Preventing deterioration of mental health in multimorbidity

-

Longitudinal mediation analysis of psychosocial resources

Inauguraldissertation zur Erlangung des Doktorgrades

der Humanwissenschaftlichen Fakultät der Universität zu Köln

nach der Promotionsordnung vom 18.12.2018

vorgelegt von:

Ibrahim Demirer

geboren in Gummersbach am 26.01.1990

August 2022

Acknowledgments

First, I would like to express my special thanks to my doctoral supervisor, Prof. Dr. Holger Pfaff, for his support, cooperation, philosophical discussions, and trust in me.

My further thanks go to my second supervisor, PD. Dr. Ute Karbach, through you, I had the opportunity to personally and academically grow in the project MamBo. The pleasant conversations and interpersonal support made every challenge bearable, no matter how difficult.

I would also like to thank PD. Dr. Timo-Kolja Pförtner for the opportunity to deepen my scientific interest and the confidence in my abilities.

My thanks go to my parents, who have consistently challenged and encouraged me. It is not self-evident to pursue a doctorate when coming from a working-class family with a migration background. You have contributed much, if not the greatest part, to make it achievable for me.

I also thank Heike for the nerdy conversations, editing, and shared experiences.

Finally, I want to thank Heidi and Charly, who have always shown me what matters in life.

Declaration of own contribution to the published articles of the cumulative Dissertation

This cumulative dissertation is based on two publications and one appended publication prepared by me, Ibrahim Demirer, as first author.

The literature research, the preparation of the research status, the data preparation and analysis, the interpretation, the conception and revision of the manuscripts as well as the communication with the journals were carried out by me. The manuscripts received support from the persons named as co-authors in the original papers. A list detailing the support is provided in the chapters of the publications following the CRediT authorship contribution statement. No other persons were involved in the intellectual production of the present work.

Table of contents

Table of figures

List of tables

1. Introduction

Multimorbidity is commonly defined as having at least two chronic and incurable diseases (van den Akker et al., 2001). Interest in research on multimorbidity has increased in recent years (Read et al., 2017; Tetzlaff et al., 2017) with different levels of perspective associated.

On the macro level, the consequences of aging societies elevated multimorbidity prevalence by increased overall life expectancies and years with morbidity (Salomon et al., 2012). Increased life expectancies also increased the relative share of older adults and the share of people with multimorbidity. Additionally, the relative onset of morbidities is earlier; thus, the average years of life without morbidities are fewer (Crimmins, 2015). As van Oostrom et al. (2016) argued, the increase in overall morbidity is also enhanced by higher survival rates despite existing morbidities caused by improvements in health services and treatments. The consequences of the interplay between aging societies with increased life expectancy and earlier onset of morbidities can be epidemiologically described in Germany by the constant increase of people aged 65 and older. Simultaneously, even at 50, more than half of the people suffer from at least one to two chronic diseases (Nowossadeck, 2012; Puth et al., 2017). Consequently, multimorbidity shifted from a special case to a normal-case scenario.

On the meso-level, polypharmacy (Maher et al., 2014), more frequent hospital stays (planned and emergency) (Lehnert et al., 2011), overall more intensive care needs (Tetzlaff et al., 2017), more frequent and prolonged physicians contacts (Welzel et al., 2017), as well as multi-professional treatment requirements (Crotty et al., 2004) lead to an increased cost burden on healthcare systems. Socioeconomically, the increased cost burdens are enhanced by decreased productivity and higher rehabilitation demand in parts of the working population (Fouad et al., 2017). These challenges are even enhanced because multimorbidity is not curable, meaning that the costs and coordination requirements are maintained and accumulated on the meso-level. The current healthcare systems designs seem to fail to address the increased coordination demands of multimorbidity treatment (Barnett et al., 2012). Especially in Germany, despite

having disease management programs (DMP) for single chronic diseases, the current structural and legal status quo does not adequately account for the challenges between care sectors and the resulting problems of interactions in multimorbidity (Hower et al., 2019; Lang et al., 2019). On the micro-level, the incurable character of multimorbidity and the complex interplay between the diseases impose various challenges on the individuals suffering from multimorbidity. The chronic conditions may even mutually reinforce each other, thus leading to increases in symptom burdens, uncertainty of symptoms (Blinderman et al., 2009), reductions in quality of life (Gould et al., 2016), and even depression (Read et al., 2017). Moreover, the association between morbidity and mortality is mediated by mental health, meaning that a major determinant for mortality in multimorbid individuals is the mental health constitution (van den Berg et al., 2021). Although multimorbidity's impact on physical health can rarely be cured or stopped, its impact on mental health can (Mercer et al., 2009), emphasizing the importance of the sociopsychological level in the treatment of multimorbidity.

1.1 Aims of thesis

This thesis targets the micro-level challenges of multimorbidity and will, therefore, focus on the individual settings and reactions to multimorbidity. There are three reasons for mental health to be of primary interest when addressing multimorbidity. First, multimorbidity is rarely curable; hence improving physical health is limited. Second, whereas the tangibility of physical health is limited, mental health is susceptible to interventions in multimorbidity (S. Rosenbaum et al., 2021; Smith et al., 2021). Third, mental health is a robust predictor of declining health and even mortality (Gallo, 2017); thus, targeting mental health is highly relevant for physical health in multimorbidity treatment.

Addressing mental health in multimorbidity requires an explanation of a) the genealogy and maintenance of mental health, b) the impact and influence of multimorbidity on mental health, and c) the contextual and intermediate pathways between a) and b). Therefore, the first part of this thesis focuses on theoretical models that give sufficient information on the genealogy and maintenance of mental health in multimorbidity and the impact of multimorbidity on mental health. In the next step, the synthesis c) will result in causal models describing the process between multimorbidity and mental health about the contextual and intermediate factors. In detail, I will point two intermediate factors. First, positive affect, as the most important individual resource, and, second, social support as the most important social resource in preventing deterioration of mental health in multimorbidity.

The final causal model aims at synthesizing the necessary theories for explaining aspects a) to c), such as the transactional model of Lazarus and Folkman (1984), the broaden-built-theory by Fredrickson (2001) aspects of coping with diseases (e.g., Folkman & Moskowitz, 2000), the buffering hypothesis of social support (Berkman et al., 2000; Cohen & Wills, 1985), and the resource depletion (or ego-depletion) theory within depressive spirals and positive affect (Tice et al., 2007). The final causal model aims not only to synthesize these theories about the interplay between multimorbidity and mental health but also to enable the location of

intermediate, tangible factors. Knowing such intermediates is especially important for designing to improve mental health in multimorbidity.

Furthermore, the causal models will also be the fundament of the empirical analysis; hence the main challenge of the empirical analysis will be the correct translation of the causal model's implications into empirical models. For this purpose, this thesis will present novel approaches to longitudinal mediation and interaction analysis with observational data (section 3.3 onwards). More precisely, this thesis demonstrates the application of cross-lagged panel models (CLPM) (Newsom, 2015) to elaborate on and model for causal issues, such as reverse-causality. Another issue the empirical models of this thesis cover is identifying and estimating complex mediations, where the mediator can also be a moderator and is time-varyingly confounded. This thesis, therefore, presents and applies the recently developed mediational g-formula, which uses various sets of inverse-probability weights (VanderWeele & Tchetgen Tchetgen, 2017). Both CLPM and mediational g-formula address specific implications of the causal model methodologically.

Although this thesis addresses the health-related sociopsychological micro-level implications of multimorbidity, the results can also serve to address multimorbidity's meso-structural challenges by identifying potential tangible resources for multimorbidity treatment.

In summary, this cumulative thesis discloses three aspects:

1) A causal model of deterioration and maintaining mental health in multimorbidity.

2) Translation of the causal model into empirical models and application of novel statistical methods.

3) Identification and quantification of intermediate factors to design future mental health interventions for individuals suffering from multimorbidity.

2. Theoretical framework

The interplay between mental and physical health in multimorbidity is quite complex. On the one hand, low physical health status can be due to multimorbidity; on the other hand, underlying conditions deteriorate physical health successively. Studies with physical health as an endpoint focus on the prevention of deterioration, the onset of additional morbidities and functional decline (e.g., Kadam & Croft; Marengoni et al., 2009), and the prevention of mortality in multimorbidity (e.g., Menotti et al., 2001). I will briefly outline the importance and interplay of physical and mental health outcomes in multimorbidity for constructing the theoretical framework

Multimorbidity may deteriorate mental health due to metabolic and or vascular changes caused by the underlying diseases that increase the risks for depressive symptoms or even cause depression (Camus et al., 2004; Pariante & Lightman, 2008). Additionally, individuals suffering of multimorbidity often face multiple medications. These polypharmacies can have adverse effects and thereby affect mental health indirectly (Holvast et al., 2017; Kuzuya, 2019). Further, multimorbidity and declining physical health could also cause increased stress levels through healthcare and coping demands, thus reducing mental health (Kendler et al., 1999; Ziarko et al., 2014). Consequently, physical health in multimorbidity is a crucial determinant of mental health and depression (Chang-Quan et al., 2010; Moussavi et al., 2007). However, since the decline in physical health cannot be easily targeted in multimorbidity, numerous studies targeted self-management ability, mental health, daily activity, or quality of life as the primary endpoint in multimorbidity treatment (e.g., Espeland et al., 2017; Smith et al., 2021). For illustration purposes of the interplay between multimorbidity, physical- and mental health, Figure 1 depicts the deterioration of physical health in path 1 and the deterioration of mental health in path 2.

There are numerous studies associating multimorbidity with lower mental health, yet, understanding intermediate factors, mechanisms, moderators, and involved processes is limited

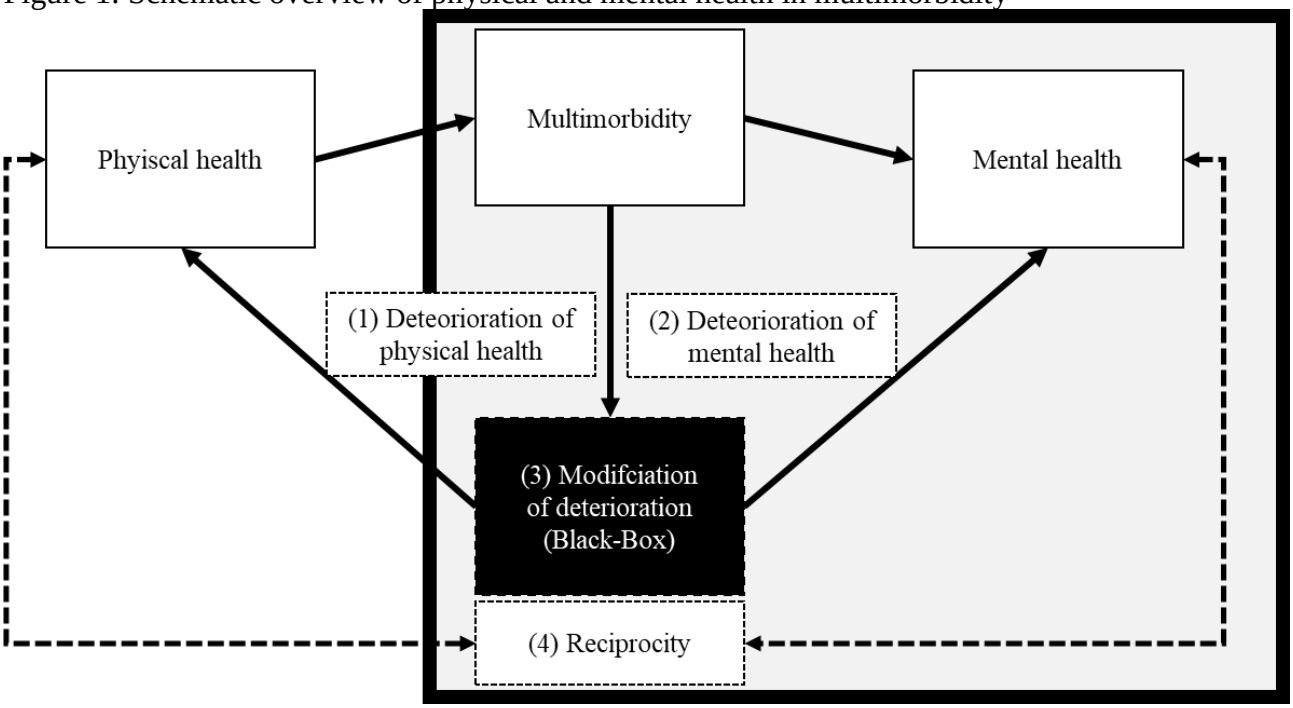
(Read et al., 2017) and, therefore, depicted as Black-Box in Figure 1. These factors and processes can strongly modify the impact of multimorbidity on mental health, and understanding these factors and processes is a necessary condition for the prevention and treatment of depression in multimorbidity.

Although mental health conditions are not directly counted into multimorbidity, low mental health could reduce physical health and thus increase the risk of multimorbidity. For instance, psychosomatic research found catastrophizing and anxiety behaviors to be more prevalent in multimorbid patients, and that these behaviors contribute to deterioration of mental and physical health (Henning et al., 2020). Lowered physical health could then decrease mental health and, again, in the long run, also decrease physical health, thus causing or worsening multimorbidity.

A deeper understanding of the pathway from mental health to physical health provides the concept of allostatic load (McEwen, 1993). In brief, the concept of allostasis describes the acute reaction of the organism to a stressor, thus the switch from homeostasis (regular organism) to allostasis. However, allostatic load means an ongoing allostasis that is due to dysregulation of the organism caused by chronic exposure to stress (Schulkin, 2003). Therefore, persistent stress leads to allostatic load, which then could pinnacle in occurrence of (additional) morbidities and even mortality. For instance, in individuals facing multimorbidity, depression increases the risks of the onset of additional diseases (Birk et al., 2019; Triolo et al., 2020) and even mortality (Gallo, 2017). The related publication (Demirer, Schmidt, et al., 2021) of this thesis (Section 6) analyzed the impact of allostatic load on the likelihood of cardiovascular morbidities and mortality.

Figure 1 path 4 displays the reciprocity by adding bidirectional bolt-dotted arrows between physical and mental health. For the outlook of this thesis, these reciprocities are one of the major topics for the theory (especially, section 2.5) and methods (especially, section 3.3.5).

Figure 1: Schematic overview of physical and mental health in multimorbidity



Note: Own illustration

An essential addition is that multimorbidity is not curable, meaning that the reciprocity between physical and mental health is maintained throughout the remaining life span.

Since this thesis is a sociopsychological investigation of mental health in multimorbidity, this thesis covers the content of the black frame of Figure 1, which are: deterioration of mental health by multimorbidity (path 2); modification of deterioration by the Black-Box (path 3); and the reciprocity between mental and physical health (path 4) within multimorbidity. Due to the fact that there are several depicted paths and factors, these cannot be disclosed by one theory or theoretical approach but by many interlinked. In the following, I will elaborate more on theory-elements already listed in section 1. These theory-elements provide a detailed theoretical explanation of the empirical findings that lead to Figure 1. Therefore, the theory-elements aim to explain the reciprocities and remove the Black-Box by detailing the various possibilities of modification.

To understand why multimorbidity leads to the deterioration of mental health (path 2), I will refer to the transactional model of Lazarus and Folkman (1984). The transactional model will

be the causal model's first theory-element (element A) and will cover the physical and mental health associations.

To shed more light on the Black-Box (path 3), the broaden-and-built theory of Fredrickson (2001) will be examined (element B). The broaden-and-built theory highlights the intra-individual psychological processes involved in coping with multimorbidity; thus, the intra-individual modifications of the multimorbidity – mental health association.

To acknowledge the interindividual sociopsychological modifications of the multimorbidity – mental health association, the next theory-element (theory-element C) is the buffering hypothesis outlined by Cohen and Wills (1985). Hence, the buffering hypothesis assesses the modification by the social environment.

The last theory-element inspects the reciprocities between physical and mental health in multimorbid individuals more deeply (path 4; Figure 1). For this purpose, I will refer to the resource-depletion (or ego-depletion) theory of Baumeister et al. (1998) as theory-element D. Theory-Element D will have a particular emphasis on theory-element B and C regarding the onset and prevention of depressive-spirals and rumination in multimorbid individuals (Nolen-Hoeksema et al., 2008; Tice et al., 2007).

Where theory-element A gives a basic understanding of multimorbidity's impact on mental health, theory-element B and C aim to reveal the Black-Box, the modification of this impact. Theory-element D addresses the longitudinal and causal questions that arise when investigating reciprocal associations. Although theory-elements A-D examine the associations sufficiently, the deterioration of physical health (1) will not be primarily focused on because this thesis aims not to explain the origin and physical health implications of multimorbidity but to identify the processes that lead from physical health/multimorbidity to mental health.

In summary, with the combination of these elements, three goals should be achieved. First, to shed light on the Black-Box between multimorbidity and mental health. Second, to have explicit instruction for the empirical evaluation of the processes. Third, to identify relevant factors that

can positively modify the association so that potential future interventions can inhibit mental health deterioration.

2.1 The stress appraisal and coping paradigm

Multimorbidity or the onset of morbidities can be reviewed as a stressful life event (Kendler et al., 1999). Additionally, individuals suffering from multimorbidity face various challenges, such as symptom burdens and uncertainty (Eckerblad et al., 2015), and losses in physical functioning (Loza et al., 2009). The "transactional model" of Lazarus and Folkman (1984) examines the origin of the stress impact. In this model, the challenges associated with multimorbidity are understood as stressors. The individual response (e.g., catastrophization) to the stressor (e.g., loss of mobility) determines the impact of such stressors.

Following the transactional model, the response to a stressor is structured along with four interlinked phases. The first phase is the perception phase, in which a stressor is either perceived as a stressor or not. The second phase is the evaluation of the stressor according to its relevancy for the individual (primary appraisal); it can be captured as the question, "What do I have at stake in this encounter?". After that, the secondary appraisal, "What can I do?" determines the reaction and coping action (reaction / coping phase) (Lazarus & Folkman, 1984). The primary appraisal decides which feelings result from stressful situations, and the secondary appraisal determines what coping actions/strategies will occur. The success of the reaction is measured by the remaining impact of the stressor on the individual (outcome). If the stressor could be solved entirely, there are no further actions required for the individual; however, if the stressor persists, a reappraisal (secondary appraisal) and reaction are again needed. If the stressor remains unsolved, the stressor will negatively affect the individual's mental health.

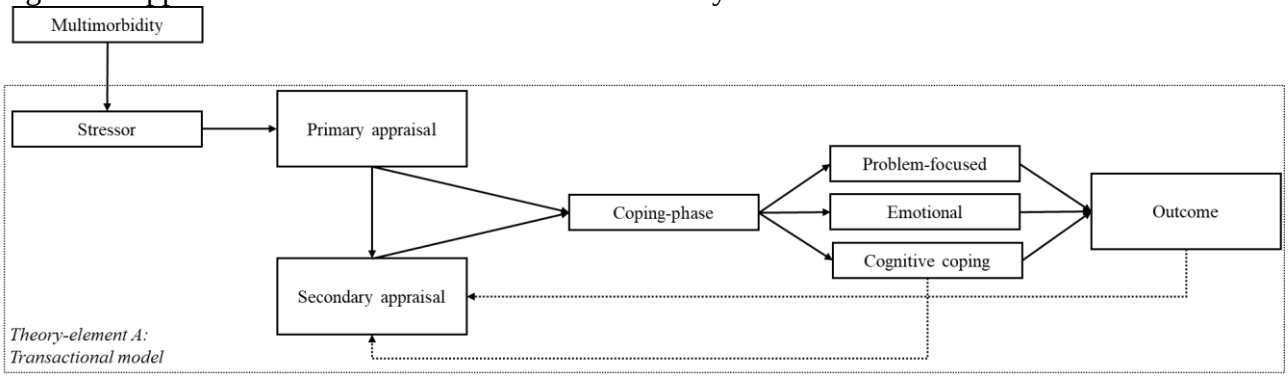
Concerning the coping strategies, Lazarus and Folkman (1984) described two main coping strategies: problem-focused and emotional coping. However, a third coping strategy is cognitive coping, characterized by reappraisal (reappraisal phase). Yet, the necessary condition for successful coping is problem-focused coping. After a coping strategy is selected and

realized, feedback on the impact and consequences is possible. This reappraisal of the coping strategy equals cognitive coping (reappraisal phase). It is important to note that the coping strategies are not mutually exclusive and potentially intertwined.

Concerning mental health deterioration by multimorbidity, the transactional model gives insights into the involved processes. More precisely, multimorbidity can be viewed as an accumulation of stressors. These stressors are more likely to be evaluated as threatening since multimorbidity is a major health concern. Concurrently, coping is required. However, the coping strategy is more likely to be unsuccessful due to the nature of the stressors since multimorbidity is incurable and gradually increasing. The accumulation of stress and the increased demands in coping lead to accumulated, unsolved stress over time, thus deteriorating mental health.

Concerning the coping strategy and multimorbidity, two further additions are required. First, if the primary appraisal phase evaluates the stressor as irrelevant, the stressor will require no secondary appraisal; thus, no stressor effect will occur. Second, the secondary appraisal and the reappraisal are highly constrained by inter- and intraindividual resources. Logically, multimorbidity as a stressor is highly variable between individuals, depending on the chosen coping strategy. Figure 2 presents a version of the transactional model that is applied and adjusted to multimorbidity.

Figure 2: Applied transactional model on multimorbidity



Note: Own illustration based on Lazarus and Folkman (1984)

The transactional model has been successfully applied in various settings, such as the treatment of HIV (Moskowitz et al., 2017) or occupational stress (Goh et al., 2010), and is generally accepted as a valid interdisciplinary framework for the evaluation of stress and coping.

The transactional model addresses the first research hypothesis of this thesis:

H1: “Does multimorbidity deteriorate mental health?”

