die die Ergebnisse aus drei deutschen bevölkerungsrepräsentativen Stichproben zusammenfasste (die verschiedene Regionen Deutschlands repräsentieren) wurde die psychische Gesundheit von Frauen und Männern untersucht. Die Ergebnisse zeigten höhere Prävalenzraten internalisierender Störungen bzw.

Beschwerden (z.B. Depression, Angst, Suizidgedanken und Einsamkeit) bei Frauen. Risiko- und Schutzfaktoren für die psychische Gesundheit umfassten soziale Faktoren, Lebensstilfaktoren (z.B. Body-Mass-Index), somatische Gesundheit (einschließlich körperlicher Erkrankungen wie Diabetes Mellitus) und genetische und biologische Faktoren. Am deutlichsten divergierten die geschlechtsspezifischen Risikoprofile für Depression. Bei Frauen wurden mehr in der Person liegende Risikofaktoren gefunden (wie Einsamkeit, soziale Isolation und geringe soziale Unterstützung), aber auch spezifische biologische Faktoren (wie niedrige Cholesterin- und höhere Leptinspiegel) waren wichtige Determinanten einer Depression. Bei Männern wurden als Risikofaktoren vor allem verhaltensbezogene, externalisierende Faktoren (z.B. Rauchverhalten, Bewegungsmangel) sowie Herz-Kreislauf-Erkrankungen (z.B. Herzinfarkt und Schlaganfall) und Infektionsmarker (höhere Interleukin-6 und hs-CRP-Spiegel) bestätigt. Schließlich beeinflussten sozioökonomische und familienbezogene Faktoren die psychische Gesundheit (insbesondere psychischer Distress und Suizidgedanken). Diese Ergebnisse unterstreichen die Wichtigkeit geschlechtsspezifischer Ansätze in der psychischen Gesundheitsforschung sowie bei der Entwicklung von Präventionsmaßnahmen.

In der zweiten Studie lag der Fokus auf der Untersuchung des Zusammenhangs psychischer und körperlicher Gesundheit. Diese Studie fokussierte den prädiktiven Wert von Depressionssymptomen bezogen auf das Neu-Auftreten (chronischer) körperlicher Erkrankungen (Herz-Kreislauf-Erkrankungen, chronische obstruktive Lungenerkrankung, Diabetes Mellitus, Krebs und Migräne) bei Frauen und Männern. Bei statistischer Kontrolle soziodemografischer und psychologischer Merkmale prädizierten depressive Symptome zum Zeitpunkt der Baseline-Untersuchung sowohl bei Frauen als auch bei Männern das Auftreten kardiovaskulärer Erkrankungen, chronisch obstruktive Lungenerkrankung, Diabetes Mellitus und Migräne fünf Jahre später. Nach weiterer Adjustierung für metabolischen Faktoren und Gesundheitsverhalten zeigte sich eine Zunahme des Risikos des Auftretens chronischer obstruktive Lungenerkrankung und Migräne um 8% pro Punkt der depressiven Symptome. Der zuvor beobachtete Effekt auf kardiovaskuläre Erkrankungen und Diabetes konnte durch metabolische Faktoren und Gesundheitsverhalten statistisch erklärt werden. In den geschlechtsspezifischen Analysen zeigten sich dennoch Trends für einen Einfluss depressiver Symptome auf das Auftreten kardiovaskulärer Erkrankungen bei Männern (4%, $p = .065$) und Diabetes Mellitus bei Frauen (5%; $p = .077$). Diese Befunde unterstreichen die Relevanz des Screenings und der Behandlung depressiver Symptome im Kontext chronischer körperlicher Erkrankungen. Gleichzeitig sollten bei Patient*innen mit Depressionen metabolische und gesundheitsverhaltensbezogene Risikofaktoren (sowie manifeste körperliche Erkrankungen) abgeklärt werden. Ein wichtiges Element können hier Interventionen zur Förderung eines gesunden Lebensstils (Rauchstopp, reduzierter Alkoholkonsum, Ernährungsberatung) darstellen.