Although the transactional model as theory-element A is a reasonable starting point for the evaluation of H1, the intraindividual modification of the stressors remains blurry since the transactional model only describes the coping process. Therefore, the next theory-element, tries to identify the main, intraindividual determining factors for successful coping. Theory-element B, the broaden-and-build-theory of the positive psychologist Fredrickson (2001), will expand the transactional model for these intra-individual determining factors of coping. Hence, the next section examines the Black-Box in Figure 1 and examines the paths between perception and secondary appraisal in Figure 2.

2.2 The broaden-and-built theory

In her broaden-and-built theory, Fredrickson (2001, p. 221) notes that positive emotions in general"(…) broaden peoples' momentary thought-action repertoires and build their enduring personal resources". Since the initial statement of this theory, an extensive body of literature throughout diverse fields of study seem to confirm the increase in action repertoire caused by experiencing positive emotions and associated increases in resilience (Cohn et al., 2009; Jackson et al., 2007; Wu et al., 2020). However, the effect of positive emotions is not stationary. Following Fredrickson's (2001) explanations further, current positive emotions will help in coping with future negative emotions; in this manner, positive emotions contribute to sustainable resilience (Cohn et al., 2009)

Applied to the transactional model of Lazarus and Folkman (1984), the broaden-and-built theory of Fredrickson (2001) shows that positive emotions are crucial for secondary-appraisal, "What can I do?", as the broaden-and-built theory highlights that positive emotions broaden the repertoire of actions for the secondary-appraisal, thus the coping-strategy. Moreover, positive emotions build up psychological resilience (Cohn et al., 2009), hence the personal resources for coping, reducing the stressor perception during primary appraisal. However, as the transactional model also suggests, the success of the coping strategy is determined by the involvement of problem-focused coping patterns. Contrary, according to the broaden-and-built theory, negative emotions reduce the repertoire of actions (Fredrickson, 2004)

Yet, a coping strategy based solely on positive emotions seems insufficient. In the context of positive emotions as a coping strategy, the term "hedonic treadmill" (Brickman et al., 1978) is often brought up to acknowledge the potential ambiguity of positive emotions. Relying solely on positive emotions could be insufficient and even contra-productive in choosing problem-focused coping strategies and, thus, might not solve but increase the stressor (Diener et al., 2006). Similarly, the emotion dysregulation model highlights that an abundance of positive

emotions or mood swings between positive and negative emotions seem to disturb psychological resilience to stress (Hofmann et al., 2012).

Transferred to multimorbidity, mental health, and the transactional model, experiencing positive emotions is necessary for maintaining psychological resilience and mental health despite being multimorbid. Positive emotions reduce the initial stress perception (primary appraisal) and promote successful coping (secondary appraisal) through broadening the repertoire of actions.

However, positive emotions alone are not sufficient for successful coping and could potentially be harmful since incorporating problem-focused coping strategies determines success in coping.

These problem-focused coping strategies and positive emotions are highly determined by another personality trait: positive affect (Ashby et al., 1999). Therefore, positive affect can be considered a personal resource crucial for coping. In the next section, this resource for coping will be defined and contextualized within the transactional model, the broaden-and-built theory, and the mental health deterioration of multimorbidity.

2.3 Positive affect: the key personal resource for successful coping in multimorbidity

Positive affect determines the individual's interaction with their surroundings. According to Ashby et al. (1999), positive affect can be defined as the ability to reflect on problems as challenges and maintain positive emotions despite facing stressful circumstances. Whereas positive emotions do not necessarily increase the chances of using problem-focused coping strategies, positive affect enables the experience of positive emotions despite facing stressors. It increases the chances of utilizing problem-focused coping strategies. With positive affect, stressors can be encountered as challenges, and positive emotions can be maintained (Lyubomirsky et al., 2005; Pressman et al., 2019).

Positive affect is the building block of positive psychology and has been associated by prior researchers with reduced stress (Sewart et al., 2019), increased health and longevity in the chronically ill (Schiavon et al., 2016), increased self-efficacy (Lindahl & Archer, 2013), quality and quantity of social contacts (Berry & Hansen, 1996; Cohen & Pressman, 2006). The absence of positive affect and the presence of high levels of negative affect are correlated with increased pathopsychological symptoms such as lethargy and social anxiety, as well as pathological psychoneuroendocrinological changes, such as decreased dopamine and increased immune-inflammatory reactions (Jones & Graham-Engeland, 2021; Steptoe et al., 2008),

Previous research showed that positive and negative affect are orthogonal, meaning that they are negatively associated but not just opposites of one another (Watson et al., 1988). In the "tripartite model of anxiety and depression" Clark and Watson (1991) note that negative affect is associated with depression and anxiety, whereas the absence of positive affect indicates depression (Lyubomirsky et al., 2005).

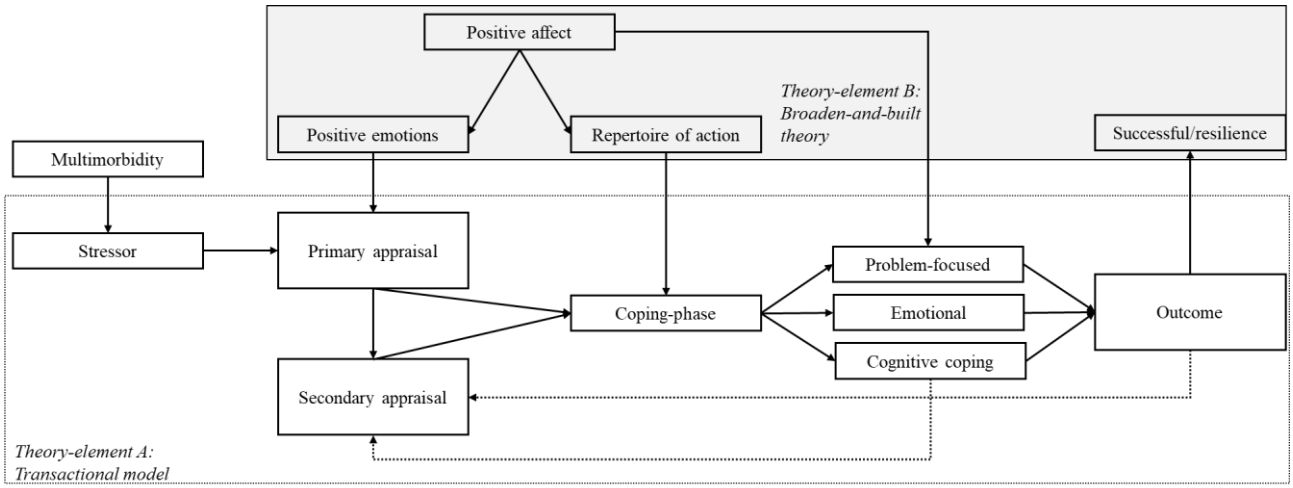
However, the tripartite model of anxiety and depression does not account for the genesis of depression. The "transdiagnostic" approaches (Nolen-Hoeksema et al., 2008; Wilamowska et al., 2010) and the emotion dysregulation models of Hofmann et al. (2012) highlight that depression is rather the endpoint of a distinct process than the same as the presence of low

positive affect or high negative affect. According to these approaches, depression results from dysregulation in the affect. Therefore, low positive affect and depression are not equivalent but interlinked within developing depression. Logically, a large body of research identifies positive affect as the key protective factor for depression (Bos et al., 2013; Chang-Quan et al., 2010; Garland et al., 2010).

Regarding the transactional model and the broaden-and-built theory, positive affect enables positive emotions, which increases the repertoire of actions, and reduces stressor perception in the primary appraisal. Additionally, positive affect promotes problem-focused coping strategies (Paterson Yeung 2016) and reduces negative overthinking, which is more associated with cognitive coping (reappraisal). Felton and Revenson (1984) differentiated the efficiency of different coping strategies as responses to chronic illnesses. They linked positive affect to cognitive coping strategies and negative affect to emotional coping strategies. Folkman and Moskowitz (2000, pp. 650–651) added that positive affect promotes problem-focused coping and the 'creation of positive events' and 'positive reappraisal', which are essential for maintaining positive emotions. Thus, positive affect is the key component in the stress-coping process, especially in later life (Ong et al., 2006).

Figure 3 combines and summarizes the transactional model, and the broaden-and-built-theory schematically. Figure 3 also highlights the centrality of positive affect within these models; it shows that positive affect combines the transactional model with the broaden-and-built theory between the primary appraisal and the coping-phase because positive affects increase positive emotions, which reduces stressor perception (primary appraisal). Positive affect also increases the repertoire of actions, increasing the contingency of potential beneficial actions during the coping-phase, and positive affect directly promotes problem-focused coping.

Figure 3: Transactional model and broaden-and-built theory combined



Note: Background shadings: white: theory-element A; light-gray: theory-element B

Concerning the broaden-and-built theory and positive affect, the associated research hypothesis is:

H2: Does positive affect prevent deterioration of mental health?

Although in H2, the most important personal resource in the stress-coping process is analyzed with positive affect, the socio-environmental resources are yet to be reflected within the current theoretical framework. Since Lazarus and Folkman (1984) and Fredrickson (2001) already pointed out individuals' socio-environment provides essential coping resources and can affect the emotional state dramatically, the next section addresses the socio-environment within the stress-coping process.

2.4 The buffering hypothesis and the stress-coping process

Cohen and Wills (1985) rated the social environment (social support) as a buffer for stress, also known as the "buffering hypothesis", meaning that the impact of the stressors is lower when social support is available. Berkman et al. (2000) presented more recent investigations on the buffering hypothesis in their paper "From social integration to health: Durkheim in the new millennium". Their paper described the impact of social relationships on health in micro and macro processes based on a multidisciplinary approach. They defined "upstream factors", which are relevant for the macro-processes, and "downstream factors", which are relevant for the micro-process. Although their explanations of "upstream factors" are highly relevant for theoretical sociological analysis, the "downstream factors" are more suitable for the current thesis because this thesis focuses on the intra-/interindividual process.

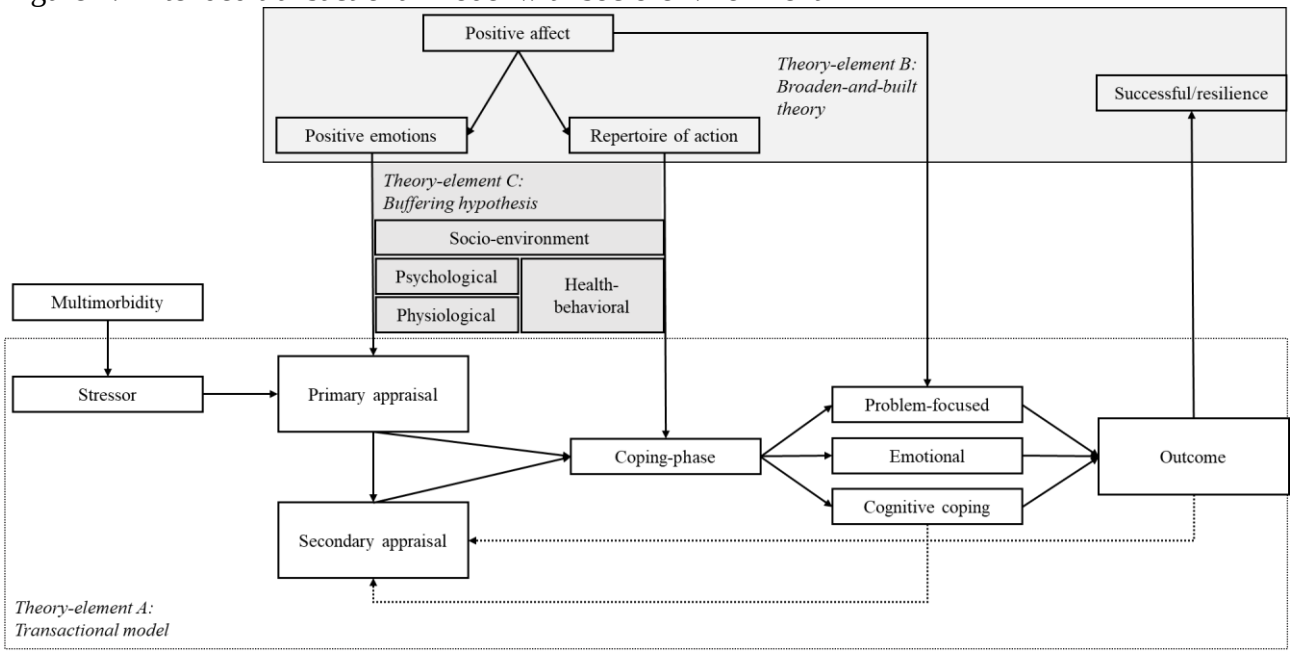
For the "downstream factors", they argued that the effect on health could be realized through four psychosocial mechanisms: "(…) (1) provision of social support; (2) social influence; (3) social engagement and attachment; (…) (4) access to resources and material goods." (Berkman et al., 2000, p. 843). More specifically, these mechanisms operate through three different pathways: health behavioral, psychological and physiological (Berkman et al., 2000).

Applying these additions to the model in Figure 3, the effects of the socio-environment on the coping processes are gaining transparency since they must operate through these three pathways. Where psychological and physiological pathways could reduce the stressor perception in the primary appraisal, health behavioral pathways affect the repertoire of actions and provide or enforce different actions in the coping-phase.

In Figure 4, the current theoretical framework of Figure 3 is extended by theory-element C in the grey areas. Figure 4 depicts the importance of the socio-environment in the stress-coping process. On the one hand, the socio-environment can inhibit stressors from multimorbidity in the primary appraisal through psychological and physiological pathways. On the other hand,

the socio-environment can increase the repertoire of actions, similar to positive affect, and provide beneficial coping actions, such as problem-focused coping.

Figure 4: Extended transactional model with socio-environment



Note: Background colors: white: theory-element A; light-gray: theory-element B; gray; theory-element C.

The next section will highlight social support as the key factor of the socio-environment in the stress-coping process, similar to positive affect in section 2.3.

2.4.1 Social support: the key social resource for successful coping in multimorbidity

There exists an abundance of evidence for social support to be positively associated with physical and mental health (for overviews, see: Thoits, 2011; Wang et al., 2018). However, as Thoits (2011) already argued, research mostly overlooks associations' mechanisms. There are two reasons why the identification of the mechanism is complex. First is the definition of social support. Second, the dynamics behind social support.

Cohen (2004) derived his definition of social support from the social networks and resource perspective. More precisely, the tasks of social networks are the "(…) provision of psychological and material resources intended to benefit an individual's ability to cope with stress" (Cohen, 2004, p. 676). Although his definition accurately reflects the stress-coping process and the transactional model, social support can be further distinguished from emotional and tangible support. Cohen (2004) already reflected these dimensions of social support with the terms "psychological" and "material resources".

Tangible support is required when a lack of material resources persists or certain coping actions cannot be achieved without further assistance from the social network (Cohen & Wills, 1985). The buffering hypothesis yields its impact on health primarily through health-behavioral or physical pathways. For instance, tangible social support can operate over behavioral health pathways in the coping-phase, increasing the repertoire of actions, thus influencing the coping-phase positively.

Emotional social support, however, operates over psychological pathways since "(…) emotional support refers to demonstrations of love and caring, esteem and value, encouragement, and sympathy." (Thoits, 2011, p. 146). Emotional social support might also be a buffer for stress beforehand through psychological pathways and promotes esteem, leading to increased positive affect and better adaptability to stress in general (Cohen, 1988).

Regarding multimorbidity, both types of social support are crucial for coping. Tangible support is more important when facing controllable stressors, whereas emotional support is more

important when facing uncontrollable stressors (Cutrona, 1990). Multimorbidity poses both types of stressors. The demand for treatments and coordination can be viewed as controllable stressors. In contrast, symptom increase and uncertainty, progredient decline in health, and incurability can be considered uncontrollable stressors requiring emotional support. As Figure 4 illustrates, social support can intervene in the stress-coping process over all three pathways identified by the buffering hypothesis; hence social support is the key interindividual or socio-environmental resource for coping with stress.

The buffering hypothesis and the implications of social support as the key socio-environmental resource for coping with stress postulate research hypothesis three:

H3: Does social support buffer multimorbidity's deterioration of mental health?

Moreover, similar to the hedonic treadmill of positive affect in the stress-coping process, social support could also negatively impact the stress-coping process. And even early research based on the transactional model considered social support as an important factor of the coping process. However, the interpersonal skills and interplay were pointed to be important modifiers, and alternates of social support's role in the coping process (Dunkel-Schetter et al., 1987). Therefore, the next section will discuss these alternatives to the buffering hypothesis.

2.4.2 Alternatives to the buffering hypothesis

One issue of the buffering hypothesis is that empirically a different observation has been made in some cases. Already Cohen and Wills (1985) mentioned that the resource (social support) must match the stressor to buffer stress. Similarly, the personality of the support giver and receiver must match each other. Under specific personality and social support combinations, support reception may even increase stress (e.g., Dakof & Taylor, 1990).

More precisely, different reactions to social support are possible in the appraisal phase. As such, the "inequity hypothesis" postulated by Walster et al. (1978) ranks fairness as the primary goal of the relationship. This hypothesis states that receiving social support produces social network inequity, leading to increased distress by the support receiver, thus accelerating stress despite the reception of social support. Similarly, the "esteem threat hypothesis" (Nadler & Jeffrey, 1986) links social support's reception to lowered self-esteem levels, which also induces stress. Similarly, the "social baseline theory" (Beckes et al., 2013) highlights that social relationships can impact health negatively, for instance, when unmet expectations or rejections confront an individual after support seeking. Overall, there is some evidence for neuroticism to confound these positive stress–support effects negatively (Asendorpf & van Aken, 2003).

Furthermore, Barrera (1986) showed that the empirical evaluation of the underlying social support assumption, e.g., buffering vs. inequity, is not simple. He concluded that the support mobilization and support seeking models could account for some findings where a positive empirical relationship between social support and stress has been found. In these models, the stressor causes the provision of support, thus, causing a positive correlation. He concluded that clarification of the pathways of the buffering or stress-causing effect is necessary for the conceptual evaluation. For the empirical evaluation, finely granulated longitudinal data is needed.

Recently, Holt-Lunstad (2018) described a more holistic approach for capturing the impact of social relationships on health. In this concept, she tries to identify causal mechanisms on the

individual relationship and community levels. For the individual level, she mostly confirms the pathways identified by Berkman et al. (2000); however, Holt-Lunstad (2018) emphasizes that there is recent evidence for buffering hypothesis operating through biological/physiological pathways (e.g., Ditzen & Heinrichs, 2014; Eisenberger, 2012; Eisenberger et al., 2016). Overall, the implications of the model by Holt-Lunstad (2018) are similar to Barrera (1986), yet not restricted to social support. Holt-Lunstad (2018) differentiates the levels of interactions (within and between) the individual.

Regarding multimorbidity, assuming the buffering hypothesis seems plausible due to three reasons. First, the vast body of empirical studies that confirm the buffering hypothesis for social support in stress and health (Aartsen et al., 2017; Backe et al., 2018; Kroenke et al., 2006; Olaya et al., 2017; Zhou et al., 2013). Second, the transactional model highlights the pathways through which social support reduces stress: appraisal and coping phases (see Figure 4). Third, Holt-Lunstad's (2018) recent multi-disciplinary synthesis suggests social relations and social support to buffer the stress effect on a biological level. Therefore, social support must be viewed as a resource for the stress-coping process with multimorbidity.

Concerning the alternative effects of social support, any analysis must at least reflect the personality of the care-receiver since neuroticism can promote these alternate effects of social support. Following Barrera's (1986) suggestions, the analysis must also be longitudinal to address the support mobilization and support-seeking models empirically.

2.4.3 Buffering hypothesis: moderation or mediation?

Cohen and Wills (1985) could not precisely distinguish between social support's moderating and mediating effect on stress. Moderation means that social support acts as a third variable between stress and health and that the level of social support stratifies the stress effect on health, or in other words, that the stress effect on health is a function of the level of social support (for definitions, see: Aiken et al., 1991; VanderWeele, 2015). In this manner, social support is a resource that buffers the stress effect when high levels of social support are present.

However, mediation does not contradict a buffering effect, but it also implies the stressors themselves induce a change in social support, e.g., through increased demands or changed perception. Therefore, the support mobilization and support-seeking models would suggest mediation instead of moderation since the stressor increases (sought) the demand for social support. If social support is available, it will buffer (mediate) a portion of the stress effect. Thereby, mediation means that social support is a mechanism of the stress effect. Still, researchers found evidence for both moderation (Cobb, 1976; Wilks & Croom, 2008; Zhou et al., 2013) and mediation (Aartsen et al., 2017; Backe et al., 2018; Kim et al., 2010) to be true.

From a practitioner’s point of view, the differentiation between mediation and moderation might seem irrelevant since social support buffers the stressor effect in both cases. However, identifying the correct causal impact is essential for two reasons—first, proper identification of the magnitude buffered by social support. Second, adequate comprehension of the stress-coping process is necessary for designing interventions. Section 3 of this thesis will discuss the statistical methods for identifying moderation, mediation, or even hybrids of both.

2.5 Depressive spirals in multimorbidity

One aspect that has not been covered yet by the theoretical framework is path 4 in Figure 1: the reciprocity between physical and mental health in multimorbidity. So far, the current theoretical framework is founded on the transactional model (element A), extended by the broaden-and-built theory (element B) and buffering hypothesis (element C). To inspect these reciprocities, the characteristics of multimorbidity must be pointed out beforehand: incurability and successive decline of health. Incurability of multimorbidity causes the stressor exposure to persist regardless of the outcome from the coping processes. Only the magnitude of the stressor impact can be changed from the coping process. The successive health decline enhances the reciprocal association between physical and mental health. From the combination of persistent stressor exposition and declining physical health, the emergence of a depressive spiral is possible (Beck, 1970; Lewinsohn, 1974).

Lewinsohn (1974, p. 170) already described that aging could cause depression and depressive spirals over four mechanisms: (1) disengagement; (2) loss of interest or feeling rejected; (3) motivation and the lack of reinforcing events; (4) introversion to the past and memories. Concerning multimorbidity and its relation to aging, these causes of depression seem to be enhanced. From this vantage point, multimorbidity could cause a downward spiral of mental health due to morbidity (decline in physical health), which causes depressive symptoms (decline in mental health), which again causes a successive decrease in physical health. Thus, the reciprocity between physical and mental health could also take a downward spiral.

Since the decline in physical can rarely be inhibited, the decline in mental health must be targeted to block the downward spiral. The tendency for a downward spiral in mental health that is caused by stressors has been described by Nolen-Hoeksema et al. (2008, p. 400) In their concept of "rumination", which is the intraindividual facilitation of depressive symptoms, and "(…) is a mode of responding to distress that involves repetitively and passively focusing on symptoms of distress and on the possible causes and consequences of these symptoms".

Through the lens of the transactional model, a ruminated stressor is persistent and increasing because the outcome of the coping-process does not solve but increases the stressor. Especially coping with multimorbidity requires prevention of rumination due to the persistency of the stressor and the decline in physical health.

The mechanisms described by Lewinsohn (1974) and the dangers of rumination described by Nolen-Hoeksema et al. (2008) underlines the importance of positive affect and social support as the key resources for coping with multimorbidity since they can intervene in these mechanisms. Positive affect could protect from loss of interest and can create reinforcing events (Folkman & Moskowitz, 2000; Pressman et al., 2019), whereas social support could encourage engagement and provide feelings of being accepted instead of rejected (Cohen, 2004); hence, both resources can prevent the onset of a depressive-spiral.

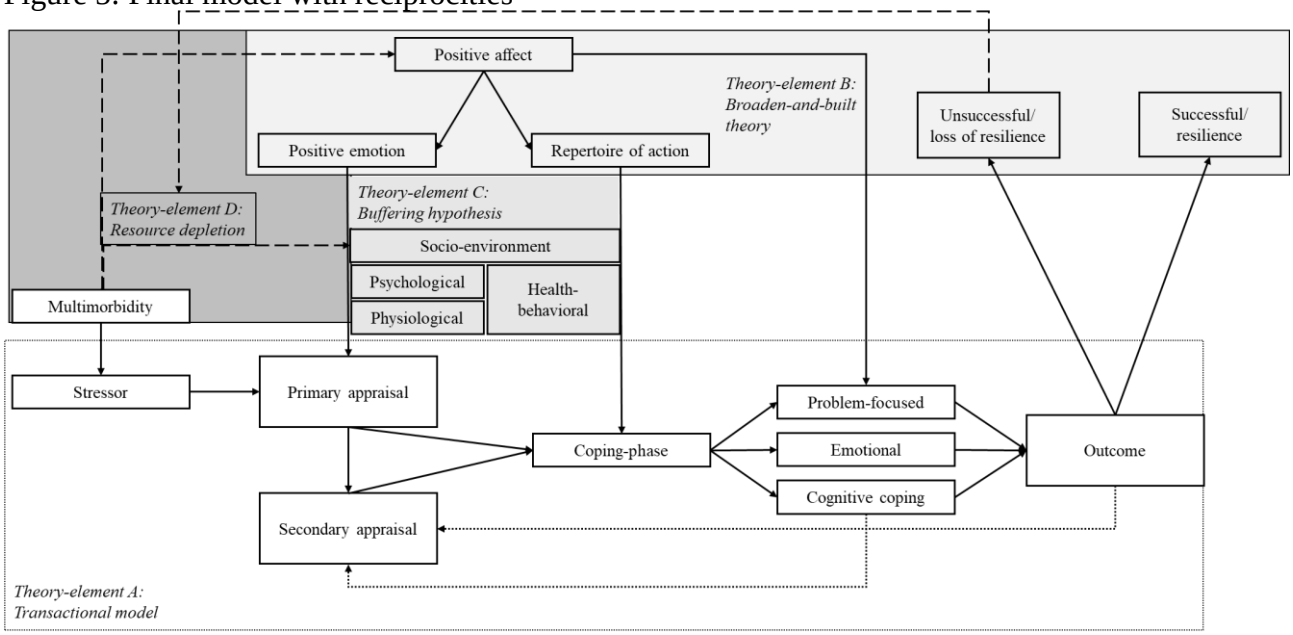
Unfortunately, these resources are depletable, as the concept of Baumeister et al. (1998) ego-depletion suggests. Ego-depletion refers to the state where resources are diminished and, thus, the tasks cannot be fulfilled. Coping with chronic diseases requires self-regulatory energy. The deposits for these self-regulatory energies are, however, depletable. Primarily positive affect has been found to be the key mediator for maintaining self-efficacy. In a series of experiments, Tice et al. (2007), and Zhu et al. (2017) have shown that positive affect is a replenishment resource for the regulatory self. Additionally, empirical longitudinal analyses indicate a decrease in positive affect after experiencing declines in physical health (Gana et al., 2016; Wahl et al., 2014). Moskowitz et al. (2012) have argued that a loss or depletion of positive affect is plausible, especially in persistent distress. Similarly, the impact of chronic disease on personality traits is well elaborated. Jokela et al. (2014) have indicated a decrease in extraversion after the onset of chronic conditions, which Lewinsohn (1974) described as mechanisms for depressive spirals.

In summary, theory-element D is based on the mechanisms of depressive spirals described by Lewinsohn (1974), which are complemented by the ego-depletion theory of Baumeister et al.

(1998) and the concept of rumination of Nolen-Hoeksema et al. (2008). Theory-element D highlights the importance of social support and positive affect in multimorbidity because these resources intervene in the mechanisms for the onset of a depressive spiral. Especially positive affect must be reconsidered concerning its depletability due to the consistent stressor exposure in multimorbidity.

To acknowledge theory-element D in Figure 5, the resource depletion is embedded in the dark-grey area, from multimorbidity to the socio-environment and positive affect. The dashed lines depict the reciprocal paths that cover the potential onset of a depressive spiral. Such a spiral could operate through the following pathways: (1) multimorbidity depleting positive affect (top left path to positive affect), (2) which then increases stressor exposition and (3) disadvantageous coping. Finally, causing an unsuccessful coping outcome (4), which then results in resilience loss, (5) thus fostering recourse depletion (dashed path from unsuccessful/ loss of resilience to theory-element D).

Figure 5: Final model with reciprocities



Note: Dotted-box equals adjusted transactional model; Dashed-box equals adjusted broaden-and-built theory. Background colours: white: theory-element A; light-grey: theory-element B; gray; theory-element C; dark-grey: theory-element D. Dashed-paths potential feedback-paths depending on outcome/success of coping process can lead to depressive spirals.

The added feedback loops further highlight the importance of the individual (positive affect) and socio-environmental resources (social support) in the ongoing coping process for

multimorbid individuals. Or, to put in other words, theory-element D highlights that managing resources with regard to accumulation, maintenance, and depletion (Hobfoll, 1989; Pfaff et al., 2011), is crucial for the long-term success of coping and the prevention of a depressive spiral, especially for multimorbid individuals.

Consequently, the research hypothesis associated with theory-element D investigates the onset and prevention of a depressive spiral in individuals suffering from multimorbidity.

H4: Does prolonged duration to multimorbidity increase the risk of a depressive spiral?

Still, the processes underlying theory-element D are time-consuming, meaning they must be observed longitudinally and dynamically, requiring sophisticated methodological approaches, which I will point out in Section 3 in depth.

2.6 Summary and implications of theory-elements A-D

This thesis aims to identify and quantify the processes through which multimorbidity deteriorates mental health. With this aim, three initial research questions were linked: (1) How does multimorbidity cause mental health deterioration? (2) How are these deteriorations modified? (3) How do the reciprocities function between multimorbidity and mental health? These three questions were depicted as the main paths of analysis in Figure 1, and the task of the theoretical framework was to address these three questions.

The transactional model, theory-element A, was applied to address the first question. The transactional model attributes the impact of multimorbidity on mental health to stress. In this regard, multimorbidity is a stressor that requires coping. The coping-process and the involved phases are pointed out in Figure 2. Although the transactional model helped to understand mental health deterioration due to stress in multimorbidity, detailing the modification; thus, addressing the second question was not achieved.

For this purpose, theory-element B was introduced, the broaden-and-built theory, which emphasized the importance of positive emotions for primary and secondary appraisal in the transactional model. Additionally, within theory-element B, positive affect was identified as the key individual resource for coping. Positive affect maintains and increases the experience of positive emotions and increases the likelihood of problem-focused coping, the creation of positive events, and thus, modifying the deterioration of mental health by increasing the chances for successful coping in the transactional model. Figure 3 added positive affect as the key individual resource for coping due to its impact on the primary appraisal and the coping-phase. However, there are some limitations to the broaden-and-built theory; the term hedonic treadmill refers to the scenario where positive emotions are aimed solely to experience positive emotions and, therefore, could lead to unsuccessful coping and even more stress. Yet, research has found positive affect to consistently be protective for mental health.

Another modifier of the multimorbidity - mental health deterioration was introduced with theory-element C, the buffering hypothesis. The buffering hypothesis considered the interindividual resources or the socio-environment. The socio-environment's impact on mental health is realized through health-behavioral, psychological, and physiological pathways. In this context, section 2.4.1 highlighted social support as a major resource for buffering the stress effect, which can be experienced as emotional (perceived) and tangible (received) social support, meaning that it can either act through psychological and physiological or through health-behavioral pathways. It should be noted that there are scenarios in which social support might reversely cause additional stress instead of preventing or modifying the impact of stress positively. The esteem-threat or the inequity hypothesis brought up these concerns. Yet, these scenarios are confounded mainly by personality traits such as neuroticism.

In theory-element D, the role of coping resources, positive affect, and social support, are contextualized within the reciprocities of multimorbidity and mental health and the potential onset of depressive spirals. Hence, theory-element D addresses the initial research question 3. On the one hand, positive affect and social support prevent the onset of a depressive spiral. On the other hand, the absence of positive affect and social support facilitates the onset of a depressive spiral in multimorbidity. Regarding the ego-depletion theory and positive affect, it can further be argued that positive affect as a resource is depletable through exposition to multimorbidity. However, the depletability and salience of positive affect in the coping process highlight the hazards of a depressive spiral in multimorbidity.

To summarize the key implication of the theoretical framework consisting of elements A to D, Table 1 gives a brief overview of the key points of each theory-element, its implication for mental health and multimorbidity, and the associated research questions of this thesis, as well as potential caveats.

Table 1: Summary and implications of theory-elements A-D

Content	Theory-elements			
	A	B	C	D
Theories & authors	• Transactional model (Lazarus & Folkman, 1984).	• Broaden-and-built theory (Fredrickson, 2001, 2004). • Positive affect (Ashby et al., 1999; Cohen & Pressman, 2006; Moskowitz et al., 2012; Pressman et al., 2019).	• Buffering hypothesis (Berkman et al., 2000; Cohen & Wills, 1985). • Social support (Barrera, 1986; Cohen & Wills, 1985; Thoits, 2011).	• Depressive spiral (Lewinsohn, 1974). • Rumination (Nolen-Hoeksema, 1991; Nolen-Hoeksema et al., 2008). • Ego-depletion (Baumeister et al., 1998; Tice et al., 2007).
Multimorbidity	• Multimorbidity is a stressor that requires coping.	• The impact of multimorbidity can be lowered by positive affect.	• The effect of multimorbidity can be buffered by social support.	• Multimorbidity promotes the onset of a depressive spiral due to persistent stressor exposition and successive decline in physical health.
Mental health	• Successful coping requires resources and an adequate choice of coping strategies. • Unsuccessful coping deteriorates mental health.	• Positive affect increases the repertoire of actions, thus promoting successful coping strategies. • Positive affect provides experiencing positive emotions and reduces the appraisal of stressors.	• Psychological and physiological pathways reduce stressor appraisal. • Health-behavioral pathways can provide adequate coping strategies (e.g., problem-focused).	• Social support and positive affect intervene in the mechanisms for a depressive spiral. • The absence of both resources promotes depressive spirals. • Multimorbidity can deplete positive affect; depletion can lead to rumination and the onset of a depressive spiral.
Research hypothesis	H1: Does multimorbidity deteriorates mental health?	H2: Does positive affect prevent deterioration of mental health?	H3: Does social support buffer multimorbidity's deterioration of mental health?	H4: Does prolonged duration of multimorbidity increase the risk of a depressive spiral?
Caveats	• A general overview of the stress-coping process does not consider individual pathways and resource utilization in coping.	• Hedonic treadmill: Relying solely on positive emotions might cause unsuccessful or adverse coping outcomes.	• Alternatives to buffering hypothesis (e.g., the esteem-threat hypothesis) indicate social support could potentially cause additional stress.	• Observation of depressive spiral requires longitudinal data of highly dynamic and individual processes.

3. Methods

3.1 Empirical translation of the causal model: directed acyclic graphs (DAGs)

The following section will translate the final causal model of Figure 5 into an empirical, testable graphical model. For this purpose, the directed acyclic graph (DAGs) framework of Pearl (1995) will be applied. The general idea of the DAGs is to use a universal notation to identify causal effects under a set of testable implications. Using DAGs to transparently illustrate a testable causal model has become a standard practice in epidemiology. The identification of causal effects with DAGs requires the fulfillment of specific criteria. Most importantly, these are the notation rules and the causal effect identification criteria (Pearl, 1995). In the following section, I will briefly note the notation rules and identification criteria, a comprehensive introduction to DAGs cannot be given within the frame of this thesis but can be found in Elwert (2013), Elwert and Winship (2014), and Pearl (2014).

Following Pearl (1995), the notation rules can be summarized in the following way:

1. The causal path is the path through which an exposure variable X impacts an outcome variable Y and can be noted as X → Y.
2. X is then the antecedent variable that impacts the descendent variable Y with a directed arrow →.
3. No cyclical logic, the DAG must be acyclic, all arrows/causal paths must point in only one direction, either ← or →.

The causal effect identification criteria are:

4. The backdoor criterion: also known as the ignorability condition (P. R. Rosenbaum & Rubin, 1983): states that all variables that affect the causal path (X → Y) are conditioned on; thereby, the non-causal paths, e.g., X ← Z → Y, are blocked. The backdoor criterion is also often referred to as confounding variables but is not restricted to confounding variables alone (Pearl & Paz, 2014). The statistical phenomenon corresponding to the backdoor criterion is that of unobserved heterogeneity.
5. The front-door criterion: this criterion states that conditioning on a descendent variable (Z) that lays on the causal (X → Z → Y); induces bias and must therefore not be

conditioned. The corresponding statistical phenomenon is over-control or endogenous selection bias (Elwert & Winship, 2014; Pearl, 2009).

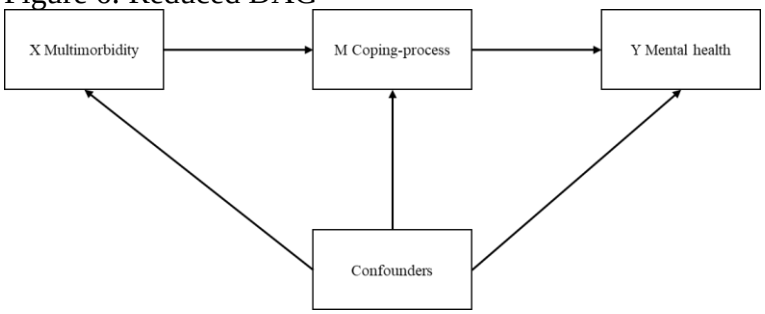
6. The collider criterion: this criterion defines variables where two arrows collide, e.g., X → Z ← Y, as collider variable. Conditioning for collider variables induces bias and could potentially open additional backdoor paths (Greenland et al., 1999). The statistical phenomenon resulting from violating the collider criterion would be the endogenous selection bias (Elwert & Winship, 2014).
7. Identification of the minimal sufficient condition sets: The sets of variables that are conditioned for in the DAG should be parsimonious, meaning that all backdoor paths must be closed and no additional variables should be conditioned. The reason for this criterion is apparent since with every additional variable conditioned, the risk of conditioning on a collider variable or violating the front-door criterion increased.

When applying these rules and criteria of DAGs to the causal model of Figure 5, the DAG must impose the following changes:

1. Definition of antecedent and descendent variables. Multimorbidity is the main exposure variable X; mental health is the outcome variable Y. The variables in the coping process are descendent variables of multimorbidity.
2. Removal of the cyclical paths between multimorbidity and mental health;
3. Closing all backdoor paths (backdoor criterion) equals the observation and conditioning of all necessary confounders.
4. Identification of all relevant frontdoor-paths (frontdoor-criterion).
5. Reduction to the minimum set of testable implications required for the identification of the causal effects. In particular:
    a. No conditioning of any descendent variable that lays on the causal path that is not of interest for the causal effect (frontdoor-criterion).
    b. No collider conditioning, which could open closed backdoor-paths.

Figure 6 illustrates the according translation to a DAG of Figure 5

Figure 6: Reduced DAG



Here, the frontdoor-path runs from X → M to → Y and the backdoor-paths must be closed by conditioning the confounders C. The DAG of Figure 6 has two main limitations. First, the reduced cooping-process M is not identifiable because conditioning on M equals the conditioning on a descendent variable, thus violating the frontdoor-criterion. Second, Figure 6 does not differentiate the coping-process because inclusion and conditioning on the single elements in the coping phase (e.g., primary appraisal, secondary appraisal, coping-phase) of Figure 5, would also equal the conditioning on descendent variables on the frontdoor-path; hence, violation of the frontdoor-criterion.

However, to still test the theory-elements B-D within theory element A, the separation of the DAG along the two key factors of the coping-process is possible through opening up an additional frontdoor-path and, in doing so, defining two mediation models.

Figure 7a&b: Positive affect and social support as mediators

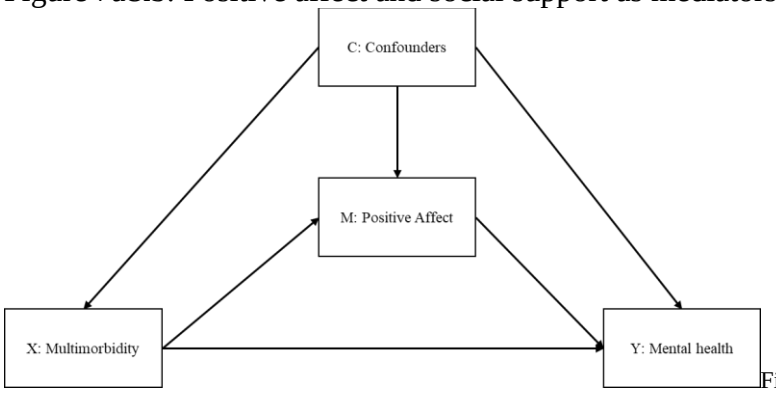


Figure 7a

Note: Confounders under C: must at be either X-Y, X-M; M-Y or a mixture of those.

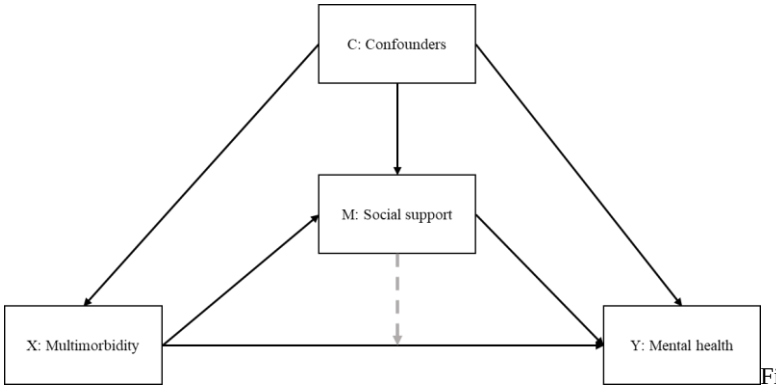


Figure 7b

Note: Confounders under C: must at be either X-Y, X-M; M-Y or a mixture of those. Dashed path from M: Social support on the X→Y path symbolizes moderation hypothesis.

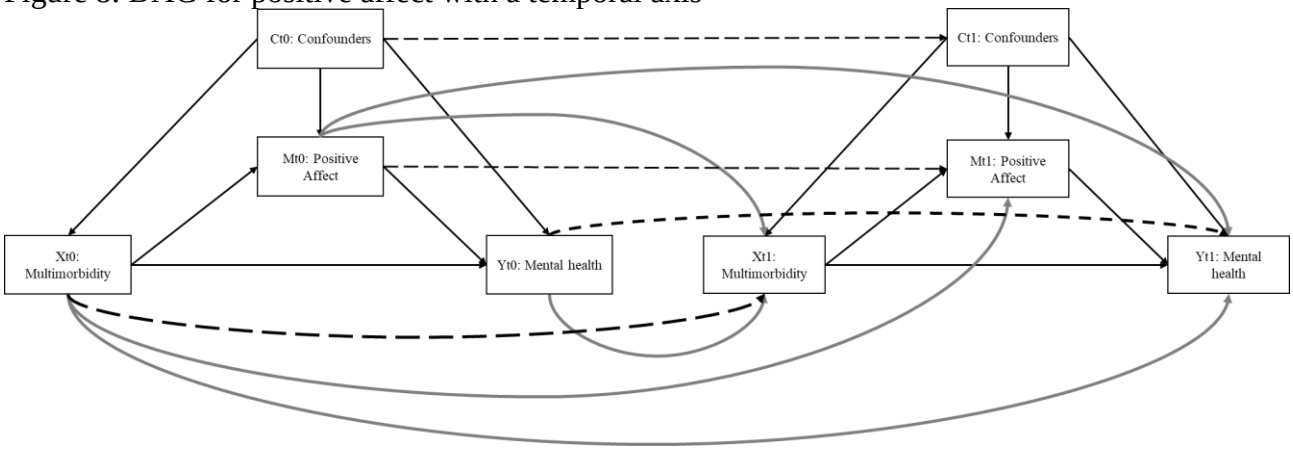
Figure 7ab depicts simple mediation models as DAGs, where the coping-process is sought to be partially captured with each key factor for coping with stress. In Figure 7b a dashed path from social support on the path of multimorbidity to mental health is also added to depict the moderation hypothesis discussed in section 2.4.3.