In der dritten Studie lag der Fokus auf Schutzfaktoren. Es wurde untersucht, ob soziale Unterstützung vor Suizidgedanken schützt, ob dieser Zusammenhang durch das Geschlecht modifiziert wird und ob der Zusammenhang sich in Ost- und Westdeutschland unterscheidet. Mehr Frauen (8.6%, $N = 565$) als Männer (6.2%, $N = 417$) berichteten Suizidgedanken. In Ostdeutschland berichteten Männer weniger Suizidgedanken als Frauen, in Westdeutschland wurden keine Unterschiede gefunden. Mittlere oder hohe soziale Unterstützung war mit einer niedrigeren Wahrscheinlichkeit für Suizidgedanken zum Follow-up-Zeitpunkt fünf Jahre später assoziiert (bei statistischer Kontrolle für soziodemografische Merkmale, Wohnsituation und Region) (OR = 0.42, 95%-CI = 0.34–0.52). Dieser Effekt war in Westdeutschland stärker als

in Ostdeutschland. Männliches Geschlecht hing negativ mit dem Bericht von Suizidgedanken zusammen; es zeigte sich jedoch keine statistisch signifikante Interaktion des Geschlechts und des Niveaus sozialer Unterstützung (Ratio ORs = 1.00, 95%-CI = 0.73–1.35). Insgesamt wiesen diese Ergebnisse auf eine starke schützende Wirkung sozialer Unterstützung gegenüber Suizidgedanken hin.

Psychischer Distress, definiert als ein Zustand emotionalen Leidens, charakterisiert durch Symptome der Depression und Angst, ist eine wichtige, verbreitete Einschränkung der psychischen Gesundheit und unterschiedet sich in der Prävalenz zwischen Frauen und Männern. In der letzten Studie wurden bezogen auf psychischen Distress zeitliche Trends über einen Zeitraum von 15 Jahren für Frauen und Männer in Ost- und Westdeutschland untersucht. Unter Anwendung hierarchischer Age-Period-Cohort-Analysen wurden signifikante Perioden- und Kohorteneffekte gefunden, wobei die stärkste Ausprägung psychischen Distress' in den Jahren 2017 (*M* = 2.05; SD = 2.42) und 2020 (*M* = 2.18; SD = 2.31) sowie in der älteste Geburtskohorte (geboren vor 1946) (*M* = 1.99, SD = 2.33) festgestellt wurde. Das Alter war negativ mit psychischer Belastung assoziiert, dieser Effekt verlor jedoch statistische Signifikanz nach der Berücksichtigung von Perioden- und Kohorteneffekten sowie soziodemografischer und sozioökonomischer Faktoren. Frauen berichteten über die Jahre konstant einen signifikant mehr psychischen Distress als Männer. Außerdem wurde ein Interaktionseffekt des Geschlechts und der Region gefunden: Männer in Ostdeutschland berichteten signifikant mehr psychischen Distress im Vergleich zu Männern in Westdeutschland, während Frauen in beiden Regionen die höchste Prävalenz aufwiesen. Insgesamt hatten Alters-, Perioden- und Kohorteneffekte keine Implikationen für die Unterschiede bezogen auf psychischen Distress zwischen Frauen und Männern.