However, it is important to note that adding descendants of the mediators, such as the coping strategy (e.g., emotional coping) would again equal the conditioning of a descendant variable of the frontdoor-path; thus, causing violation of the frontdoor criterion; however, with separation of the frontdoor-paths into a direct (X → Y) and indirect path (X → M → Y) the identification of these two causal paths is possible; and further the identification modification of the key coping resources.

Although Figure 7a&b allow the causal effect identification of multimorbidity on mental health and the mediation through positive affect as well as social support, the reciprocities are yet to be considered in the DAG. The main issue with the reciprocities is that DAGs must be acyclic,

but reciprocities imply a form of cyclicity. To still account for reciprocities or feedback processes in DAGs, the DAG requires the addition of a temporal axis. The temporal axis can be denoted as t0/t1 for the observation of a variable at each point in time. In Figure 8, the temporal axis is added for positive affect as a mediator. The dashed arrows between the same variables in t0 and t1 indicate the autoregression between the same variables, for instance, stating that the multimorbidity status at t0 predicts the multimorbidity status at t1. The curved grey arrows highlight the reciprocity between the different variables, for example, between positive affect at t0 and multimorbidity status at t1. Adding these arrows allows the incorporation of reciprocities without violating the acyclicity criterion.

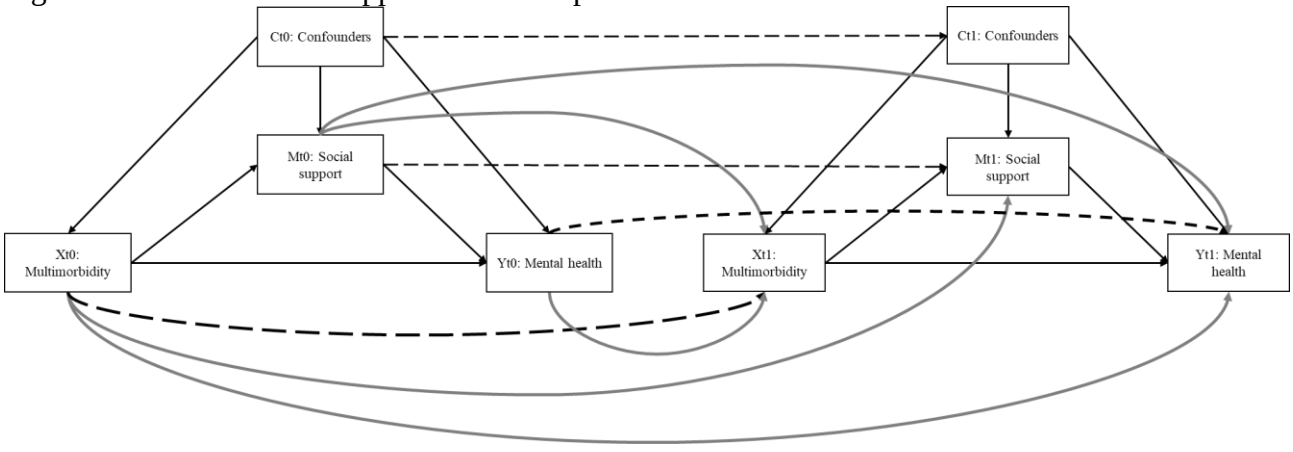
Figure 8: DAG for positive affect with a temporal axis



Note: Dashed paths = autoregressive, gray paths = lagged, bolt paths = cross-sectional

Similar to the DAG in Figure 8, the DAG in Figure 9 adds social support as the mediator of the coping-process.

Figure 9: DAG for social support with a temporal axis



Note: Dashed paths = autoregressive, gray paths = lagged, bolt paths = cross-sectional. Moderation hypothesize omitted.

However, the DAGs in Figure 8 and Figure 9 are still only rough depictions for causal mediation analysis. Although the exposure-outcome confounders, e.g., Xt0 ← Ct0 → Yt0, between multimorbidity and mental health, should be the same for the DAGs in Figure 8 and Figure 9, the mediator–outcome confounders, e.g., Mt0 ← Ct0 → Yt0, and the exposure – mediator confounders, e.g., Xt0 ← Ct0 → Mt0, could be different variables between the DAGs. Such aspects are detailed further in the associated publications of this thesis (Demirer et al., 2022; Demirer, Bethge, et al., 2021).

Moreover, adding the temporal axis also illustrates the increased complexities investigators must face when investigating reciprocal processes, especially in the settings of causal mediation analysis. For this purpose, the next section will briefly cover the statistical methods for applying causal, longitudinal mediation analysis.

3.2 Mediation analysis

Figure 7a&b highlighted that positive affect and social support are intermediates in the coping process. Analysis of intermediate variables has a long tradition in social science and psychology. Baron and Kenny (1986) provided the most prominent attempt at analysis of a "third" intermediate variable in their article titling "The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations". The general strategy to identify mediation is by calculating three different effects. A total effect (TE) that is decomposable into a direct effect (DE) and an indirect effect (IE). To obtain these effects there are different methods, mainly originating from the product and difference method. A detailed explanation of these methods and their conceptual and statistical differences are given elsewhere (VanderWeele, 2015). The logic of dividing the TE into DE and IE represents the argument that a proportion of the effect between treatment (multimorbidity) and outcome (mental health) is transmitted directly (DE) and indirectly (IE) through the mediator(s) (positive affect; social support). Baron and Kenny (1986) proposed the four step-procedure for statistically testing the presence of mediation. These steps require a

correlation between treatment and outcome (Step 1), a correlation between treatment and mediator (Step 2), a correlation between mediator and outcome while still controlling for the treatment on the outcome (Step 3), and finally, the correlation of Step 1 must be changed partially or entirely after controlling for the mediator in Step 3.

However, this strictly parametric approach to identifying has been the objective of criticism in the last decades (Hayes, 2009; VanderWeele et al., 2014; VanderWeele & Vansteelandt, 2009). Especially Step 1 and 4 are, under certain scenarios, parametrically invalid (VanderWeele et al., 2014). More importantly, the recently pointed out non-parametric assumptions provide a more general framework for identifying mediation. These non-parametric assumptions are also known as the "unconfoundedness assumptions" (Pearl, 2014) or "sequential ignorability" (Imai et al., 2010). These assumptions require adjustment (conditioning in terms of DAGs) of the common causes between treatment, mediator, and outcome. In detail, these assumptions are:

1. No unobserved treatment outcome confounding
2. No unobserved treatment mediator confounding
3. No unobserved mediator outcome confounding
4. No mediator outcome confounder that is affected by the treatment, regardless of the observability of such confounders

These assumptions hold irrespective of the parametrical model, e.g., logistic regression or generalized linear models. Details on the mathematical proofs of the non-parametrical assumption as well as practical application have been pointed out by VanderWeele (2015).

3.3 Longitudinal mediation analysis

There are three main motivations for identifying longitudinal mediation in the context of multimorbidity and mental health. First, the stressor (multimorbidity) persists and affects the outcome (mental health) continuously; therefore, the longitudinal process is of primary interest. Second, the depletion of the individual resource (positive affect) and the socio-environmental resource (social support) can only be registered by longitudinal analyses (theory-element D). Third, mediation analysis can provide practical implications for the potency of healthcare interventions. Especially in the case of multimorbidity and mental health, where the stressor itself is not solvable, targeting intermediates is required. Mediation analysis can provide a clear-cut policy implication on to what extent intervening on the intermediate can cause a reduction of mental health deterioration.

Since the aim of mediation analysis is to identify the contribution of the intermediate, the mediator (IE), to an association, mediation analysis is inherently longitudinal. In the last decade, numerous methods evolved to estimate longitudinal mediation, reflecting the importance of temporal order in mediation. Generally, it is assumed that the exposure (or treatment) must precede the mediator and the mediator the outcome (Gollob & Reichardt, 1987; Granger, 1969). However, identifying a particular temporal causal order is not trivial and has been an issue of causal thinking since its beginnings (e.g., the question of chicken or egg?). The term "granger causality" (Granger, 1969) captures this issue, and concerning mediation, this issue inflates (Maxwell & Cole, 2007).

Another main challenge of longitudinal mediation analysis is that of time-varying confounding, which can, in the same cases, lead to violation of assumption 4 through treatment-induced mediator outcome confounding (VanderWeele & Tchetgen Tchetgen, 2017). Both can only be partially captured by traditional methods such as structural equation modeling (SEM) or other traditional approaches such as fixed-effect regressions (Newsom, 2015).

Even in scenarios where time-varying confounding can be mostly eliminated, e.g., in a randomized controlled trial with a clinical setting, treatment-induced mediator outcome confounding can still be present. The DAGs in Figure 8 and Figure 9 further illustrate that with the inclusion of the time frame, assumption 4 is violated. For example, the directed path from multimorbidity at t0 points to positive affect at t0 and from positive affect at t0 to positive affect at t1 (autoregressive), and the path from positive affect at t1 to mental health in t1, shows that positive affect at t0 is a confounder of the effect of positive affect t1 on mental health in t1 that is induced (affected) by the treatment (multimorbidity) at t0. In such a scenario, the treatment-induced mediator outcome confounding assumption (assumption 4) is violated. Likewise, the violation of the assumption also applies to social support since a similar process is assumed.

In this thesis, I will present a parametric method to perform longitudinal mediation analysis and a non-parametrical method. Both methods have been developed and applied within the context of mediation just recently (Euteneuer et al., 2021; Newsom, 2015). These methods identify indirect effects (mediations) in a longitudinal process. The first method is a cross-lagged-panel model design (Newsom, 2015), extended to the context of mediation. This method explicitly tries to solve the issue of "granger causality" by including cross-lagged paths (see also: Demirer, Bethge, et al., 2021).

The second model is a more sophisticated method, which uses inverse-probability weighting within the mediational g-formula (VanderWeele & Tchetgen Tchetgen, 2017) to adjust for time-varying confounding and treatment-induced mediator outcome confounding, as well as for the longitudinal process itself. This method solves the inherent violation of assumption 4 in longitudinal mediations.

3.3.1 Cross-lagged-panel-model

SEMs have wide usage in social sciences and psychology. SEM's general idea is empirically testing a theoretical structure through multiple directed multivariate regressions. A vast amount of literature is available for explanations in SEM, and it will not be detailed further in this thesis (e.g., Bollen, 1987, 2006; Newsom, 2015). Cross-lagged panel models (CLPM) are a subset of SEM. CLPM aims to "(…) investigate the causal direction of the relation between two variables over time" (Newsom, 2015, p. 122); thus, CLPM allows for addressing the question of cause or effect in a longitudinal setting (Granger causality). To identify cause or effect, the SEM requires a particular structure, which consists of at least four elements:

1. The measurements: measurements can be latent or manifest and should be measured repeatedly over time.
2. The autoregressive paths: they account for the previous state of a measurement predicting the current state of a measurement
3. The bidirectional (co-varying) paths: bidirectional paths are a core element for CLPM because they statistically account for assuming no directions of the associations at a cross-sectional level through shared variances.
4. The cross-lagged paths: The cross-lagged paths are another core element of CLPM. They define the model's core structure and depend on the given time span. Cross-lagged paths cannot be linked cross-sectionally.

3.3.2 Applied cross-lagged-panel-model for social support

To investigate the buffering mediation by social support, I applied the CLPM for mediation in publication 1 of this thesis (Demirer, Bethge, et al., 2021). There are three reasons for using this particular method for social support's assumed mediation. First the granger causality between social support and mental wellbeing in multimorbidity. As described, the CLPM for mediation allows the identification of the causal direction in the temporal process through the integration of bidirectional and cross-lagged paths. Therefore, I could determine whether social support affects mental wellbeing, or mental wellbeing affects social support beforehand. The second reason is the flexibility of the SEM framework utilized by the CLPM, which allows the calculation and specification of various mediation models. As such, publication 1 also provided a synchronous effect model, where the CLPM assumptions are relaxed (see: Demirer, Bethge, et al., 2021, p. 5, Fig.3). The third reason is somewhat of practical nature. CLPM and SEM for mediation are widely applied and accepted across various disciplines.

The statistical calculation of the direct and indirect effects is straightforward in CLPM with mediation. The general logic is to consider all paths as products starting from multimorbidity at t0 and ending at mental wellbeing at t2. The direct paths do not run through the mediator, whereas the indirect paths are those that at least run once through the mediator. Depending on the length of the process, these effects can be calculated for specific years or all years. The minimum for a CLPM with mediation is at least three time periods (t0, t1, t2) but can be shortened to two time periods (t0, t1) in some cases with additional assumptions (Newsom, 2015). Below I show the equation for the overall effects.

Equation 1: Decomposition of the total in direct and indirect effect

$$\mathbf{OTE = ODE + OIE = [c_1 * d_1] + [a_1 * b_2]}$$

Where the overall total effect (OTE) can be decomposed into the overall direct effect (ODE) and the overall indirect effect (OIE). The ODE is the product of the direct effect of multimorbidity at t0 on mental health at t1 ($\mathbf{c_1}$) and the autoregressive effect of mental health

at t1 on mental health at t2 ($\mathbf{d_1}$). The OIE is the product of the effects of multimorbidity at t0 on social support at t1 ($\mathbf{a_1}$) and social support at t1 on mental health at t2 ($\mathbf{b_2}$). Note that a clear-cut lag of one time period between the effects is a necessity for the CLPM, which allows for differentiating on temporal order and Granger causality. However, the temporal lag also imposes a relatively restrictive structure on the phenomenon. The assumed temporal order of the causal process is critical because it defines the process (Gollob & Reichardt, 1987). Yet, CLPM models with mediation can hardly account for the presence of a treatment-mediator interaction (or moderated mediation) (MacKinnon et al., 2020; VanderWeele & Tchetgen Tchetgen, 2017). In the case of multimorbidity, social support, and mental wellbeing, moderated mediation would mean that the importance of social support as a buffering resource is different across the levels (severity and or duration) of multimorbidity, which is also in line with the mobilization hypothesis (Barrera, 1986). MacKinnon et al. (2020) recently suggested a moderated mediation (XM-interaction) should standardly be tested before the mediation model.

To account for moderated mediation and a possible more immediate causal process, my analysis tested for moderated mediation before applying the CLPM mediation model. Moreover, I also presented a synchronous mediation model (Demirer, Bethge, et al., 2021), which allows for different cross-sectional mediation processes to take place, thus, relaxing the assumption of the CLPM.

However, CLPM with mediation remains a parametrical approach and does not adequately account for treatment-induced mediator outcome time-varying confounding (assumption 4) (VanderWeele & Tchetgen Tchetgen, 2017). Therefore, in the next section, I will demonstrate a non-parametrical approach to longitudinal mediation initially presented by VanderWeele and Tchetgen Tchetgen (2017).

3.3.4 The mediational g-formula

As mentioned in Section 3.2, there are four unconfoundedness assumptions or sequential ignorability assumptions, and the longitudinal mediation process inherently violates assumption 4, the no treatment-induced mediator outcome confounding.

VanderWeele and Tchetgen Tchetgen (2017) presented a solution to these issues within the counterfactual analysis (also potential outcome framework). Counterfactual analysis has the benefit that it is a non-parametrical approach for identifying causal effects. The classic counterfactual approach to mediation aims at the identification of "natural" indirect (NIE) and direct effects (NDE). The term "natural" refers to the value the mediator, here positive affect, would have taken, given a counterfactual value of multimorbidity (Demirer et al., 2022). The conceivable (counterfactual) levels of exposure and mediator can be noted as $X = x$, $M = m$ and $X = x^*$ $M = m^*$. Thus, the value of Y that would have been observed if multimorbidity-status would have been $X = x$ (multimorbid) and positive affect $M =$ m (high level of positive affect) notes as Y_{xm}. The total effect (TE) can then again be calculated as the sum of NDE and NIE, as denoted in Equation 2.

Equation 2: Standard counterfactual approach to mediation analysis

$$TE = NIE + NDE = E\left(Y_{xM_x} - Y_{xM_{x^*}}\right) + E\left(Y_{xM_{x^*}} - Y_{x^*M_{x^*}}\right)$$

However, in Equation 2, no temporal axis is added, meaning that all variables are only measured cross-sectionally. As shown in Figure 8, adding the temporal axis with the measurement would lead to an inherent violation of assumption 4.

VanderWeele and Tchetgen Tchetgen (2017) proposed the mediational g-formula to solve the violation of assumption 4. In principle, their method cancels this confounding out through multiple sets of inverse-probability weights (IPWs). They do not estimate “natural” effects but “interventional analogues” of these effects. The logic of the interventional analogs is to fix the mediator (intervene) to a level randomly drawn from the distribution of the mediator at a given point in time (M_{ti}). Simultaneously, the mediator distribution is fixed, conditional to the given

treatment and confounder levels. In this way, the treatment-induced mediator outcome confounding is removed (for detailed mathematical proof, see:VanderWeele & Tchetgen Tchetgen, 2017, pp. 920–923).

Applied to longitudinal mediational analysis, the random draw of M_{ti} for the entire history vector of M_t, noted as $\overrightarrow{G}$Which is the basis for effect estimation. Similarly, $\overrightarrow{X}$is the history vector of X_t, and v is the vector of confounding variables. As expressed in Figure 8, previous values, e.g. $M_{t(i-1)}$, are included as a subset of confounding variables as well under v at M_{ti}. Again, interventional overall effect (IOE), indirect effect (IIE), and direct effect (IDE) are computable and decomposable. Variations and reductions of this formula are also applicable.

Equation 3: Decomposition of the interventional overall effect based on VanderWeele & Tchetgen Techetgen (2017, pp. 921-922)

$$\mathrm{IOE} = \mathrm{IIE} + \mathrm{IDE} = \mathrm{E}\left(Y_{\overrightarrow{x}\overrightarrow{G}_{\overrightarrow{x}|v}(t)}|v\right) - \mathrm{E}\left(Y_{\overrightarrow{x^*}G_{\overrightarrow{x^*}|v}}|v\right)$$

$$= \left\{\mathrm{E}\left(Y_{\overrightarrow{x}\overrightarrow{G}_{\overrightarrow{x}|v}}|v\right) - \mathrm{E}\left(Y_{\overrightarrow{x}\overrightarrow{G}_{\overrightarrow{x^*}|v}}|v\right)\right\} + \left\{\mathrm{E}\left(Y_{\overrightarrow{x}\overrightarrow{G}_{\overrightarrow{x^*}|v}}|v\right) - \mathrm{E}\left(Y_{\overrightarrow{x^*}\overrightarrow{G}_{\overrightarrow{x^*}|v}}|v\right)\right\}$$

The difference between natural effects is further expressed in interpreting the interventional effects. The interpretation of the natural effects would entail the differences in positive affect if the individual were not multimorbid. Due to the predominantly incurable character of multimorbidity, this interpretation seems unreasonable. In contrast, the interventional effects provide an analysis based on the difference in depressive symptoms if the positive affects' distribution would have been the same (intervened), irrespective of multimorbidity status. Thus, the interpretation of the interventional effects is of more practical relevance for this thesis because it displays the effect of a potential intervention on positive affect on the mental health of multimorbid individuals.

3.3.5 Applied mediational g-formula for positive affect

In the following, I will briefly cover the motivations for applying the mediational g-formula to evaluate positive affect as an intermediate. In detail, I will cover how the mediational g-formula allows accounting for theory-element A, B, and D. In the next step, the parametric application of the mediational g-formula will be demonstrated based on the formula given in publication 2 of this thesis (Demirer et al., 2022).

The CLPM applied in publication 1 and the mediational g-formula applied in publication 2 both considered multimorbidity as a stressor (theory-element A). Therefore, in publication 2, multimorbidity is, again, the exposure (X). Theory-element B argued that positive affect is the key individual resource for coping with stress (multimorbidity). However, theory-element B, in combination with theory-element D, also examined the depletion of positive affect due to persistent exposure to stress, which can even end in a depressive-spiral. In publication 2, this depletion process of positive affect modifies the assumed mediation process and, therefore, the methodological translation. More precisely, the mediation method requires accounting for A) the longitudinal mediation process and B) the interaction between multimorbidity and positive affect in mediation (XM-interaction). XM-interaction, often synonymously referred to as moderated mediation. Unlike the moderation hypothesis of social support, XM-interaction is not a competing hypothesis to mediation, but a supplementary. XM-interaction means that the mediated effect is different for the duration of multimorbidity (X) and the level of positive affect (M) (MacKinnon et al., 2020). Allowing for XM-interactions accounts for the implications of theory-element D, which means that the longer the duration of multimorbidity is, the lower positive affect will get (ego-/resource-depletion); hence, the more severe mental health deterioration.

The mediational g-formula procedure itself aims to obtain the interventional indirect effect (IIE) and the interventional direct effect (IDE), which means the indirect effect of multimorbidity on mental health that is transmitted or altered by positive affect (IIE) and the direct of

multimorbidity on mental health. These are obtained through the calculation of two marginal structural models (MSM), one for the outcome model and one for the mediator model, both weighted by their own set of IPWs. From these two models, the effect estimates can be multiplied to obtain the IIE and the IDE. The order of the required steps is, therefore, straightforward:

1. Calculation of outcome model IPW
2. Calculation of the mediator model IPW
3. Estimate effects in an outcome MSM
4. Estimate effects in a mediator MSM
5. Calculation of cross-model coefficient products to obtain IIE and IDE.

In this section, all equations for the calculation of the outcome model IPW are taken from my publication Demirer et al. (2022), which are based on VanderWeele and Tchetgen Tchetgen (2017)

Equation 4: IPW calculation for Outcome Model

$$\widehat{\mathrm{P}}\{\mathrm{M(t)}|\,\overrightarrow{\mathrm{X}}(\mathrm{t}),\overrightarrow{\mathrm{M}}(\mathrm{t}-1)\}\,\widehat{\mathrm{P}}\{\mathrm{X(t)}|\,\overrightarrow{\mathrm{X}}(\mathrm{t}-1),\overrightarrow{\mathrm{M}}(\mathrm{t}-1)\}\,/$$

$$[\widehat{\mathrm{P}}\{\mathrm{M(t)}\mid\overrightarrow{\mathrm{X}}(\mathrm{t}),\overrightarrow{\mathrm{M}}(\mathrm{t}-1),\overrightarrow{\mathrm{D}}(\mathrm{t}-1),\mathrm{V}\}\,\widehat{\mathrm{P}}\{\mathrm{X(t)}\mid\overrightarrow{\mathrm{X}}(\mathrm{t}-1),\overrightarrow{\mathrm{M}}(\mathrm{t}-1),\overrightarrow{\mathrm{D}}(\mathrm{t}-1),\mathrm{V}\}]$$

This formula estimates the probability of being multimorbid (treatment) at each time point $\overrightarrow{\mathrm{X}}(\mathrm{t})$ and the probability for the level of positive affect (mediator) at each time point $\mathrm{M(t)}$ based on the previous statuses/levels $\overrightarrow{\mathrm{X}}(\mathrm{t}-1),\overrightarrow{\mathrm{M}}(\mathrm{t}-1)$. In the denominator, the time-constant confounders V and time varying-confounders $\overrightarrow{\mathrm{D}}(\mathrm{t}-1)$ are also considered. In this way, a stabilized IPW is obtained (Robins et al., 2000).

The second IPW is calculated for the mediator MSM. This IPW accounts for the probability of being multimorbid at a given time point $\widehat{\mathrm{P}}\{\mathrm{X(t)}|\ldots$ dependent on the prior levels of positive affect $\overrightarrow{\mathrm{M}}(\mathrm{t}-1)$ and multimorbidity $\overrightarrow{\mathrm{X}}(\mathrm{t}-1)$. Similarly, the time-constant confounders V and time-varying confounders $\overrightarrow{\mathrm{D}}(\mathrm{t}-1)$ are placed in the denominator. Different from Equation 4

is that in Equation 5 only the denominator adjusts for the prior levels of positive affect $\overrightarrow{M}(t-1)$.

Equation 5: IPW calculation for Mediator Model

$$\widehat{P}\{X(t)|\,\overrightarrow{X}(t-1)\} \,/\, \widehat{P}\{X(t)|\,\overrightarrow{X}(t-1), \overrightarrow{M}(t-1), \overrightarrow{D}(t-1), V\}$$

A last step, optional step is to truncate the IPWs. This is recommended by Cole and Hernán (2008) when weighting for non-binary measurements or when some combination or changes are rarely observable. Truncation caps the range of the IPW to the 99th and 1th percentile observation. Truncation has also been applied in my publication Demirer et al. (2022) because transitions from multimorbidity to non-multimorbid occur in extremely rare cases.

Steps 3 and 4 are given in Equation 4 and Equation 5. The outcome MSM is shown in Equation 6.

Equation 6:Coefficients from Outcome MSM

$$E(Y_{\overrightarrow{xm}}) = \Delta_0 + \Delta_1 \mathrm{cum}(\overrightarrow{x}) + \Delta_2 \mathrm{cum}(\overrightarrow{m})$$

Equation 6 is straightforward; it shows an intercept Δ_0 a cumulative effect of multimorbidity $\Delta_1 \mathrm{cum}(\overrightarrow{x})$ and the cumulative effect of positive affect $\Delta_2 \mathrm{cum}(\overrightarrow{m})$ on mental health. This outcome model is a simple generalized linear model weighted by the IPW Equation 4.

However, Equation 6 does not allow to account for theory-element D yet (XM-interaction). For this purpose, Equation 6 can be easily extended by an interaction term $\Delta_3 \mathrm{cum}(\overrightarrow{x})\mathrm{cum}(\overrightarrow{m})$, as shown in Equation 7, thus testing for a potential XM-interaction. In Demirer et al. (2022) moderated mediation was also tested.

Equation 7: Coefficients from Outcome MSM with Interaction

$$E(Y_{\overrightarrow{xm}}) = \Delta_0 + \Delta_1 \mathrm{cum}(\overrightarrow{x}) + \Delta_2 \mathrm{cum}(\overrightarrow{m}) + \Delta_3 \mathrm{cum}(\overrightarrow{x})\mathrm{cum}(\overrightarrow{m})$$

The second MSM is the mediator model, given in Equation 8, and is weighted by the IPW in Equation 8.

Equation 8: Coefficients from Mediator MSM

$$g^{-1}[E\{M_{\overrightarrow{x}}(t)\}] = \beta_0(t) + \beta_1(t)\mathrm{avg}\{\overrightarrow{x}(t)\}$$

In this equation g^{-1} refers to the link function, and the mediator, positive affect, is taken as the dependent variable of the generalized linear model. The predictor is the average multimorbidity exposure duration over the observation period $\beta_1(t)\text{avg}\{\vec{x}(t)\}$ and captures the change in positive affect based on the average multimorbidity duration.

The final step is to calculate the products of the coefficients from Equation 6 or Equation 7, depending on the model specification, with Equation 8. Without testing moderated mediation, the IDE and IIE are given by:

Equation 9:Interventional analogs effects without interaction (moderated mediation)

$$\text{IDE} = \Delta_1 \text{T}$$

$$\text{IIE} = \beta_1 \Delta_2 \text{T}$$

With assuming a moderated mediation, Equation 9 gets more complex.

Equation 10: Interventional analogs effects with interaction (moderated mediation)

$$\text{IDE} = \Delta_1 \text{T} + \beta_0 \Delta_3 \text{T}^2$$

$$\text{IIE} = \beta_1 \text{T}(\Delta_2 + \Delta_3 \text{T})$$

In both formulas, T is the sum of observed time periods. However, this only holds when assuming time-constant effects. Including time-specific effects, for instance, in more dynamic or time-specific scenarios, is also possible.

Yet, no statistical software tool or package provides a simple calculation of the mediational g-formula. Therefore, in my publication Demirer et al. (2022), a step-by-step template code for applying the mediational g-formula in Stata was provided in the Online Appendix A. Moreover, to my knowledge, publication 2 of this thesis was the first published study that applied the mediational g-formula with XM-interaction. VanderWeele (2015) and VanderWeele and Tchetgen Tchetgen (2017) mathematically derived and proofed the XM-interaction to hold within the mediational g-formula only, but did not provide exemplarily application. In addition, the provided Stata template code in the Appendix of the publication sought to encourage future researchers to apply these methods.

4. Publication I

Does social support mediate the effect of multimorbidity on mental wellbeing in the German working population? A longitudinal mediation analysis using structural equation modelling

Ibrahim Demirer[1], Matthias Bethge[2], Karla Spyra[3], Ute Karbach[4], Holger Pfaff[5]

Affiliations:

[1]Institute of Medical Sociology, Health Services Research, Rehabilitation Science (IMVR) at the Faculty of Human Sciences and the Faculty of Medicine of the University of Cologne, Eupener Str. 129, 50933, Köln, Germany

[2]Department Rehabilitation and Work. Institute for Social Medicine and Epidemiology at University of Lübeck, Ratzeburger Allee 160; Haus V50, 23538, Lübeck, Germany

[3]Head of the Rehabilitation Department Charité – University Medicine Berlin, Charitéplatz 1, Virchowweg 23, 10117, Berlin, Germany

[4]Department Rehabilitation Sociology. Faculty of Rehabilitation Sciences. Technical University Dortmund, Emil-Figge-Str. 50; EF50, 44227, Dortmund, Germany

[5]Director of Institute of Medical Sociology, Health Services Research, And Rehabilitation Science (IMVR) at the Faculty of Human Sciences and the Faculty of Medicine of the University of Cologne, Eupener Str. 129, 50933, Köln, Germany

CRediT authorship contribution statement (Allen et al., 2019):

Ibrahim Demirer: Conceptualization, Theoretical Framework, Methodology, Software, Formal analysis, Writing - Original Draft, Visualization

Matthias Bethge: Conceptualization, Methodology, Writing - Review & Editing, Data Curation

Karla Spyra: Writing - Review & Editing, Data Curation

Ute Karbach: Conceptualization, Theoretical Framework, Writing - Review & Editing

Holger Pfaff: Conceptualization, Writing - Review & Editing, PhD Supervisor

Journal Metrices:

Journal: Social Science and Medicine – Population Health

Volume: Volume 13, March 2021, 100744

Q-Index: Q1: Health Policy

IF (2021): 4.086 (Clarivate Analytics)

Real-time IF: 4.2

5-year IF: N. A.

DOI: 10.1016/j.ssmph.2021.100744

Abstract

This study provides insights into the longitudinal relation between multimorbidity, mental wellbeing, and social support. The analysis used the German Sociomedical Panel of Employees, a study of the German working population aged 40 to 54. In the context of multimorbidity, this population has been little studied. Multimorbidity is significantly associated with reduced mental wellbeing and social support, whereas social support increases mental wellbeing. We argue that, especially among the working population, multimorbidity reduces perceived social support and decreases mental wellbeing.

We elaborate on the mediation process empirically by comparing two distinct structural equation models: a cross-lagged panel mediation model that models a potential reverse-causality between social support and mental wellbeing; and a synchronous mediation model that allows for more immediate mediation. Both models estimated significant mediation. The relative size of the mediation effect, however, varied widely based on the added mediational paths (8.57% vs. 28%). Fit statistics for both models were good, and the comparison did not favour either model.

We conclude that theoretical reasoning must prevail over empirical testing. The cross-lagged model implies a more longitudinal (lagged) mediation process for social support. However, we suggest an immediate, flexible mediation as more plausible. Nevertheless, we suggest that cross-lagged models, when given a data structure and time gaps, reflect the social processes adequately.

Keywords: Mediation; Mental wellbeing; Multimorbidity; Social support; Structural equation modelling; Working population.

5. Publication II

Does positive affect mediate the association of multimorbidity on depressive symptoms?

Authors: Ibrahim Demirer[1], Michael Kühhirt[2], Ute Karbach[3], Holger Pfaff[4]

Affiliations:

[1]Institute of Medical Sociology, Health Services Research, Rehabilitation Science (IMVR) at the Faculty of Human Sciences and the Faculty of Medicine of the University of Cologne, Eupener Str. 129, 50933, Köln, Germany

[2]Institute of Sociology and Social Psychology, University of Cologne, Cologne, Germany, Albertus-Magnus-Platz, 50923, Köln, Germany

[3]Department Rehabilitation Sociology. Faculty of Rehabilitation Sciences. Technical University Dortmund, Emil-Figge-Str. 50; EF50, 44227, Dortmund, Germany

[4]Director of Institute of Medical Sociology, Health Services Research, And Rehabilitation Science (IMVR) at the Faculty of Human Sciences and the Faculty of Medicine of the University of Cologne, Eupener Str. 129, 50933, Köln, Germany

CRediT authorship contribution statement (Allen et al., 2019):

Ibrahim Demirer: Conceptualization, Theoretical Framework, Methodology, Software, Formal Analysis, Writing - Original Draft, Visualization

Michael Kühhirt: Conceptualization, Methodology, Writing - Review & Editing

Ute Karbach: Conceptualization, Theoretical Framework, Writing - Review & Editing

Holger Pfaff: Conceptualization, Writing - Review & Editing, PhD Supervisor

Journal Metrices:

Journal: Aging & Mental Health

Volume: Volume 26, 2022 - Issue 1

Q-Index: Q1: Gerontology

IF (2021): 3.514 (Clarivate Analytics)

Real-time IF: 5.4

5-year IF: 4.115

DOI: 10.1080/13607863.2020.1870209

Abstract

Multimorbidity poses various challenges, and previous research has indicated a causal relation with depression. As multimorbidity is not curable, the underlying mechanisms are of great interest. Positive affect is a major resource for coping with chronic conditions and for the prevention of depression. Long-term multimorbidity, however, may deplete positive affect. The purpose of this paper is to investigate the role of positive affect in the association between multimorbidity and depressive symptoms.

We used four consecutive waves (2008, 2011, 2014, 2017) of the nationally representative German Ageing Survey (DEAS) with a total of 1,558 older adults aged 40 and over. To account for time-varying confounding, exposure-induced mediator-outcome confounding, and reciprocities, we applied the mediational g-formula with inverse-probability weighting techniques. We also tested for exposure-mediator interaction to adjust for differences in mediation across the duration of multimorbidity. We confirmed a positive longitudinal relation between multimorbidity and depressive symptoms, both of which were negatively associated with while positive affect. The model without interaction indicated a share mediated of ca. 18.3% on the total effect of multimorbidity on depressive symptoms. Addition of interaction led to substantial differences for multimorbidity duration and levels of positive affect. Associations for long-term multimorbidity (at least two survey waves) were more substantial, and the share mediated doubled (>40%). Additionally, the direct effect of multimorbidity on depressive symptoms diminished for short-term multimorbidity.

Strengthening positive affect could reduce depressive symptoms in those facing multimorbidity. This study also discusses methodological challenges in performing longitudinal mediation analysis. We advise researchers to consider the mediational g-formula and exposure-mediator interaction.

Keywords: Multimorbidity; depression; inverse probability weighting; mediation; mediational g-formula; positive affect.

6. Related Publication

Does allostatic load predict incidental coronary events differently among sexes?

Authors: Ibrahim Demirer[1], Börge Schmidt[2], Sara Schramm[2], Raimund Erbel[2], Karl-Heinz Jöckel[2], Timo-Kolja Pförtner[1]

Affiliations:

[1]Institute of Medical Sociology, Health Services Research, Rehabilitation Science (IMVR) at the Faculty of Human Sciences and the Faculty of Medicine of the University of Cologne, Eupener Str. 129, 50933, Köln, Germany

[2]Institute for Medical Informatics, Biometry and Epidemiology (IMIBE), University Hospital of Essen (AöR), Zweigertstraße 37, 45130, Essen, Germany

CRediT authorship contribution statement (Allen et al., 2019):

Ibrahim Demirer: Conceptualization, Theoretical Framework, Methodology, Software, Formal Analysis, Writing - Original Draft, Visualization

Börge Schmidt: Conceptualization, Methodology, Writing - Review & Editing, Data Curation

Sara Schramm: Writing - Review & Editing, Data Curation

Raimund Erbel: Writing - Review & Editing, Data Curation

Karl-Heinz Jöckel: Writing - Review & Editing, Data Curation

Timo-Kolja Pförtner: Conceptualization, Methodology, Writing - Review & Editing

Journal Metrices:

Journal:	Comprehensive Psychoneuroendocrinology
	(Open Access Companion title to Psychoneuroendocrinology)
Volume:	Volume 8, November 2021, 100089
Q-Index:	N. A. / Q1: Psychiatry and Mental Health (only for Psychoneuroendocrinology)
IF (2021):	N. A. / 4.693 (only for Psychoneuroendocrinology)
Real-time IF:	N. A. / 8.0 (only for Psychoneuroendocrinology)
5-year IF:	N. A. / 4.715 (only for Psychoneuroendocrinology)
DOI:	10.1016/j.cpnec.2021.100089

Abstract

One measure to quantify the degree of dysregulation is allostatic load (AL). Typically, AL incorporates information on diverse biomarkers and is associated with health outcomes such as cardiovascular diseases or the incidence of coronary events (C-E).

This study investigates the predictive performance of different AL scoring methods on the incidence of coronary events (C-E). This study also elaborates sex differences in the baseline risks of C-E and the AL associated risks of C-E.

Longitudinal data analysis of the Heinz Nixdorf Recall Study (Risk Factors, Evaluation of Coronary Calcification, and Lifestyle) of 4327 participants free of C-E at study baseline aged 45-75. The data contains over 13 biomarkers measuring AL.

After conducting multiple imputations on missing values on AL for 826 participants, the analysis sample consisted of N = 4327 participants. We applied the two most commonly used methods of AL scoring AL (count-based and Z-score) and a recently developed logistic regression weighting method (LRM) approach. Cox regression was used to predict the incidence of C-E for each AL score. Results were estimated without (M0) and with (M1) covariate adjustment, and in a final model (M2), with an interaction between AL and sex.

We found no violation of the proportional hazard assumption and significant differences in the survival curves between the sexes for C-E (Log-rank test: prob. > Chi2 = 0.000). In M0, all AL-scoring methods predicted C-E significantly, with the LRM based AL-score having the best performance (hazard ratio = 3.133; CI: [2.630, 3.732]; Somer's D = 0.717). After covariate inclusion, differences between the scoring methods levelled, though the count-based method and LRM performed better than the Z-scoring method. The interaction analysis in M2 showed a significant multiplicative interaction for the count-based method (1.254; [1.066, 1.475]) and for the LRM (1.746; [1.132, 2.692]). The additive relative excess risk due to interaction (RERI) measure was negative for the count-based method (RERI = -1.967; [-3.778; -0.156]) and the LRM (RERI = -1.909 [-3.910; 0.091]), indicating subadditivity.

AL scores are suitable for predicting C-E. Differences between the AL-scoring algorithms were only present after including interactions. We value the count-based method as suitable for clinical practice since its calculation is relatively simple, and performance was among the best. Interaction analysis revealed that despite strong sex differences in baseline C-E, the effect of AL is more pronounced for females at high levels of AL; thus, females could benefit more from a potential intervention on AL. We suggest further investigation of sex differences concerning the mediation by physiological and psychological intermediates.

Keywords: Allostatic load; Biomarkers; Cardiovascular diseases; Hazard Cox regression; Older adults; Sex interaction.

7. Summary and comparison

In the following, I will provide a summary of each publication and compare the corresponding publications to this thesis. These sections aim to recapitalize the contribution of the publications to this thesis and compare the publications with regard to their methodology, implications, and limitations. Section 7 will discuss aspects left unconsidered by the publications and this thesis so far. The closing section, section 8, will point to future directions of multidisciplinary research that is needed in treating multimorbidity.

7.1 Summary Publication 1

Publication 1 (Demirer, Bethge, et al., 2021) performed a longitudinal mediation analysis on social supports' buffering capacities of multimorbidity's impact on mental health. For this purpose, the publication utilized data from the Third German Sociomedical Panel of Employees – Rehabilitation and Participation (GSPE-III) (Bethge et al., 2015). The GSPE-III is a large-scale cohort study of individuals aged between 40 and 54 randomly drawn from the register of the Federal German Pension Insurance Agency. The GSPE-III has its baseline survey in 2013 and two consecutive follow-ups, one in 2015 and one in 2017. The dataset was provided for my research purpose by Matthias Bethge and Karla Spyra after reviewing my research proposal.

The GSPE-III allowed the identification of multimorbidity via a list of diseases for which the respondents were asked to tick the applicable ones. Throughout both publications, multimorbidity was defined as the presence of at least three chronic physical conditions, which is in accordance to the definition of this thesis and the definition of van den Akker et al. (2001). The GSPE-III provided information on mental health via the SF-36 questionnaire (Mental Wellbeing Subscale), a validated international instrument to measure mental health (Ware & Sherbourne, 1992). Similarly, information on social support and instrument/tangible and emotional support was provided by the Oslo-3 Social Support Scale (Dalgard et al., 1995). Moreover, the GSPE-III gave information on additional variables (confounding variables), such as personality types, socioeconomic status, age, sex, and living conditions. The variables were

selected and included according to the implications of confounding variables in Publication 1 (Demirer, Bethge, et al., 2021, pp. 2–4).

Publication 1 focused on theory-element A and C, meaning that multimorbidity was assumed to be a stressor for the working population, reducing mental health (theory-element A). Social support was defined as a buffer of multimorbidity's impact on mental health. Since social support was measured in the data via the Oslo-3-Scale, emotional and tangible support were considered only. However, Publication 1 defined multimorbidity as a mediator, not a moderator. Regarding the question of whether social support is a moderator or mediator (see section 2.4.3), publication 1 acknowledged multimorbidity's impact on social support by arguing that multimorbidity causes a reduction of the ability to work or even job loss (Kadijk et al., 2019), which then increases the risks of disruptions in social networks (Brand, 2015; Darity & Goldsmith, 1996) and finally, a loss in social support.

Methodologically Publication 1 applied SEM for longitudinal mediation analysis. The application of SEM allowed two different modeling strategies, a synchronous effect model and a cross-lagged-panel model. The first assumes the buffering effect of social support and the deteriorating effect of multimorbidity simultaneously. The latter implies a temporal lag between those effects so that the buffering effect of social support temporally intervenes in the deteriorating effect of multimorbidity, thus, allowing explicit modeling for the Granger causality issues as discussed in section 3.3.1.

Overall, the statistical analysis revealed a share of mediation of around 28% in the synchronous effect model, but in the CLPM mediation model, this share was reduced to only around 9%. However, the results were significant and coherent with theory-element A, and C. Multimorbidity reduced mental health, and social support buffered this reduction. A limitation of the cross-lagged-panel method was that the required temporal lags translate into a lag of ca. five years (e.g., multimorbidity in 2013, social support in 2015, and mental wellbeing in 2017), which means that the data structure and modeling approach inappropriately considered the

social dynamics occurring between the observation periods. Hence, the synchronous effect model was favored, despite leaving the Granger causality issue unaccounted.