Die vielfältigen Einflüsse biologischer, psychologischer, somatischer, sozialer und kultureller Faktoren auf die psychische Gesundheit und ihr Zusammenwirken werden durch die Ergebnisse der in dieser Dissertation vorgestellten Studien differenziert bestätigt. Biologische und genetische Faktoren führen nicht unbedingt zu Beeinträchtigungen der psychischen Gesundheit, konstituieren jedoch eine gewisse Vulnerabilität für die Entwicklung von psychischen Belastungssymptomen oder -störungen dar. Es bestehen starke Zusammenhänge zwischen psychischer und körperlicher Gesundheit, die jedoch zwischen Frauen und Männern unterschiedlich sind. Depressionssymptome prädizieren das Neu-Auftreten körperlicher Erkrankungen, aber metabolische und Lebensstilfaktoren spielen in diesem Zusammenhang eine wichtige Rolle. Im Sinne der Resilienz stellt soziale Unterstützung sowohl für Frauen als auch für Männer einen Schutzfaktor gegenüber Suizidgedanken dar. Soziale und regionale Faktoren spielen in der psychischen Gesundheit auf Gesellschaftsebene eine wichtige Rolle und so nimmt auch psychischer Distress bei Krisen zu. Psychischer Distress wurde konsistent häufiger von Frauen als von Männern berichtet. Biologische, psychologische, somatische und soziale Faktoren sind eng miteinander verwoben, auch hinsichtlich ihres Zusammenhangs mit psychischer Gesundheit. Die spezifischen Mechanismen ihres Zusammenspiels und dessen Folgen für Entwicklung und Verlauf von Erkrankungen unterscheiden sich zwischen Frauen und Männer und gehen über die rein biologischen Geschlechterunterschieden hinaus.

Die existierenden Unterschiede zwischen Frauen und Männern werden vermutlich zusätzlich durch das soziale Geschlecht (*Gender*) gestaltet. Geschlechterrollen und der Ausdruck dieser Rollen (Verhaltensnormen, die Frauen und Männern in einer gegebenen Gesellschaft zugeschrieben werden, und das Handeln entsprechend dieser Rollen) sowie institutionalisiertem Gender (Machtverteilung zwischen Frauen und Männern in Institutionen

der Gesellschaft, die soziale Normen prägen und unterschiedliche Erwartungen und Chancen für Frauen und Männer begründen) spielen dabei eine Rolle. Diese Genderaspekte spiegeln sich in sozialen Determinanten wider und fördern Gesundheitsunterschiede zwischen Frauen und Männern, indem sie sie 1) verschiedenen Gesundheitsrisiken aussetzen, 2) Unterschiede im Gesundheitsverhalten verursachen, 3) Unterschiede im Zugang zur Gesundheitsversorgung gestalten und 4) eine bestehende Voreingenommenheit/ungleiche Behandlung im Kontext des Gesundheitssystems bedingen. Geschlechtergleichstellung wäre vorteilhaft für eine bessere psychische Gesundheit sowohl bei Frauen als auch bei Männern. Zukünftige Studien sollten daher diese Disparität bezogen auf die Manifestation, den Umgang und die Versorgung gesundheitsrelevanter Beschwerden bei Frauen und Männern untersuchen, indem sie 1) prüfen, ob Frauen und Männer ähnliche oder unterschiedliche Symptome bestimmter psychische Störungen berichten, 2) in Stichproben Frauen und Männer mit diversen soziodemografischen und sozioökonomischen Hintergründen auswählen, um zumindest teilweise Geschlechtsaspekte im Kontext gesellschaftlicher und kultureller Perspektiven einzubeziehen, 3) die Gesamtgruppe sowie Frauen und Männer getrennt untersuchen, um zu sehen, ob Effekte für Frauen und Männer abweichen, unterschiedliche Effektstärken aufweisen oder um Interaktionen mit dem biologischen bzw. Geburtsgeschlecht zu untersuchen. Diese letztgenannte Strategie ermöglicht festzustellen, 1) welche Risiko- und Schutzfaktoren für wen relevanter sind, 2) welche Risikofaktoren häufiger bei Frauen oder Männern vorhanden sind, 3) welche Risikofaktoren nur Frauen oder Männer betreffen.