There are three main implications of Publication 1. First, the multimorbidity - social support association is more diverse than the multimorbidity - mental wellbeing association, which hints at potential alternatives of the buffering hypothesis in some of the analyzed individuals. Second, that empirical modeling strategies must not prevail over theoretical implications, as shown by the differences between the synchronous effect model and the CLPM. Although the CLPM for mediation would provide a more sophisticated analysis, the theoretical implications would be violated to the substantive temporal lags in the processes imposed by the data (two to three years between each survey wave). Lastly, the policy implication indicates that interventions to reduce mental health deterioration in individuals suffering from multimorbidity could be achieved by increasing social support. However, those interventions must consider their participants more holistically; prior to increasing social support, it should be assured that for this individual participant, social support operates as a buffer of stress and not as an additional stressor; thus, the buffering hypothesis (theory-element C) can be assumed.

7.2 Summary Publication 2

Publication 2 of this thesis (Demirer et al., 2022) performed a longitudinal mediation analysis of the mental health deterioration by multimorbidity and the potential protective function of positive affect in coping with multimorbidity. The publication addresses the question, to what degree does multimorbidity deteriorate positive affect and mental health? - As well as how much a hypothetical intervention on positive affect could prevent mental health deterioration.

For analyses, the German Ageing Survey (DEAS) was used, a national representative study of people aged 40 and older (Klaus et al., 2017), funded by the German Ministry of Family Affairs, Senior Citizens, Women and Youth (BMFSFJ). Since 1996 The DEAS is an ongoing longitudinal study with cross-sectional sample additions over the years. In 2008 the DEAS started balancing its panel waves, meaning that the gaps between the survey years are held

constant with a gap of three years. Therefore, for my study Demirer et al. (2022), information from respondents from 2008 up to 2017 (2011, 2014) were used. In total, an eligible panel population of 2,109 individuals born between 1923 to 1968 were obtainable. However, only 1,558 remained for final analysis. The dataset is available to the public as a scientific use file after applying a research proposal. More details on the sample selection process can be found in Publication 2 of this thesis (Demirer et al., 2022, pp. 66–67).

The DEAS measured mental health using the ADS-K (Allgemeine Depressions Skala–Kurzform) (Hautzinger & Bailer, 1993), which is the German version of the CES-D depression scale (Radloff, 1977). The mediator, positive affect, was measured with the PANAS-Scale (Watson et al., 1988). Multimorbidity was assessed similar to publication 1 of this thesis (Demirer, Bethge, et al., 2021). Additionally, information on a wide variety of confounding variables was available in the DEAS, described in the publication at pp. 66.

The theory-elements applied in Publication 2 are A, B, and D. Again, as in Publication 1, theory-Element A, the transactional model, was the basis because multimorbidity was defined as a stressor that deteriorates mental health. Theory-element B, the broaden-and-built-theory, was applied to inspect the coping process since positive affect was identified as the key resource for coping (Ashby et al., 1999; Folkman & Moskowitz, 2000; Ong et al., 2006). Further, theory-element D, argued for a potential depressive spiral approach due to resource/ego depletion caused by prolonged exposure to stressors that are unsolvable (Evans et al., 2016; Tice et al., 2007). Therefore, theory-element D intervenes between theory-element A and B by potentially enhancing the deterioration of mental health through depletion of positive affect, as depicted in Figure 5 by the feedback paths.

Methodologically, Publication 2 applied the mediational g-formula, explained in section 3.3.4 of this thesis. The mediational g-formula is a novel approach, and only a few studies so far have applied it, and even fewer studies in the field of sociopsychology and health. To encourage the wider use of the mediational g-formula and increase its feasibility for interested researchers,

the Appendix of Publication 2 also provided the template Stata code for programming the mediational g-formula. In Publication 2, the mediational g-formula was applied to determine the interventional effect of positive affect on the multimorbidity – mental health association over nearly a decade (2008-2017). Furthermore, the mediational g-formula was extended by an exposure-mediator interaction (XM-interaction), which allowed the interventional effect of positive affect to be different based on the exposure duration of multimorbidity. Adding the XM-interaction was necessary to consider theory-element D since the onset of a depressive spiral would partly operate through the loss of positive affect, which is more likely after longer exposure-duration to multimorbidity. Hence, assuming the interventional effect of positive affect to be equal across all exposure durations would contradict theory-element D.

The results highlight two aspects. First, positive affect is a key resource for preventing mental health deterioration in multimorbid individuals since, on average, 18.3% of the mental health deuteriation operates through positive affect. Second, accounting for theory-element D through modeling an XM-interaction is necessary to estimate the mediation by positive affect correctly. The longer the exposure duration to multimorbidity, the more substantial the resource/ego depletion. Therefore, the impact of prolonged durations of multimorbidity (e.g., more than six years), is stronger on mental health and positive affect as well. Consequently, the mediational g-formula with the added XM-interaction estimated an interventional effect of positive affect of over 40%, whereas, for recent multimorbidity (less than three years), no deterioration of mental health could be found.

There are four implications to these results. First, positive affect is an important mediator of the multimorbidity – mental health association and gains importance with increasing exposure durations to multimorbidity. Second, the advantages of articulating a theoretical framework and translating it into statistical methods, as shown by theory-element D, revealed substantial differences in the interventional effect of positive affect depending on the exposure duration of multimorbidity. Third, the mediational g-formula performs more efficiently than traditional

methods for mediation analysis while being more flexible with regard to parametric assumptions and the consideration of non-parametric assumptions (see also, section 3.3.4-5). Fourth, Publication 2 strongly supports integrating positive affect intervention in multimorbidity treatment, especially when coping resources are already sparse. The results showed that when fixing positive affect to an average level over a duration of at least six years (two-interventions periods in the sample), 40% of the effect on mental health could be mitigated.

7.3 Comparison: Publication 1 and Publication 2

In the following section, I will briefly compare Publication 1 and Publication 2. The comparison is along the theoretical implications (Table 2) and the methodological approaches to mediation analysis (Table 3).

Overall, regarding the theoretical implications, it can be stated that Publication 2 is more complex than Publication 1 since it consists of more theory-elements (A, B, D), and due to theory-element D requires a more differentiated causal model. However, Publication 1 has its advantage in the straightforwardness of the causal chain. Here, multimorbidity is assumed to increase demands for social support (support-demand/seeking hypothesis), simultaneously decrease available social support, and then deteriorate mental health.

Another difference lies in the population studied. Publication 2 included multimorbid individuals aged 40 and older. The age on average in Publication 1 was around 48 years old. However, the vast majority of the studied multimorbid population in Publication 2 was, on average, around 60 years old. Thus, publication 1 allowed the analysis of a population yet little studied, that is, multimorbid individuals in the working population.

However, overall the findings of publication 2 are more robust than those of publication 1. This is due to the fact that publication 2 found higher shares of mediation and additionally modeled for XM-interactions. Though, publication 1 applied a CLPM for mediation and, therefore, could explicitly model for reverse-causality (Granger causality).

Further, there was less heterogeneity in the a-path, the relation between multimorbidity and positive affect, found in Publication 2, whereas in Publication 1, more heterogeneity in the a-path, the relation between multimorbidity and social support, were found. The theoretical implications in section 2.4.2 already implied the a-path to be more heterogeneous due to alternative and competing assumptions on social support, such as the esteem-threat hypothesis. While this heterogeneity suggests different models of social support to take place simultaneously, the average effect of social support's mediation was found to be consistent with the buffering hypothesis. Hence, more research is needed on the combination of social support giver – receiver, interactions, and potential conflicting effects of social support (e.g., esteem-threat).

Concerning mediation from a methodological vantage point, I presented two approaches to longitudinal mediation analysis. In the following, I will compare both methods concerning their technical application, methodological benefits, and significance for the topic of analysis. Table 3 contains these aspects in the rows while the methods are separated by the columns.

As Table 3 suggests, the main advantages of the CLPM for mediation are its more straightforward applicability and wide acceptance across multiple disciplines. Moreover, it explicitly models reverse causality (Granger causality) and can help distinguish cause or effect. However, the main disadvantage of the CLPM is its parametric approach which increases assumptions while being unable to account for parts of the unconfoundedness assumptions, especially violation of assumption 4.

Table 2: Summary of the corresponding publications

	Social Support (Demirer, Bethge, et al., 2021)	Positive Affect (Demirer et al., 2022)
Theories applied / Hypothesis	• Theory-Element A Transactional Model. • Theory-Element C Buffering Hypothesis and Social Support. • Does social support buffer multimorbidity's deterioration of mental health?	• Theory-Element A Transactional Model. • Theory-Element B Broaden-and-Built-Theory; Positive Affect. • Theory-Element D; Rumination. • Does positive affect prevent deterioration of mental health in multimorbidity? • Does positive affect deteriorate with multimorbidity?
Context (Study / Population)	• GSEP-III: Older working population (40-54) in Germany with pre-existing health issues (Rehabilitation). • Panel Study, three points in time (2010/11; 2013/14; 2015/16). • Multimorbidity identified as at least three chronic physical conditions. • Mental health measured as mental well-being (SF-36). • Social Support measured with Oslo-3-Social Support Scale.	• German Ageing Survey (DEAS) older population (40+). • Panel Study, four utilized points in time spanning approx. (2008, 2011, 2014, 2017). • Multimorbidity identified as at least three chronic physical conditions. • Mental health is measured as depressive symptoms with CES-D-15. • Positive Affect measured with PANAS.
Method applied	• SEM: CLPM and synchronous effect model Equation 1.	• Mediational g-formula with Inverse-Probability Weighting and Moderated Mediation Equation 4 to Equation 10.
Results	• Social Support mediates around 28% in synchronous effect models. and only around 8.57% in CLPM.	• Positive affect mediated around 18.3% on average. When exposed to long-term multimorbidity, mediation more than doubled to >40%; and when exposed to short-term multimorbidity, mediation diminished.
Implications	• Decisions on methods should be driven by implications of data and theory. • Multimorbidity social support associations are more heterogeneous than multimorbidity mental health associations. Also supports alternatives to the buffering hypothesis. • Designing interventions on social support for multimorbid individuals could prevent the deterioration of mental health.	• Interventions that address positive affect in individuals suffering from prolonged durations of multimorbidity could substantially (>40%) reduce depressive symptoms. • However, stabilizing positive affect when being exposed to multimorbidity should be addressed first-hand. • Methods of mediation analysis should incorporate the mediational g-formula and test for moderated mediation.
Limitations	• Underestimation of effect parameters due to missing comparisons to healthy individuals in the data (multimorbidity vs. slightly morbid). • More immediate time points in data could be useful for applying CLPM.	• Underestimation of effect parameters due to selectivity in panel attrition towards less depressed and less morbid individuals.

Table 3: Comparison of longitudinal mediation analysis methods

	CLPM mediation	Mediational g-formula
Technical application	✓ SEM approach is widely supported by – and integrated into statistic software. † Depending on the SEM, computational and convergence issues may arise.	✓ It can be computed relatively fast by statistics software. † No statistic software command/package or ado yet available in any statistics software; requires own coding.
Methodological advantages and disadvantages	✓ SEM is used around multiple disciplines and is widely accepted. ✓ Allows the integration of latent variables/factors. ✓ Explicitly models for "Granger causality". † Requires parametric assumption. † Does not easily allow for the integration of treatment-mediator interactions. † Does not account for violation of assumption 4 (Exposure-induced-mediator outcome confounding).	✓ It is highly flexible toward time-specific effects. ✓ Accounts for violation of assumption 4. ✓ Allows integration of treatment-mediator interactions in models. † Requires more steps of analysis and calculation of IPWs. † Does not integrate latent variables.
Interpretation	✓ Effects can be interpreted overall and time-specific. † Effects are rather interpreted as a share of association that is due to the mediator.	✓ The effect can be interpreted overall and time-specific. ✓ Effects can be interpreted as interventional, expressing the effect of a potential intervention on the mediator for the outcome.

The main advantages of the mediational g-formula are located at the methodological level and the interpretation of the effects. Since the mediational g-formula is a non-parametric approach to mediation, it requires less assumption, and, simultaneously, the mediational g-formula explicitly accounts for the violation of assumption 4. However, the main advantage is the interpretation of the effects as interventional analogs. This interpretation can directly quantify how much a potential intervention on the mediator could cause a change in the outcome. As in the corresponding publication 2 Demirer et al. (2022) of this thesis, applying the mediational g-formula allowed identification of how much a potential intervention on positive affect for multimorbid individuals could reduce their depressive symptoms (approx. 40%). Although these advantages of the mediational g-formula are compelling, the disadvantages are also

present. The disadvantages are mainly caused by the complexity of the method combination and the missing software application (command/package /ado) in statistic software. To address the latter issue, an exemplary Stata code for the programming of mediational g-formula was provided. Yet, further integration into statistics software is still to be developed.

Finally, I conclude that the mediational g-formula is superior to the CLPM for longitudinal mediation analysis when reverse causality is not of primary interest due to four reasons:

First, violation of assumption 4, the exposure-induced mediator-outcome confounding, is highly prevalent when investigating time-varying phenomena (VanderWeele, 2015; VanderWeele & Tchetgen Tchetgen, 2017) such as mental health deteriorations in multimorbid individuals.

Second, as argued by MacKinnon et al. (2020), the presence of XM-interaction, meaning different shares of mediation between exposure and mediator levels (e.g., multimorbidity duration and positive affect level), is more likely than the absence of such interactions, hence, modeling for XM-interactions is in most cases necessary.

Third, the mediational g-formula allows modeling for non-linear relations and is less dependent on parametric assumptions. Future researchers should consider modeling for non-linearities more often. For instance, the counter-argument for positive affect being an essential resource of coping was the hedonic-treadmill (Diener et al., 2006). Indeed, non-linear analysis of the mediation could model for a negative or "u-shaped" effect of positive affect, where very low and very high levels of positive affect could increase mental health deterioration in multimorbid individuals.

Fourth, the mediational g-formula provides an effect interpretation based on hypothetical interventions on the mediator, here positive affect. Indeed, when investigating chronic diseases or incurable conditions, such as multimorbidity, an effect interpretation based on potential interventions on the mediator is favorable since it gives a "Hand-On" interpretation for public health.

However, when these four aspects are not applicable or relevant for the investigated phenomena, or where investigating “Granger causality” or latent variables are necessary, the SEM/CLPM approach to mediation provides an easy-to-use correct alternative.

Irrespective of the described difference in both publications, the results suggested interventions on social support and positive affect to prevent mental health deterioration in multimorbid individuals since mediation was found to be significant and high.

8. Discussion

With reconsideration of Section 1, this thesis attempted to provide:

1) A causal model of deterioration and maintaining mental health in multimorbidity.

2) Translation of the causal model into empirical models and application of novel statistical methods.

3) Identification and quantification of intermediate factors to design future mental health interventions for individuals suffering from multimorbidity.

I will discuss these three aspects concerning motivation, strengths, and limitations in the following.

8.1 Causal model of deterioration and maintaining mental health in multimorbidity

Concerning 1), the causal model depicted in Figure 5 consisted of four theory-elements (A-D). However, theory-element A was the basis and most essential element. The impact of multimorbidity on mental health is complex, and theory-element A provided the background for reducing and sorting the complexity. The transactional model of Lazarus and Folkman (1984) allowed multimorbidity to be regarded as a stressor. Further, the transactional model explained how individual stress processing is accomplished in different phases. Although defining multimorbidity as a stressor "only", might not reflect the whole reach of multiple chronic diseases for an individual, it provides a basic understanding of the impact a stressor/multimorbidity can have on one's mental health. Or, to put it in other words:

"If men define situations as real, they are real in their consequences" (Thomas & Thomas, p. 572). Hence, if the primary appraisal in an individual evaluates multimorbidity as a stressor, it is a stressor for this individual. Further, the transactional model described the coping process in more depth.

Besides the coping-phase, coping strategy selection, and secondary appraisal, the transactional model, allowed the inclusion of further theory-elements. I selected these additional theory-elements intending to provide a holistic understanding of the modifications and processes of

the coping-phase. For this purpose, theory-element B, consisting of the broaden-and-built theory (Fredrickson, 2001, 2004) and positive affect (Ashby et al., 1999; Moskowitz et al., 2012), highlighted that positive affect reduces the stressor perception in the primary appraisal and enables the utilization of beneficial coping strategies, such as problem-focused coping in the coping-phase. Consequently, H2 of this thesis asked, "Does positive affect prevent deterioration of mental health?"; And the results of Publication 2 showed that, especially for long-term multimorbidity, maintaining positive affect is important to prevent deterioration of mental health. However, future researchers should investigate more the presence of U-shaped effects, such as was concerned by the hedonic-treadmill argument of Diener et al. (2006). Accounting for U-shaped effects in mediation would not only help in targeting future interventions more precisely but also would require advances in current designs of mediation analysis.

Concerning socio-environmental modification, based on the buffering hypothesis of Cohen and Wills (1985), I advocated for social support to be an important mediator. In the causal model of this thesis theory-element C assumed social support to buffer stressors in the primary appraisal and to enable the utilization of coping strategies through tangible and emotional support. Hence, H3 of this thesis asked: "H3: Does social support buffer multimorbidity's deterioration of mental health?". On average, Publication 1 of this thesis supported the buffering hypothesis. Yet, as acknowledged in section 2.4.2, alternative or even competing effects of social support are possible, e.g., the esteem-threat hypothesis. Concurrently, the heterogeneity found in Publication 1 on the a-path hinted at those alternative effects in some parts of the population. The heterogeneity could also be due to combinations between support-giver and support-receiver. Therefore, when analyzing social interactions, future research should consider adjusting for support-giver characteristics or even apply social network analysis (e.g., van Rijsewijk et al., 2016).

Theory-element D elaborates on the longitudinal reciprocity between multimorbidity, physical- and mental health, already hinted at in Figure 1. For this purpose, the concepts of depressive-spiral (Lewinsohn, 1974), rumination (Nolen-Hoeksema, 1991; Nolen-Hoeksema et al., 2008), as well as ego-depletion (Baumeister et al., 1998; Tice et al., 2007) were applied. H4 of this thesis asked: "Does prolonged duration to multimorbidity increase the risk of a depressive spiral?" Against this background, the results of Publication 2 showed that the longer the duration of multimorbidity is, the lower the levels of positive affect (ego-depletion) are and the heavier (rumination into depressive-spiral) the mental health deterioration. However, although these results seem to confirm depressive spirals in multimorbidity, more fine-granulated data is necessary to make the timing of the onset more transparent. For instance, does the onset of an additional chronic disease cause the outburst of the depressive spiral?

Concerning the chronic diseases of multimorbidity further, the latter question raises the issue of the impact's quantity and quality differentiation. A major limitation of both publications and this thesis is the fact that multimorbidity was used as a homogenous concept. However, the diseases counting into multimorbidity can be substantially different. For example, chronic diabetes in combination with kidney failure and heart insufficiency could be more severe for mental health than the combination of hypertonia, hyperlipidemia, and diabetes. Yet, both of those conjunctions would be counted as multimorbid. Hence, there is a need for further differentiation in multimorbidity. So far, only a few studies have applied such analysis with multimorbidity differentiated for the severity of the diseases (e.g., Wei et al., 2016). Future research should either apply such empirical weighting-based strategies for multimorbidity or use disease differentiating approaches.

Another aspect that has, unfortunately, come too short in this thesis is the genesis of multimorbidity, meaning the life-course processes prior to the emergence of multimorbidity. Although there is already research evaluating frameworks in this direction, such as the life course model of multimorbidity resilience by Wister et al. (2016), empirical research on this is

limited. Future empirical research should apply the transactional model of Lazarus and Folkman (1984) with such life course models to investigate the time-varying process of stress exposition, mediation and resource depletion, and health impact.

The stress-caused pathophysiological changes that may culminate in morbidity are captured in the concept of allostatic load by McEwen (1993). This dysregulation, or allostatic load, is a pathophysiological process that may cause the onset of morbidities, thus multimorbidity. Since in this thesis, multimorbidity itself was understood as a persistent stressor, the concept of allostatic load could also help explain the severity of the progredient progression of multimorbidity. In understanding the genesis of multimorbidity, the concept of allostatic load details the psychoneuroendocrinological processes and can, therefore, provide information for preventive medical and psychological interventions. In the related publication to this thesis, together with the co-authors, I applied the concept of allostatic load to predict incidental coronary events in older adults (Demirer, Schmidt, et al., 2021). Future publications should outline the life-course risk for multimorbidity based on allostatic load and intermediates, such as social support and positive affect. Such analysis could express the degree of risk reduction for developing multimorbidity and having high allostatic load based on interventions on social support, or positive affect.

Overall, the causal model developed in this thesis has limitations towards differentiation of multimorbidity, missing integration of the life-course perspective, and related concepts such as allostatic load. Still, the aim was to identify intermediate factors in the mental health deterioration process for individuals suffering from multimorbidity, to provide health services guidance in designing interventions. From this vantage point, using theory-element A-D ‘only’ for developing the causal model in Figure 5 was justified.

That said, the ambivalence must be reflected concerning mental health measurements used in the publication. On the one hand, mental wellbeing (Ware & Sherbourne, 1992) in Publication 1 and depressive symptoms (Radloff, 1977) in Publication 2, correspond to different sub-

concepts of mental health, thus, causing heterogeneity in the outcome measures. On the other hand, this heterogeneity can be evaluated as an additional validity check for the causal paths between multimorbidity and mental health. Yet, it would have been desirable to access mental wellbeing and depressive symptoms in both datasets of the publications. In that manner, differentiation between mental wellbeing and depressive symptoms within the concept of mental health could have been carried out in individuals suffering from multimorbidity.