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Chapter 1 – General Introduction

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Chapter 2 – Theoretical Background

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Chapter 3 - Study 1: Similarities and differences of mental health in women and men: A systematic review of findings in three large German cohorts

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Chapter 4 – Study 2: Study 2: Depressive symptoms predict the incidence of common chronic diseases in women and men in a representative community sample

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Chapter 5 - Study 3: Does social support prevent suicidal ideation in women and men? Gender-sensitive analyses of an important protective factor within prospective community cohorts

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Chapter 6 – Study 4: Gender differences in the prevalence of mental distress in East and West Germany over time: a hierarchical age-period-cohort analysis

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Chapter 7 – Discussion

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12 Curriculum Vitae

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Wissenschaftliche Mitarbeiterin zum Thema belastender Kindheitserfahrungen und Kindesmisshandlung, v.a. untersuchen von genaueren Charakteristika erlebter Kindesmisshandlung und deren Folgen für psychische und somatische Gesundheit über die Lebensspanne.
Aufgaben: Erstellung von wissenschaftlichen Publikationen, statistische Auswertungen, methodische Beratung, präsentieren von Studienergebnissen auf Konferenzen.

03/2019 – heute: **Universitätsmedizin der Johannes-Gutenberg-Universität, Mainz**
Klinik und Poliklinik für Psychosomatische Medizin und Psychotherapie
Wissenschaftliche Mitarbeiterin in Forschungsprojekten zu Geschlechterunterschieden in der psychischen Gesundheit und DDR-Vergangenheit und psychische Gesundheit, Fokus auf Risiko- und Schutzfaktoren.
Forschungsgebiete: Depression und chronische physische Erkrankungen, soziokulturelle Determinanten psychischer Gesundheit, Migration
Aufgaben: Projektkoordination, statistische Auswertungen, Erstellung von wissenschaftlichen Publikationen, schreiben von Forschungsanträgen, präsentieren von Studienergebnissen auf Konferenzen.

06/2016 – 10/2018: **Centraal Bureau voor de Statistiek [statistisches Bundesamt der Niederlande], Heerlen (die Niederlande)**
Erstellen von Statistiken und schreiben von Berichten und Pressemitteilungen.
Themen: Bildung, Jugend, Kriminalitätsdelikte, Arbeit und Einkommen

12/2014 – 07/2015: **Nationale Politie [Landespolizei], Arnhem (die Niederlande)**
Praktikum und explorative Studie zum Thema Verbesserung der Sichtbarkeit von Kindesmisshandlung in Polizeiakten im Rahmen der Masterarbeit.

09/2014 – 12/2014: **Radboud Universiteit, Nijmegen (die Niederlande)**
Als studentische Lehrbeauftragte Erstsemester Studenten der Politikwissenschaften und Betriebswissenschaftslehre in einem Grundlagenkurs Statistik und statistische Methoden unterrichtet.

09/2012 – 01/2013: **Rode Kruis [Rotes Kreuz], Utrecht (die Niederlande)**
Praktikum und Studie zu dem Einfluss von sozialen Aktivitäten des Roten Kreuzes um die Selbständigkeit von Senioren zu erhöhen und die soziale Isolierung zu verringern im Rahmen der Bachelorarbeit.

Hochschule und Schulbildung

11/2018 – 02/2019: **DID Deutsch Institut, Frankfurt am Main**
Deutsch Kurs Niveau B2/C1.

09/2013 – 09/2015: **Radboud Universiteit Nijmegen (die Niederlande)**
Master Program: *Research Master Social and Cultural Science: comparative research on societies.*
Englischsprachiges Master Programm zur Durchführung von Forschungsstudien in den Sozialwissenschaften. Kenntnisse über theoretische Ansätze, Forschungsdesigns, Datensammlungsverfahren, Analyse Techniken und Schreiben von wissenschaftlichen Artikeln erworben.

09/2010 – 07/2013: **Universiteit Utrecht (die Niederlande)**
Bachelor Program: *Algemene Sociale Wetenschappen.*
Interdisziplinäres Studium der Psychologie, Soziologie und Pädagogik. Vertiefung im Fachbereich der statistischen Methoden.

09/2004 –07/2010: **Stella Maris College Meerssen (die Niederlande)**
VWO *(Abschluss Abitur)*

Qualifikationen

Programmkenntnisse
Excel, SPSS, R, DataSHIELD, NVivo, Rapidminer und Amos.