8.2 Translation into an empirically testable model

In addition to the causal model, this thesis attempted to provide a translation of the causal model into an empirically testable model. For this purpose, the concept of DAGs was introduced (Pearl, 1995), and its application has been demonstrated in section 3.1. The causal model in Figure 5 was translated, according to the logic of DAGs, into an empirically testable model. A special emphasis was laid on the fact that longitudinal mediation processes inherently lead to violation of assumption 4, as depicted in Figure 8 and Figure 9. However, many aspects concerning confounding and time-varying confounding, in general, have come too short in this thesis. These aspects are detailed in more depth in the corresponding publications. In summary, section 3.1 should give future researchers a blueprint on how to transfer theoretical/causal models into empirically testable models.

8.3 Identification and quantification of longitudinal mediation

Concerning the empirical models, aim 3) of this thesis attempted to identify and quantify intermediates of the multimorbidity mental health association. Within this scope, I detailed two novel methods for longitudinal mediation analysis, which are currently subject to scientific debate. In sections 3.3.1 and 3.3.2 of this thesis, the SEM approach to longitudinal mediation was introduced and applied to multimorbidity, social support, and mental wellbeing. In sections 3.3.4 and 3.3.5, the mediational g-formula was introduced and applied to multimorbidity, positive affect, and depressive symptoms. Contrasting both methods, section 7.3 Table 3 highlighted the strengths and limitations. Overall, I advise the usage of the mediational g-

formula in more complex scenarios, where reciprocity between the exposure, mediator, and outcome is expected, violation of assumption 4 is likely, and XM-interactions are plausible. The importance of incorporating XM-interactions was demonstrated in Publication 2 of this thesis. Contrasting average multimorbidity duration (e.g., three years) with long-term multimorbidity (e.g., six years), it revealed a more than twofold (18.3% vs.>40%) share of mediation by positive affect for individuals affected by long-term multimorbidity. Hence, providing important information on the potencies of future healthcare interventions. However, in simpler scenarios, e.g., when no XM-interaction is expected, the parametric assumption hold, assumption 4 is not violated, and investigation of the Granger causality is of interest, I would recommend researchers the application of CLPM for longitudinal mediation. In this manner, I hope that sections 3.3.-3.3.5 and 7.3 help future researchers gain an overview of these methods and provide guidance in selecting the appropriate method.

Still, one limitation is that no explicit method comparison has been carried out by me, meaning a comparison of the methods using the same datasets. This has been left out in the publications because the aim of Publication 1 and Publication 2 was rather content related than method related. Though VanderWeele and Tchetgen Tchetgen (2017) acknowledged when assumption 4 is not violated, XM-interaction is not present, and the parametric assumptions hold, both methods should provide similar estimates.

9. Conclusion

In summary, this thesis demonstrated that multimorbidity is a stressor that deteriorates mental health. Social support and positive affect are key mediators of this process. I recommend treating multimorbidity not as a physical state only but as an intertwined psychophysiological burden of an individual. That is why the physical conditions of multimorbidity and mental health conditions resulting from multimorbidity should be treated equally. Additionally, due to the incurability of multimorbidity, public health policies should tackle the prevention of occurrence and deterioration of multimorbidity.

However, research is demanded that incorporates the life-course perspective and focuses on psychophysiological processes prior to the manifestation of multimorbidity. I suggest incorporating the allostatic load concept in the related publication of this thesis because it can help identify the psychosocial genealogy of multimorbidity. Yet, incorporating the allostatic load concept requires a higher depth and quality of data with multiple longitudinal measurements of biological data (biomarkers) in addition to longitudinal life-course surveys.

Regarding methodological aspects of future research, I highlighted the importance and obstacles of longitudinal mediation analysis in this thesis. Against this background, I demonstrated the application of two novel methods, CLPM for longitudinal mediation, and the mediational g-formula. I strongly recommend using the mediational g-formula when analyzing complex, reciprocal phenomena.

10. References

Aartsen, M., Veenstra, M., & Hansen, T. (2017). Social pathways to health: On the mediating role of the social network in the relation between socio-economic position and health. *SSM - Population Health*, *3*, 419–426. https://doi.org/10.1016/j.ssmph.2017.05.006

Aiken, L. S., West, S. G., & Reno, R. R. (1991). *Multiple regression: Testing and interpreting interactions*. sage.

Allen, L., O'Connell, A., & Kiermer, V. (2019). How can we ensure visibility and diversity in research contributions? How the Contributor Role Taxonomy (CRediT) is helping the shift from authorship to contributorship. *Learned Publishing*, *32*(1), 71–74. https://doi.org/10.1002/leap.1210

Asendorpf, J. B., & van Aken, M. A. G. (2003). Personality–relationship transaction in adolescence: Core versus surface personality characteristics. *Journal of Personality*, *71*(4), 629–666.

Ashby, F. G., Isen, A. M., & Turken, A. U. (1999). A neuropsychological theory of positive affect and its influence on cognition. *Psychological Review*, *106*(3), 529–550. https://doi.org/10.1037/0033-295x.106.3.529

Backe, I. F., Patil, G. G., Nes, R. B., & Clench-Aas, J. (2018). The relationship between physical functional limitations, and psychological distress: Considering a possible mediating role of pain, social support and sense of mastery. *SSM - Population Health*, *4*, 153–163. https://doi.org/10.1016/j.ssmph.2017.12.005

Barnett, K., Mercer, S. W., Norbury, M., Watt, G., Wyke, S., & Guthrie, B. (2012). Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *The Lancet*, *380*(9836), 37–43. https://doi.org/10.1016/S0140-6736(12)60240-2

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, *51*(6), 1173–1182. https://doi.org/10.1037//0022-3514.51.6.1173

Barrera, M. (1986). Distinctions between social support concepts, measures, and models. *American Journal of Community Psychology*, *14*(4), 413–445. https://doi.org/10.1007/BF00922627

Baumeister, R. F., Bratslavsky, E., Muraven, M., & Tice, D. M. (1998). Ego depletion: Is the active self a limited resource? *Journal of Personality and Social Psychology*, *74*(5), 1252–1265. https://doi.org/10.1037/0022-3514.74.5.1252

Beck, A. T. (1970). Cognitive therapy: Nature and relation to behavior therapy. *Behavior Therapy*, *1*(2), 184–200. https://doi.org/10.1016/S0005-7894(70)80030-2

Beckes, L., Coan, J. A., & Hasselmo, K. (2013). Familiarity promotes the blurring of self and other in the neural representation of threat. *Social Cognitive and Affective Neuroscience*, *8*(6), 670–677. https://doi.org/10.1093/scan/nss046

Berkman, L. F., Glass, T., Brissette, I., & Seeman, T. E. (2000). From social integration to health: Durkheim in the new millennium. *Social Science & Medicine*, *51*(6), 843–857. https://doi.org/10.1016/S0277-9536(00)00065-4

Berry, D. S., & Hansen, J. S. (1996). Positive affect, negative affect, and social interaction. *Journal of Personality and Social Psychology*, *71*(4), 796–809. https://doi.org/10.1037/0022-3514.71.4.796

Bethge, M., Spanier, K., Neugebauer, T., Mohnberg, I., & Radoschewski, F. M. (2015). Self-Reported Poor Work Ability--An Indicator of Need for Rehabilitation? A Cross-Sectional Study of a Sample of German Employees. *American Journal of Physical Medicine & Rehabilitation*, *94*(11), 958–966. https://doi.org/10.1097/PHM.0000000000000281

Birk, J. L., Kronish, I. M., Moise, N., Falzon, L., Yoon, S., & Davidson, K. W. (2019). Depression and multimorbidity: Considering temporal characteristics of the associations between depression and multiple chronic diseases. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *38*(9), 802–811. https://doi.org/10.1037/hea0000737

Blinderman, C. D., Homel, P., Billings, J. A., Tennstedt, S., & Portenoy, R. K. (2009). Symptom distress and quality of life in patients with advanced chronic obstructive pulmonary disease. *Journal of Pain and Symptom Management*, *38*(1), 115–123. https://doi.org/10.1016/j.jpainsymman.2008.07.006

Bollen, K. A. (1987). Total, Direct, and Indirect Effects in Structural Equation Models. *Sociological Methodology*, *17*, 37. https://doi.org/10.2307/271028

Bollen, K. A. (2006). *Latent curve models: A structural equation perspective*. Wiley-Interscience. https://onlinelibrary.wiley.com/doi/book/10.1002/0471746096 https://doi.org/10.1002/0471746096

Bos, S. C., Macedo, A., Marques, M., Pereira, A. T., Maia, B. R., Soares, M. J., Valente, J., Gomes, A. A., & Azevedo, M. H. (2013). Is positive affect in pregnancy protective of postpartum depression? *Revista Brasileira De Psiquiatria (Sao Paulo, Brazil : 1999)*, *35*(1), 5–12. https://doi.org/10.1016/j.rbp.2011.11.002

Brand, J. E. (2015). The Far-Reaching Impact of Job Loss and Unemployment. *Annual Review of Sociology*, *41*, 359–375. https://doi.org/10.1146/annurev-soc-071913-043237

Brickman, P., Coates, D., & Janoff-Bulman, R. (1978). Lottery winners and accident victims: Is happiness relative? *Journal of Personality and Social Psychology*, *36*(8), 917–927. https://doi.org/10.1037//0022-3514.36.8.917

Camus, V., Kraehenbühl, H., Preisig, M., Büla, C. J., & Waeber, G. (2004). Geriatric depression and vascular diseases: What are the links? *Journal of Affective Disorders*, *81*(1), 1–16. https://doi.org/10.1016/j.jad.2003.08.003

Chang-Quan, H., Xue-Mei, Z., Bi-Rong, D., Zhen-Chan, L., Ji-Rong, Y., & Qing-Xiu, L. (2010). Health status and risk for depression among the elderly: A meta-analysis of published literature. *Age and Ageing*, *39*(1), 23–30. https://doi.org/10.1093/ageing/afp187

Clark, L. A., & Watson, D. (1991). Tripartite model of anxiety and depression: Psychometric evidence and taxonomic implications. *Journal of Abnormal Psychology*, *100*(3), 316–336. https://doi.org/10.1037/0021-843X.100.3.316

Cobb, S. (1976). Presidential Address-1976. Social support as a moderator of life stress. *Psychosomatic Medicine*, *38*(5), 300–314. https://doi.org/10.1097/00006842-197609000-00003

Cohen, S. (1988). Psychosocial models of the role of social support in the etiology of physical disease. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *7*(3), 269–297. https://doi.org/10.1037//0278-6133.7.3.269

Cohen, S. (2004). Social relationships and health. *American Psychologist*, *59*(8), 676–684. https://doi.org/10.1037/0003-066x.59.8.676

Cohen, S., & Pressman, S. D. (2006). Positive Affect and Health. *Current Directions in Psychological Science*, *15*(3), 122–125. https://doi.org/10.1111/j.0963-7214.2006.00420.x

Cohen, S., & Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychological Bulletin*, *98*(2), 310–357. https://doi.org/10.1037/0033-2909.98.2.310

Cohn, M. A., Fredrickson, B. L., Brown, S. L., Mikels, J. A., & Conway, A. M. (2009). Happiness unpacked: Positive emotions increase life satisfaction by building resilience. *Emotion (Washington, D.C.)*, *9*(3), 361–368. https://doi.org/10.1037/a0015952

Cole, S. R., & Hernán, M. A. (2008). Constructing inverse probability weights for marginal structural models. *American Journal of Epidemiology*, *168*(6), 656–664. https://doi.org/10.1093/aje/kwn164

Crimmins, E. M. (2015). Lifespan and Healthspan: Past, Present, and Promise. *The Gerontologist*, *55*(6), 901–911. https://doi.org/10.1093/geront/gnv130

Crotty, M., Rowett, D., Spurling, L., Giles, L. C., & Phillips, P. A. (2004). Does the addition of a pharmacist transition coordinator improve evidence-based medication management and health outcomes in older adults moving from the hospital to a long-term care facility? Results of a randomized, controlled trial. *The American Journal of Geriatric Pharmacotherapy*, *2*(4), 257–264. https://doi.org/10.1016/j.amjopharm.2005.01.001

Cutrona, C. E. (1990). Stress and Social Support—in Search of Optimal Matching. *Journal of Social and Clinical Psychology*, *9*(1), 3–14. https://doi.org/10.1521/jscp.1990.9.1.3

Dakof, G. A., & Taylor, S. E. (1990). Victims' perceptions of social support: What is helpful from whom? *Journal of Personality and Social Psychology*, *58*(1), 80–89. https://doi.org/10.1037/0022-3514.58.1.80

Dalgard, O. S., Bjørk, S., & Tambs, K. (1995). Social support, negative life events and mental health. *British Journal of Psychiatry*, *166*(1), 29–34. https://doi.org/10.1192/bjp.166.1.29

Darity, W., & Goldsmith, A. H. (1996). Social Psychology, Unemployment and Macroeconomics. *Journal of Economic Perspectives*, *10*(1), 121–140. https://doi.org/10.1257/jep.10.1.121

Demirer, I., Bethge, M., Spyra, K., Karbach, U., & Pfaff, H. (2021). Does social support mediate the effect of multimorbidity on mental wellbeing in the German working population? A longitudinal mediation analysis using structural equation modelling. *SSM - Population Health*, *13*, 100744. https://doi.org/10.1016/j.ssmph.2021.100744

Demirer, I., Kühhirt, M., Karbach, U., & Pfaff, H. (2022). Does positive affect mediate the association of multimorbidity on depressive symptoms? *Aging & Mental Health*, *26*(1), 65–76. https://doi.org/10.1080/13607863.2020.1870209

Demirer, I., Schmidt, B., Schramm, S., Erbel, R., Jöckel, K.-H., & Pförtner, T.-K. (2021). Does allostatic load predict incidental coronary events differently among sexes? *Comprehensive Psychoneuroendocrinology*, *8*, 100089. https://doi.org/10.1016/j.cpnec.2021.100089

Diener, E., Lucas, R. E., & Scollon, C. N. (2006). Beyond the hedonic treadmill: Revising the adaptation theory of well-being. *American Psychologist*, *61*(4), 305–314. https://doi.org/10.1037/0003-066X.61.4.305

Ditzen, B., & Heinrichs, M. (2014). Psychobiology of social support: the social dimension of stress buffering. *Restorative Neurology and Neuroscience*, *32*(1), 149–162. https://doi.org/10.3233/RNN-139008

Dunkel-Schetter, C., Folkman, S., & Lazarus, R. S. (1987). Correlates of social support receipt. *Journal of Personality and Social Psychology*, *53*(1), 71–80. https://doi.org/10.1037/0022-3514.53.1.71

Eckerblad, J., Theander, K., Ekdahl, A., Unosson, M., Wirehn, A.-B., Milberg, A., Krevers, B., & Jaarsma, T. (2015). Symptom burden in community-dwelling older people with multimorbidity: A cross-sectional study. *BMC Geriatrics*, *15*, 1. https://doi.org/10.1186/1471-2318-15-1

Eisenberger, N. I. (2012). The pain of social disconnection: Examining the shared neural underpinnings of physical and social pain. *Nature Reviews. Neuroscience*, *13*(6), 421–434. https://doi.org/10.1038/nrn3231

Eisenberger, N. I., Moieni, M., Inagaki, T. K., Muscatell, K. A., & Irwin, M. R. (2016). In Sickness and in Health: The Co-Regulation of Inflammation and Social Behavior. *Neuropsychopharmacology*, *42*, 242 EP -. https://doi.org/10.1038/npp.2016.141

Elwert, F. (2013). Graphical Causal Models. In S. L. Morgan (Ed.), *Handbooks of Sociology and Social Research. Handbook of Causal Analysis for Social Research* (pp. 245–273). Springer. https://doi.org/10.1007/978-94-007-6094-3_13

Elwert, F., & Winship, C. (2014). Endogenous Selection Bias: The Problem of Conditioning on a Collider Variable. *Annual Review of Sociology*, *40*, 31–53. https://doi.org/10.1146/annurev-soc-071913-043455

Espeland, M. A., Crimmins, E. M., Grossardt, B. R., Crandall, J. P., Gelfond, J. A. L., Harris, T. B., Kritchevsky, S. B., Manson, J. E., Robinson, J. G., Rocca, W. A., Temprosa, M., Thomas, F., Wallace, R., & Barzilai, N. (2017). Clinical Trials Targeting Aging and Age-Related Multimorbidity. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *72*(3), 355–361. https://doi.org/10.1093/gerona/glw220

Euteneuer, F., Schäfer, S. J., Neubert, M., Rief, W., & Süssenbach, P. (2021). Subjective social status and health-related quality of life-A cross-lagged panel analysis. *Health*

Psychology : Official Journal of the Division of Health Psychology, American Psychological Association, *40*(1), 71–76. https://doi.org/10.1037/hea0001051

Evans, D. R., Boggero, I. A., & Segerstrom, S. C. (2016). The Nature of Self-Regulatory Fatigue and "Ego Depletion": Lessons From Physical Fatigue. *Personality and Social Psychology Review : An Official Journal of the Society for Personality and Social Psychology, Inc*, *20*(4), 291–310. https://doi.org/10.1177/1088868315597841

Felton, B. J., & Revenson, T. A. (1984). Coping with chronic illness: A study of illness controllability and the influence of coping strategies on psychological adjustment. *Journal of Consulting and Clinical Psychology*, *52*(3), 343–353. https://doi.org/10.1037//0022-006x.52.3.343

Folkman, S., & Moskowitz, J. T. (2000). Positive affect and the other side of coping. *American Psychologist*, *55*(6), 647–654. https://doi.org/10.1037/0003-066X.55.6.647

Fouad, A. M., Waheed, A., Gamal, A., Amer, S. A., Abdellah, R. F., & Shebl, F. M. (2017). Effect of Chronic Diseases on Work Productivity: A Propensity Score Analysis. *Journal of Occupational and Environmental Medicine*, *59*(5), 480–485. https://doi.org/10.1097/JOM.0000000000000981

Fredrickson, B. L. (2001). The role of positive emotions in positive psychology: The broaden-and-build theory of positive emotions. *American Psychologist*, *56*(3), 218–226. https://doi.org/10.1037/0003-066X.56.3.218

Fredrickson, B. L. (2004). The broaden-and-build theory of positive emotions. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *359*(1449), 1367–1378. https://doi.org/10.1098/rstb.2004.1512

Gallo, J. J. (2017). Multimorbidity and Mental Health. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry*, *25*(5), 520–521. https://doi.org/10.1016/j.jagp.2017.02.007

Gana, K., Saada, Y., Broc, G., Quintard, B., Amieva, H., & Dartigues, J.-F. (2016). As long as you've got your health: Longitudinal relationships between positive affect and functional health in old age. *Social Science & Medicine (1982)*, *150*, 231–238. https://doi.org/10.1016/j.socscimed.2015.11.038

Garland, E. L., Fredrickson, B., Kring, A. M., Johnson, D. P., Meyer, P. S., & Penn, D. L. (2010). Upward spirals of positive emotions counter downward spirals of negativity: Insights from the broaden-and-build theory and affective neuroscience on the treatment of emotion dysfunctions and deficits in psychopathology. *Clinical Psychology Review*, *30*(7), 849–864. https://doi.org/10.1016/j.cpr.2010.03.002

Goh, Y. W., Sawang, S., & Oei, T. P. (2010). The Revised Transactional Model (RTM) of Occupational Stress and Coping: An Improved Process Approach. *The Australian and New Zealand Journal of Organisational Psychology*, *3*, 13–20. https://doi.org/10.1375/ajop.3.1.13

Gollob, H. F., & Reichardt, C. S. (1987). Taking Account of Time Lags in Causal Models. *Child Development*, *58*(1), 80. https://doi.org/10.2307/1130293

Gould, C. E., O'Hara, R., Goldstein, M. K., & Beaudreau, S. A. (2016). Multimorbidity is associated with anxiety in older adults in the Health and Retirement Study. *International Journal of Geriatric Psychiatry*, *31*(10), 1105–1115. https://doi.org/10.1002/gps.4532

Granger, C. W. J. (1969). Investigating Causal Relations by Econometric Models and Cross-spectral Methods. *Econometrica*, *37*(3), 424. https://doi.org/10.2307/1912791

Greenland, S., Pearl, J., & Robins, J. M. (1999). Causal Diagrams for Epidemiologic Research. *Epidemiology (Cambridge, Mass.)*, *10*(1), 37–48. https://journals.lww.com/epidem/Fulltext/1999/01000/Causal_Diagrams_for_Epidemiologic_Research.8.aspx

Hautzinger, M., & Bailer, M. (1993). *ADS, Allgemeine Depressions-Skala: Manual*. Beltz.

Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical Mediation Analysis in the New Millennium. *Communication Monographs*, *76*(4), 408–420. https://doi.org/10.1080/03637750903310360

Henning, M., Subic-Wrana, C., Wiltink, J., & Beutel, M. (2020). Anxiety Disorders in Patients With Somatic Diseases. *Psychosomatic Medicine*, *82*(3), 287–295. https://doi.org/10.1097/PSY.0000000000000779

Hobfoll, S. E. (1989). Conservation of resources: A new attempt at conceptualizing stress. *American Psychologist*, *44*(3), 513–524. https://doi.org/10.1037/0003-066X.44.3.513

Hofmann, S. G., Sawyer, A. T., Fang, A., & Asnaani, A. (2012). Emotion dysregulation model of mood and anxiety disorders. *Depression and Anxiety*, *29*(5), 409–416. https://doi.org/10.1002/da.21888

Holt-Lunstad, J. (2018). Why Social Relationships Are Important for Physical Health: A Systems Approach to Understanding and Modifying Risk and Protection. *Annual Review of Psychology*, *69*, 437–458. https://doi.org/10.1146/annurev-psych-122216-011902

Holvast, F., van Hattem, B. A., Sinnige, J., Schellevis, F., Taxis, K., Burger, H., & Verhaak, P. F. M. (2017). Late-life depression and the association with multimorbidity

and polypharmacy: A cross-sectional study. *Family Practice*, *34*(5), 539–545. https://doi.org/10.1093/fampra/cmx018

Hower, K., Şahin, C., Stock, S., & Pfaff, H. (2019). Medizinisch-pflegerische Versorgung älterer Menschen in Deutschland. In K. Hank, F. Schulz-Nieswandt, M. Wagner, & S. Zank (Eds.), *Alternsforschung: Handbuch für Wissenschaft und Praxis* (1st ed., pp. 285–312). Nomos Verlagsgesellschaft mbH & Co. KG. https://doi.org/10.5771/9783845276687-285

Imai, K., Keele, L., & Tingley, D. (2010). A general approach to causal mediation analysis. *Psychological Methods*, *15*(4), 309–334. https://doi.org/10.1037/a0020761

Jackson, D., Firtko, A., & Edenborough, M. (2007). Personal resilience as a strategy for surviving and thriving in the face of workplace adversity: A literature review. *Journal of Advanced Nursing*, *60*(1), 1–9. https://doi.org/10.1111/j.1365-2648.2007.04412.x

Jokela, M., Hakulinen, C., Singh-Manoux, A., & Kivimäki, M. (2014). Personality change associated with chronic diseases: Pooled analysis of four prospective cohort studies. *Psychological Medicine*, *44*(12), 2629–2640. https://doi.org/10.1017/S0033291714000257

Jones, D. R., & Graham-Engeland, J. E. (2021). Positive affect and peripheral inflammatory markers among adults: A narrative review. *Psychoneuroendocrinology*, *123*, 104892. https://doi.org/10.1016/j.psyneuen.2020.104892

Kadam, U. T., & Croft, P. R. (2007). Clinical multimorbidity and physical function in older adults: A record and health status linkage study in general practice. *Family Practice*, *24*(5), 412–419. https://doi.org/10.1093/fampra/cmm049

Kadijk, E. A., van den Heuvel, S., Ybema, J. F., & Leijten, F. R. M. (2019). The Influence of Multi-morbidity on the Work Ability of Ageing Employees and the Role of Coping Style. *Journal of Occupational Rehabilitation*, *29*(3), 503–513. https://doi.org/10.1007/s10926-018-9811-9

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *The American Journal of Psychiatry*, *156*(6), 837–841. https://doi.org/10.1176/ajp.156.6.837

Kim, J., Han, J. Y., Shaw, B., McTavish, F., & Gustafson, D. (2010). The roles of social support and coping strategies in predicting breast cancer patients' emotional well-being: Testing mediation and moderation models. *Journal of Health Psychology*, *15*(4), 543–552. https://doi.org/10.1177/1359105309355338

Klaus, D., Engstler, H., Mahne, K., Wolff, J. K., Simonson, J., Wurm, S., & Tesch-Römer, C. (2017). Cohort Profile: The German Ageing Survey (DEAS). *International Journal of Epidemiology*, *46*(4), 1105-1105g. https://doi.org/10.1093/ije/dyw326

Kroenke, C. H., Kubzansky, L. D., Schernhammer, E. S., Holmes, M. D., & Kawachi, I. (2006). Social networks, social support, and survival after breast cancer diagnosis. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *24*(7), 1105–1111. https://doi.org/10.1200/JCO.2005.04.2846

Kuzuya, M. (2019). Era of geriatric medical challenges: Multimorbidity among older patients. *Geriatrics & Gerontology International*, *19*(8), 699–704. https://doi.org/10.1111/ggi.13742

Lang, C., Gottschall, M., Sauer, M., Köberlein-Neu, J., Bergmann, A., & Voigt, K. (2019). „Da kann man sich ja totklingeln, geht ja keiner ran" – Schnittstellenprobleme zwischen stationärer, hausärztlicher und ambulant-fachspezialisierter Patientenversorgung aus Sicht Dresdner Hausärzte [Interface Problems Between Inpatient, GP and Outpatient Specialist Care: Viewpoint of General Practitioners in Dresden]. *Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany))*, *81*(10), 822–830. https://doi.org/10.1055/a-0664-0470

Lazarus, R. S., & Folkman, S. (1984). *Stress, Appraisal, and Coping*. Springer publishing company.

Lehnert, T., Heider, D., Leicht, H., Heinrich, S., Corrieri, S., Luppa, M., Riedel-Heller, S., & König, H.-H. (2011). Review: Health care utilization and costs of elderly persons with multiple chronic conditions. *Medical Care Research and Review : MCRR*, *68*(4), 387–420. https://doi.org/10.1177/1077558711399580

Lewinsohn, P. M. (1974). *A behavioral approach to depression*. In R. J. Friedman & M. M. Katz (Eds.), The psychology of depression: Contemporary theory and research. John Wiley & Sons.

Lindahl, M., & Archer, T. (2013). Depressive Expression and Anti-Depressive Protection in Adolescence: Stress, Positive Affect, Motivation and Self-Efficacy. *Psychology*, *04*(06), 495–505. https://doi.org/10.4236/psych.2013.46070

Loza, E., Jover, J. A., Rodriguez, L., & Carmona, L. (2009). Multimorbidity: Prevalence, effect on quality of life and daily functioning, and variation of this effect when one condition is a rheumatic disease. *Seminars in Arthritis and Rheumatism*, *38*(4), 312–319. https://doi.org/10.1016/j.semarthrit.2008.01.004

Lyubomirsky, S., King, L., & Diener, E. (2005). The benefits of frequent positive affect: Does happiness lead to success? *Psychological Bulletin*, *131*(6), 803–855. https://doi.org/10.1037/0033-2909.131.6.803

MacKinnon, D. P., Valente, M. J., & Gonzalez, O. (2020). The Correspondence Between Causal and Traditional Mediation Analysis: The Link Is the Mediator by Treatment Interaction. *Prevention Science : The Official Journal of the Society for Prevention Research*, *21*(2), 147–157. https://doi.org/10.1007/s11121-019-01076-4

Maher, R. L., Hanlon, J., & Hajjar, E. R. (2014). Clinical consequences of polypharmacy in elderly. *Expert Opinion on Drug Safety*, *13*(1), 57–65. https://doi.org/10.1517/14740338.2013.827660

Marengoni, A., Rizzuto, D., Wang, H.-X., Winblad, B., & Fratiglioni, L. (2009). Patterns of chronic multimorbidity in the elderly population. *Journal of the American Geriatrics Society*, *57*(2), 225–230. https://doi.org/10.1111/j.1532-5415.2008.02109.x

Maxwell, S. E., & Cole, D. A. (2007). Bias in cross-sectional analyses of longitudinal mediation. *Psychological Methods*, *12*(1), 23–44. https://doi.org/10.1037/1082-989X.12.1.23

McEwen, B. S. (1993). Stress and the Individual. *Archives of Internal Medicine*, *153*(18), 2093. https://doi.org/10.1001/archinte.1993.00410180039004

Menotti, A., Mulder, I., Nissinen, A., Giampaoli, S., Feskens, E. J., & Kromhout, D. (2001). Prevalence of morbidity and multimorbidity in elderly male populations and their impact on 10-year all-cause mortality. *Journal of Clinical Epidemiology*, *54*(7), 680–686. https://doi.org/10.1016/S0895-4356(00)00368-1

Mercer, S. W., Smith, S. M., Wyke, S., O'Dowd, T., & Watt, G. C. M. (2009). Multimorbidity in primary care: Developing the research agenda. *Family Practice*, *26*(2), 79–80. https://doi.org/10.1093/fampra/cmp020

Moskowitz, J. T., Carrico, A. W., Duncan, L. G., Cohn, M. A., Cheung, E. O., Batchelder, A., Martinez, L., Segawa, E., Acree, M., & Folkman, S. (2017). Randomized controlled trial of a positive affect intervention for people newly diagnosed with HIV. *Journal of Consulting and Clinical Psychology*, *85*(5), 409–423. https://doi.org/10.1037/ccp0000188

Moskowitz, J. T., Shmueli-Blumberg, D., Acree, M., & Folkman, S. (2012). Positive Affect in the Midst of Distress: Implications for Role Functioning. *Journal of Community & Applied Social Psychology*, *22*(6), 502–518. https://doi.org/10.1002/casp.1133

Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., & Ustun, B. (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet*, *370*(9590), 851–858. https://doi.org/10.1016/S0140-6736(07)61415-9

Nadler, A., & Jeffrey, D. (1986). The Role of Threat to Self-Esteem and Perceived Control in Recipient Reaction to Help: Theory Development and Empirical Validation. In *Advances in experimental social psychology* (Vol. 19, pp. 81–122). Elsevier. https://doi.org/10.1016/S0065-2601(08)60213-0

Newsom, J. T. (2015). *Longitudinal structural equation modeling: A comprehensive introduction*. *Multivariate applications series*. Routledge Taylor & Francis Group. https://doi.org/10.4324/9781315871318

Nolen-Hoeksema, S. (1991). Responses to depression and their effects on the duration of depressive episodes. *Journal of Abnormal Psychology*, *100*(4), 569–582. https://doi.org/10.1037//0021-843x.100.4.569

Nolen-Hoeksema, S., Wisco, B. E., & Lyubomirsky, S. (2008). Rethinking Rumination. *Perspectives on Psychological Science : A Journal of the Association for Psychological Science*, *3*(5), 400–424. https://doi.org/10.1111/j.1745-6924.2008.00088.x

Nowossadeck, E. (2012). Demografische Alterung und Folgen für das Gesundheitswesen, *2*. www.rki.de/gbe-kompakt

Olaya, B., Domènech-Abella, J., Moneta, M. V., Lara, E., Caballero, F. F., Rico-Uribe, L. A., & Haro, J. M. (2017). All-cause mortality and multimorbidity in older adults: The role of social support and loneliness. *Experimental Gerontology*, *99*, 120–126. https://doi.org/10.1016/j.exger.2017.10.001

Ong, A. D., Bergeman, C. S., Bisconti, T. L., & Wallace, K. A. (2006). Psychological resilience, positive emotions, and successful adaptation to stress in later life. *Journal of Personality and Social Psychology*, *91*(4), 730–749. https://doi.org/10.1037/0022-3514.91.4.730

Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: Classical theories and new developments. *Trends in Neurosciences*, *31*(9), 464–468. https://doi.org/10.1016/j.tins.2008.06.006

Pearl, J. (1995). Causal diagrams for empirical research. *Biometrika*, *82*(4), 669–688. https://doi.org/10.1093/biomet/82.4.669

Pearl, J. (2009). Causal inference in statistics: An overview. *Statistics Surveys*, *3*. https://doi.org/10.1214/09-SS057

Pearl, J. (2014). Interpretation and identification of causal mediation. *Psychological Methods*, *19*(4), 459–481. https://doi.org/10.1037/a0036434

Pearl, J., & Paz, A. (2014). Confounding Equivalence in Causal Inference. *Journal of Causal Inference*, *2*(1), 75–93. https://doi.org/10.1515/jci-2013-0020

Pfaff, H., Ernstmann, N., Driller, E., Jung, J., Karbach, U., Kowalski, C., Nitzsche, A., & Ommen, O. (2011). Elemente einer Theorie der sozialen Gesundheit. In T. Schott & C. Hornberg (Eds.), *Gesundheit und Gesellschaft. Die Gesellschaft und ihre Gesundheit: 20 Jahre Public Health in Deutschland ; Bilanz und Ausblick einer Wissenschaft* (1st ed., pp. 39–68). VS Verl. für Sozialwiss. https://doi.org/10.1007/978-3-531-92790-9_2

Pressman, S. D., Jenkins, B. N., & Moskowitz, J. T. (2019). Positive Affect and Health: What Do We Know and Where Next Should We Go? *Annual Review of Psychology*, *70*, 627–650. https://doi.org/10.1146/annurev-psych-010418-102955

Puth, M.-T., Weckbecker, K., Schmid, M., & Münster, E. (2017). Prevalence of multimorbidity in Germany: Impact of age and educational level in a cross-sectional study on 19,294 adults. *BMC Public Health*, *17*(1), 826. https://doi.org/10.1186/s12889-017-4833-3

Radloff, L. S. (1977). The CES-D Scale. *Applied Psychological Measurement*, *1*(3), 385–401. https://doi.org/10.1177/014662167700100306

Read, J. R., Sharpe, L., Modini, M., & Dear, B. F. (2017). Multimorbidity and depression: A systematic review and meta-analysis. *Journal of Affective Disorders*, *221*, 36–46. https://doi.org/10.1016/j.jad.2017.06.009

Robins, J. M., Hernán, M. A., & Brumback, B. (2000). Marginal structural models and causal inference in epidemiology. *Epidemiology (Cambridge, Mass.)*, *11*(5), 550–560. https://doi.org/10.1097/00001648-200009000-00011

Rosenbaum, P. R., & Rubin, D. B. (1983). The central role of the propensity score in observational studies for causal effects. *Biometrika*, *70*(1), 41–55. https://doi.org/10.1093/biomet/70.1.41

Rosenbaum, S., McKeon, G., Stubbs, B., Teychenne, M., Parker, A., Stanton, R., Schuch, F., Mistry, A., Steel, Z., & Firth, J. (2021). Redefining mental healthcare: Going multidisciplinary to manage multimorbidity. *British Journal of Sports Medicine*, *55*(1), 7–8. https://doi.org/10.1136/bjsports-2019-101691

Salomon, J. A., Wang, H., Freeman, M. K., Vos, T., Flaxman, A. D., Lopez, A. D., & Murray, C. J. L. (2012). Healthy life expectancy for 187 countries, 1990–2010: a

systematic analysis for the Global Burden Disease Study 2010. *The Lancet*, *380*(9859), 2144–2162. https://doi.org/10.1016/S0140-6736(12)61690-0

Schiavon, C. C., Marchetti, E., Gurgel, L. G., Busnello, F. M., & Reppold, C. T. (2016). Optimism and Hope in Chronic Disease: A Systematic Review. *Frontiers in Psychology*, *7*, 2022. https://doi.org/10.3389/fpsyg.2016.02022

Schulkin, J. (2003). *Rethinking homeostasis: Allostatic regulation in physiology and pathophysiology*. *Bradford Bks*. MIT Press. http://cognet.mit.edu/book/rethinking-homeostasis

Sewart, A. R., Zbozinek, T. D., Hammen, C., Zinbarg, R. E., Mineka, S., & Craske, M. G. (2019). Positive Affect as a Buffer between Chronic Stress and Symptom Severity of Emotional Disorders. *Clinical Psychological Science : A Journal of the Association for Psychological Science*, *7*(5), 914–927. https://doi.org/10.1177/2167702619834576

Smith, S. M., Wallace, E., Clyne, B., Boland, F., & Fortin, M. (2021). Interventions for improving outcomes in patients with multimorbidity in primary care and community setting: A systematic review. *Systematic Reviews*, *10*(1), 271. https://doi.org/10.1186/s13643-021-01817-z

Steptoe, A., O'Donnell, K., Badrick, E., Kumari, M., & Marmot, M. (2008). Neuroendocrine and inflammatory factors associated with positive affect in healthy men and women: The Whitehall II study. *American Journal of Epidemiology*, *167*(1), 96–102. https://doi.org/10.1093/aje/kwm252

Tetzlaff, J., Muschik, D., Epping, J., Eberhard, S., & Geyer, S. (2017). Expansion or compression of multimorbidity? 10-year development of life years spent in multimorbidity based on health insurance claims data of Lower Saxony, Germany. *International Journal of Public Health*, *62*(6), 679–686. https://doi.org/10.1007/s00038-017-0962-9

Thoits, P. A. (2011). Mechanisms linking social ties and support to physical and mental health. *Journal of Health and Social Behavior*, *52*(2), 145–161. https://doi.org/10.1177/0022146510395592

Thomas, W. I., & Thomas, D. S. (1928). *The child in America.* Knopf.

Tice, D. M., Baumeister, R. F., Shmueli, D., & Muraven, M. (2007). Restoring the self: Positive affect helps improve self-regulation following ego depletion. *Journal of Experimental Social Psychology*, *43*(3), 379–384. https://doi.org/10.1016/j.jesp.2006.05.007

Triolo, F., Harber-Aschan, L., Belvederi Murri, M., Calderón-Larrañaga, A., Vetrano, D. L., Sjöberg, L., Marengoni, A., & Dekhtyar, S. (2020). The complex interplay between depression and multimorbidity in late life: Risks and pathways. *Mechanisms of Ageing and Development*, *192*, 111383. https://doi.org/10.1016/j.mad.2020.111383

van den Akker, M., Buntinx, F., Roos, S., & Knottnerus, J. (2001). Problems in determining occurrence rates of multimorbidity. *Journal of Clinical Epidemiology*, *54*(7), 675–679. https://doi.org/10.1016/S0895-4356(00)00358-9

van den Berg, K. S., Wiersema, C., Hegeman, J. M., van den Brink, R. H. S., Rhebergen, D., Marijnissen, R. M., & Oude Voshaar, R. C. (2021). Clinical characteristics of late-life depression predicting mortality. *Aging & Mental Health*, *25*(3), 476–483. https://doi.org/10.1080/13607863.2019.1699900

van Rijsewijk, L., Dijkstra, J. K., Pattiselanno, K., Steglich, C., & Veenstra, R. (2016). Who helps whom? Investigating the development of adolescent prosocial relationships. *Developmental Psychology*, *52*(6), 894–908. https://doi.org/10.1037/dev0000106

VanderWeele, T. J. (2015). *Explanation in causal inference: methods for mediation and interaction*. Oxford University Press.

VanderWeele, T. J., & Tchetgen Tchetgen, E. J. (2017). Mediation analysis with time varying exposures and mediators. *Journal of the Royal Statistical Society. Series B, Statistical Methodology*, *79*(3), 917–938. https://doi.org/10.1111/rssb.12194

VanderWeele, T. J., & Vansteelandt, S. (2009). Conceptual issues concerning mediation, interventions and composition. *Statistics and Its Interface*, *2*(4), 457–468. https://doi.org/10.4310/SII.2009.v2.n4.a7

VanderWeele, T. J., Vansteelandt, S., & Robins, J. M. (2014). Effect decomposition in the presence of an exposure-induced mediator-outcome confounder. *Epidemiology (Cambridge, Mass.)*, *25*(2), 300–306. https://doi.org/10.1097/EDE.0000000000000034

Wahl, H.-W., Drapaniotis, P. M., & Heyl, V. (2014). Functional ability loss in sensory impaired and sensory unimpaired very old adults: Analyzing causal relations with positive affect across four years. *Experimental Gerontology*, *59*, 65–73. https://doi.org/10.1016/j.exger.2014.06.008

Walster, E., Walster, G. W., & Berscheid, E. (1978). *Equity: Theory and research*. Allyn and Bacon.

Wang, J., Mann, F., Lloyd-Evans, B., Ma, R., & Johnson, S. (2018). Associations between loneliness and perceived social support and outcomes of mental health problems: A

systematic review. *BMC Psychiatry*, *18*(1), 156. https://doi.org/10.1186/s12888-018-1736-5

Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-ltem Short-Form Health Survey (SF-36). *Medical Care*, *30*(6), 473–483. https://doi.org/10.1097/00005650-199206000-00002

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: The PANAS scales. *Journal of Personality and Social Psychology*, *54*(6), 1063–1070. https://doi.org/10.1037//0022-3514.54.6.1063

Wei, M. Y., Kawachi, I., Okereke, O. I., & Mukamal, K. J. (2016). Diverse Cumulative Impact of Chronic Diseases on Physical Health-Related Quality of Life: Implications for a Measure of Multimorbidity. *American Journal of Epidemiology*, *184*(5), 357–365. https://doi.org/10.1093/aje/kwv456

Welzel, F. D., Stein, J., Hajek, A., König, H.-H., & Riedel-Heller, S. G. (2017). Frequent attenders in late life in primary care: A systematic review of European studies. *BMC Family Practice*, *18*(1), 104. https://doi.org/10.1186/s12875-017-0700-7

Wilamowska, Z. A., Thompson-Hollands, J., Fairholme, C. P., Ellard, K. K., Farchione, T. J., & Barlow, D. H. (2010). Conceptual background, development, and preliminary data from the unified protocol for transdiagnostic treatment of emotional disorders. *Depression and Anxiety*, *27*(10), 882–890. https://doi.org/10.1002/da.20735

Wilks, S. E., & Croom, B. (2008). Perceived stress and resilience in Alzheimer's disease caregivers: Testing moderation and mediation models of social support. *Aging & Mental Health*, *12*(3), 357–365. https://doi.org/10.1080/13607860801933323

Wister, A. V., Coatta, K. L., Schuurman, N., Lear, S. A., Rosin, M., & MacKey, D. (2016). A Lifecourse Model of Multimorbidity Resilience: Theoretical and Research Developments. *International Journal of Aging & Human Development*, *82*(4), 290–313. https://doi.org/10.1177/0091415016641686

Wu, W., Zhang, Y., Wang, P., Zhang, L., Wang, G., Lei, G., Xiao, Q., Cao, X., Bian, Y., Xie, S., Huang, F., Luo, N., Zhang, J., & Luo, M. (2020). Psychological stress of medical staffs during outbreak of COVID-19 and adjustment strategy. *Journal of Medical Virology*, *92*(10), 1962–1970. https://doi.org/10.1002/jmv.25914

Zhou, X., Zhu, H., Zhang, B., & Cai, T. (2013). Perceived Social Support as Moderator of Perfectionism, Depression, and Anxiety in College Students. *Social Behavior and*

Personality: An International Journal, *41*(7), 1141–1152. https://doi.org/10.2224/sbp.2013.41.7.1141

Ziarko, M., Mojs, E., Piasecki, B., & Samborski, W. (2014). The mediating role of dysfunctional coping in the relationship between beliefs about the disease and the level of depression in patients with rheumatoid arthritis. *The Scientific World Journal*, *2014*, 585063. https://doi.org/10.1155/2014/585063