Analyse Techniken
Deskriptive Auswertungen, Gruppenvergleichen, Regressionsanalysen (inklusiv logistische Regressionsmodellen), Multilevel-Analysen, hierarchische Alter-Periode-Kohorte Analysen, Strukturgleichungsmodellen, Faktoren-Analysen, Messinvarianz-Analysen, Klassifikationsbaum-Analysen und Data Mining Techniken.

Sprachen
Niederländisch (Muttersprache), Deutsch (Fließend), Englisch (Fließend), Französisch (Grundkenntnisse).

Publikationen

Zeitschriftenartikel

Erstautorin

Otten, D., Schalinski, I., Fegert, J.M., Jud, A., Brähler, E., Bürgin, D., & Clemens, V. (2025). Child Maltreatment Characteristics and Adult Physical Multimorbidity in Germany. *JAMA Network Open, 8*(1):e2456050. doi:10.1001/jamanetworkopen.2024.56050

Otten, D., Ernst, M., Schuster, A.K., Tesarz,J., Gißler, S., Mildenberger, E., Pfeiffer, N., Beutel, M.E., & Fieß, A. (2024). Recalled Maternal Rearing Behaviour of Individuals Born Preterm and Their Mothers: The Impact of Intimate Mother–Child Contact. *Journal of Clinical Medicine, 13*(6):1822. doi:10.3390/jcm13061822

Otten, D., Heller, A., Schmidt, P., Beutel, M.E., & Brähler, E. (2023). Gender differences in the prevalence of mental distress in East and West Germany over time: A hierarchical age=period-cohort analysis, 2006-2021. *Social Psychiatry and Psychiatric Epidemiology*. doi:10.1007/s00127-023-02479-z

Otten, D., Heller, A., Kasinger, C., Brähler, E., Sachser, C., Alweck, L., Beutel, M.E., & Fegert, J.M. (2022). Somatisierung, Depressivität und Angst bei Binnenmigrierten in einer deutschen repräsentatven Stichprobe. [Associations of Internal Migration and Somatoform Symptoms, Depression, and Anxiety in a German Representative Sample]. Psychotherapie Psychosomatik Medizinische Psychologie, 72(12):542-549. doi:10.1055/a-1880-0347

Otten, D., Ernst,M., Tibubos, A.N., Brähler, E., Fleischer, T., Schomerus, G., Wild, P.S., Zöller, D., Binder, H., Kruse, J., Johar, H., Atasoy, S., Grabe, H.J., Ladwig, K-H., Münzel, T., Völzke, H., König, J., & Beutel, M.E. (2022). Does social support prevent suicidal ideation in women and men? Gender-sensitive analyses of an important protective factor within prospective community cohorts. *Journal of Affective Disorders*, 306:157-166. doi:10.1016/j.jad.2022.03.031

Otten, D., Ernst, M., Werner, A.M., Tibubos, A.N., Reiner, I., Brähler, E., Wiltink, J., Michal, M., Nagler, M., Wild, P.S., Münzel, T., König, J., Lackner, K.J., Pfeiffer, N., & Beutel, M.E. (2022). Depressive symptoms predict the incidence of common chronic diseases in women and men in a representative community sample. *Psychological Medicine*, 1-9. doi:10.1017/S0033291722000861

Otten, D., Tibubos, A.N., Schomerus, G., Brähler, E., Binder, H., Kruse, J., Ladwig, K-H., Wild, P.S., Grabe, H.J., & Beutel, M. E. (2021). Similarities and differences of mental health in women and men: A systematic review of findings in three large German cohorts. *Frontiers in Public Health, 9*(40). doi:10.3389/fpubh.2021.553071

Co-Autorin

Döge, J., Hackenberg, B., Beutel, M.E., Otten, D., Wild, P.S., Chalabi, J., GHS Research Consortium, Matthias, C., & Bahr-Hamm, K. (2025). Hearing Loss and its Relation to Loneliness and Depression – A Population-Based Cohort Study. *Laryngoscope*. doi:10.1002/lary.32060

Wicke, F.S., **Otten, D.**, Schulz, A., Wild, P.S., Lackner, K.J., Münzel, T., König, J., Ernst, M., Wiltink, J., Reiner, I., Ghaemi Kerahrodi, J., Pfeiffer, N., & Beutel, M.E. (2024). Current and past depression as risk factors for incident type 2 diabetes mellitus and pre-diabetes in men and women: evidence from a longitudinal community cohort. *Diabetology & Metabolic Syndrome 16*(34). doi:10.1186/s13098-024-01273-4

Reinwarth, A.C., Wicke, F., Hettich-Damm, N., Ernst, M., **Otten, D.**, Brähler, E., Wild, P.S., Münzel, T., König, J., Lackner, K.J., Pfeiffer, N., & Beutel, M.E. (2023). Self-rated physical health predicts mortality in aging persons beyond objective health risks. *Scientific Reports, 13*:19531. doi:10.1038/s41598-023-46882-7

Helmert, C., Speerforck, S., Fleischer, T., **Otten, D.**, Kasinger, C., Brähler, E., Muehlan, H., Altweck, L., Hahm, S., Schmidt, S., Reusche, M., Glaesmer, H., Hinz, A., Reyes, N., Wirkner, K., Engel, C., Schomerus, G., & Ulke, C. (2023). Explorative analyses on spatial differences in the desire for social distance towards people with mental illness in a diverging city. *Frontiers in Public Health,* 11:1260118. doi:10.3389/fpubh.2023.1260118

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Schmalbach, B., Tibubos, A.N., **Otten, D.**, Hinz, A., Decker, O. Zenger, M., Beutel, M.E., & Brähler, E. (2023). Regional differences in the assessment of depressive symptoms in the

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Tibubos A.N., **Otten, D.**, Beutel, M.E., & Brähler, E. (2022). Validation of the Personal Attributes Questionnaire-8: Gender Expression and Mental Distress in the German Population in 2006 and 2018. *International Journal of Public Health*, 67. doi:10.3389/ijph.2022.1604510

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Kasinger, C., **Otten, D**., Stöbel-Richter, Y., Beutel, M.E., Zenger, M., Brähler, E., Berth, H. (2022). Binnenmigration und psychische Gesundheit in der Sächsischen Längsschnittstudie - Relevante Faktoren 20 und 30 Jahre nach der Wiedervereinigung. [Internal Migration and Mental Health – Results from a longitudinal study in Germany – relevant factors 20 and 30 years after unification]. *Zeitschrift für Psychosomatische Medizin und Psychotherapie*, 72:199-206*.* doi:10.1055/a-1662-5395

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Beutel, M.E., Tibubos, A.N., Michal, M., Wiltink, J., **Otten, D**., Werner, A., Wild, P.S., Münzel, T., Lackner, K.J., Pfeiffer, N., König, J., Brähler, E. (2020). Psychosomatische Medizin in der Gutenberg-Gesundheitsstudie (GHS) – Fragestellungen, Messverfahren, ausgewählte Ergebnisse. *Zeitschrift für Psychosomatische Medizin und Psychotherapie, 66*(4), 355-375. doi:10.13109/zptm.2020.66.4.355

Burghardt, J., Tibubos, A.N., **Otten, D**., Brähler, E., Binder, H., Grabe, H., Kruse, J., Ladwig, K-H., Schomerus, G., Wild, P.S., & Beutel, M.E. (2020). A multi-cohort consortium for Gender-Sensitive Analyses of mental health trajectories and implications for prevention (GESA) in the general population in Germany. *BMJ Open, 10*(e034220). doi:10.1136/bmjopen-2019-034220

Geijtenbeek, L., Joosten, M., **Otten, D**., & Posthumus, H. (2019). Profielen voor instroom naar jeugdhulp, in de gemeente Heerlen. Den Haag: Centraal Bureau voor de Statistiek.

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Centraal Bureau voor de Statistiek (2017). Helft niet werkenden met uitkering kan/wil niet werken. Veröffentlicht: https://www.cbs.nl/nl-nl/nieuws/2017/40/helft-niet-werkenden-met-uitkering-kan-wil-niet-werken

Arts, K., **Otten, D**., Droomers, M. & Otten, F. (2016). Wijkenaanpak en stijgende armoederisico's tijdens de economische crisis. Economisch Statistische Berichten.

Van Dijk, A. M. M. & **Otten, D**. (2013). Verslag van evaluatie Sociaal Huisbezoek en Telefooncirkel. Utrecht: Nieuwsbrief Rode Kruis maart 2013.

Buchbeiträge

Otten, D., Brähler, E., Beutel, M.E., Hinz, A., & Ernst, M. (2024). Disentangling age, period and cohort effects shaping suicidal ideation in East and West Germany: An analysis of representative survey data spanning 18 years. In: Heller, A., Schmidt, P. (Eds.) *Thirty years after the Berlin wall: German unification and transformation research* (pp. 73-99). Routledge. doi:10.4324/9781003427469

Otten, D., Tibubos, A.N., Schomerus, G., Brähler, E., Binder, H., Kruse, J., Ladwig, K-H., Wild, P.S., Grabe, H.J., & Beutel, M. E. (2021). Similarities and differences of mental health in women and men: A systematic review of findings in three large German cohorts. In: Rössler, W. (Ed.), *Insights in public mental health: 2021* (pp. 18-32). Frontiers in Public Health. doi:10.3389/fpubh.2022.935922

Konferenzen, Symposien und Vorträge

Jahrestagung der Deutschsprachigen Gesellschaft für Psychotraumatologie (DeGPT)
„Personalisierte Traumatherapie“, 22-24.02.2024 Wien, Österreich
Symposium „Was ist wann besonders relevant? Von der Methodik und Erfassung zu den vielfältigen gesundheitlichen Konsequenzen belastender Kindheitserfahrungen“
Vortrag **Otten, D.** „Zeitpunkt und Dauer von Kindesmisshandlung und deren Zusammenhänge mit somatischen Erkrankungen im Erwachsenalter bei Frauen und Männern“

International Association for Cross Cultural Psychology (IACCP)
„Global Minds and Hearts: Pathways Towards a Sustainable Future”, 01.-04.08.2023 Limerick, Ireland
Symposium “Moving for a better life?: Sociodemographic and health factors of inner German migration”
Vortrag **Otten, D.** „Prevalence of depression and anxiety symptoms in inner German migrants“

Deutsches Kollegium für Psychosomatische Medizin (DKPM)
“Gesund Altern im Wandel“, 03.-05.05.2023 Berlin, Deutschland
Vortrag **Otten, D.** „Depressive Symptome sagen Neuauftreten chronischer körperlicher Erkrankungen bei Frauen und Männern vorher“
Vortrag **Otten, D.** „soziale Unterstützung schützt vor Suizidgedanken bei Frauen und Männern“

ReALity Workshop Johannes Gutenberg-Universität Mainz
„Gender as a biological variable“, 24.04.2023 Mainz, Deutschland
Vortrag Engwicht, E. & **Otten, D.** “Sex and gender – relevance for mental and physical health”

Fachsymposium Universitätsmedizin Mainz
„Mainzer Fachsymposium zur Lehre von geschlechtersensibler Medizin“, 23.-24.02.2023 Mainz, Deutschland

Nachwuchswissenschaftler:innen-Konferenz der DDR-Forschung, 14.-15.07.2022 Leipzig, Deutschland
Symposium „Psychische Komponenten der Transformation“

Vortrag **Otten, D.** „Somatisierung, Depressivität und Angst bei Binnenmigrierten in einer deutschen repräsentativen Stichprobe“

Konferenz INGER Verbundprojekt
„Integration von Geschlecht in die Forschung zu umweltbezogener Gesundheit (INGER) – Projektkonferenz 2021“, 29.11.2021 (online)

Workshop Bundesministerium für Bildung und Forschung (BMBF)
“Same, but different? The role of sex and gender in health research”, 22.06.2021 (online)

Vorlesung Frau Dr. Ute Seeland
„Exzellente Medizin ist geschlechtersensibel“, 05.05.2021 (online)