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Missing relationships: neuroendocrine and psychological mechanisms of social isolation and social loss – results across different contexts

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Content

List of publications

I. **Hopf, D.**, Schneider, E., Aguilar-Raab, C., Scheele, D., Morr, M., Klein, T., Ditzen, B., & Eckstein, M. (2022, September). Loneliness and diurnal cortisol levels during COVID-19 lockdown: the roles of living situation, relationship status and relationship quality. *Scientific Reports, 12*, 15076. https://doi.org/10.1038/s41598-022-19224-2

II. **Hopf, D.**, Eckstein, M., Aguilar-Raab, C., Warth, M., & Ditzen, B. (2020, August). Neuroendocrine mechanisms of grief and bereavement: A systematic review and implications for future interventions. *Journal of Neuroendocrinology, 32*(8), e12887. https://doi.org/10.1111/jne.12887

III. **Hopf, D.**, Eckstein, M., Ditzen, B., & Aguilar-Raab, C. (2022, March). Still with me? Assessing the persisting relationship to a deceased loved-one - Validation of the "Continuing Bonds Scale" in a German population. *OMEGA Journal of Death and Dying.* https://doi.org/10.1177/00302228221076622

Note: For individual author contributions see Appendices I to III.

Summary

Social isolation and social loss are amongst the most stressful experiences in life. Although the individuals affected can cope with the situation and adapt after a certain amount of time, there is nevertheless ample evidence of long-term psychological and physical consequences in certain subgroups. For example, about 10% of mourners develop *complicated grief* (CG) symptoms after loss, such as intense yearning, preoccupation with thoughts of the deceased, identity disruption, marked sense of disbelief about the death or intense emotional pain. To better understand which subgroups are affected and to take preventive measures, it is important to explore factors and underlying mechanisms that might elevate the chronification risk of psychological and physical health issues following social isolation and social loss. The aim of the present dissertation is to contribute to ongoing research on moderators and mechanisms of long-term adaptation to isolation and loss by using a multifactorial approach. More precisely, 1) I analyse and compare reactions to social isolation and social loss both on a neuroendocrine and a psychological level, and 2) I examine psychological and contextual factors that are promoting vs. hindering adaptive reactions to social isolation and social loss.
Paper I aims to test associations between widowhood and temporary separation in romantic relationships on state and trait loneliness as well as cortisol levels and the role of relationship status as moderator during social isolation (COVID-19 lockdown). Paper II systematically reviews neuroendocrine correlates of grief and bereavement and identifies factors that moderate those responses. Finally, Paper III analyses whether various aspects of continuing bonds (CB) to the deceased loved one differentially affect CG and post-traumatic growth. In addition, it examines whether insecure attachment style and features of the loss event are linked to CB. All in all, results reveal divorce and widowhood (permanent separation) as risk factors for trait loneliness during extreme social isolation. More interestingly, loneliness was equally high in those who were not living with their partner (temporary separation) and those who were single. Furthermore, neuroendocrine stress responses were higher in singles compared to individuals who were in a relationship during social isolation. Higher relationship quality additionally predicted lower levels of loneliness in the latter (Paper I). Neuroendocrine stress responses were also found in social loss, e.g., flattened diurnal cortisol slopes and elevated mean cortisol levels, which are indicators of neuroendocrine dysregulation (Paper II). Neuroendocrine responses after social loss were moderated by closeness to the deceased, psychiatric symptoms, time since death, emotional reactions, suddenness of the loss, grief severity, age, and sex[1].

[1] In line with recommendations of the American Psychological Association (7th edition), within this dissertation, the term *sex* as biological distinction, whereas “gender” represents the social construct and social identity.

Regarding the role of CB in adaptation to social loss (Paper III), externalized CB, which has been assumed to be higher in unresolved grief, was elevated in individuals who suffered a violent loss, who felt responsible for the death and who had a closer relationship to the deceased. Contrary to our expectations, both internalized and externalized CB were associated with CG and post-traumatic growth. Lastly, insecure attachment style predicted higher levels of CG symptoms.

To sum up, results indicate that it is the subjective reaction to social isolation and social loss, as well as features of the person, the relationship, and the loss event itself, that determine the adaptivity of the trajectories. Although social isolation and social loss do not represent the same situation, they both are associated with loneliness and neuroendocrine disruptions. This dissertation contributes particularly to research on psychological and neuroendocrine correlates of social isolation and social loss, while also revealing important future research questions.

1 Introduction

1.1 The role of social attachments in mental and physical health

From the first formative bond between parents and their offspring at the beginning of life, humans are born as social creatures that engage in constantly changing relationships with other human beings. By affecting their thoughts, feelings, and actions, they play a crucial role in the way humans shape their lives. Taking parent-child bonds as an example, they not only ensure survival of the offspring, but fundamentally influence its emotional, cognitive, and social development, affecting mental and physical health in later life (Ammerman, 1991; Fernald & Gunnar, 2009; Gunlicks & Weissman, 2008). Health effects of close relationships not only include parent-child bonds, but also sibling relationships, meaningful friendships, and romantic partnerships. Romantic partnership is one of the most central social buffers in adulthood and is a popular focus in psychological research and practice (Cohen & Wills, 1985; Robles & Kiecolt-Glaser, 2003). Romantic partners who are seen as the primary attachment figure during adulthood (Hazan & Shaver, 1994; Qualter et al., 2015) fulfil needs such as intimacy, emotional support and deep attachment (Beach et al., 1996) and exert a high influence on mental well-being and physical health (Glenn & Weaver, 1981; Pohl et al., 2019; Robles et al., 2014; Uchino et al., 1996). In addition, meaningful friendships, co-worker relationships, and close roommate relationships may positively influence physiological and psychological well-being. Especially in early adolescence, friendships provide a rich source of companionship and social support and thus highly influence the youth's social and emotional well-being (Bagwell & Bukowski, 2018; Flannery & Smith, 2021). Just to take one example, having meaningful friendships is associated with lower susceptibility towards depression and distress (Beach et al., 1993; Kenny et al., 2013; Lepore, 1992; Pohl et al., 2019) and reduced blood pressure (Kamarck et al., 1990; Uchino, 2006).

Although the positive effects of social attachments are frequently studied and shown, their qualitative and quantitative complexity suggests a non-linear impact on physical and mental health. As a result, social buffering does not seem to occur under all circumstances. Taking romantic relationships as an example, meaningful and positive interactions with the partner reduce pain, stress and psychological burden (Frisch et al., 2017) and ameliorate immunological markers and wound healing (Ditzen et al., 2023; Pfeifer et al., 2020). There is also vast evidence from the last few decades about reduced mortality risk in romantic couples (Cheung, 2000; Hemström, 1996; Hu & Goldman, 1990; Manzoli et al., 2007; Rendall et al., 2011). On the other hand, co-regulating cortisol stress responses or negative emotions such as stress or anger during couple conflicts, might be disadvantageous regarding well-being (Liu et al., 2013; Schoebi, 2008). Research is increasingly focusing on investigating under which

circumstances meaningful relationships are health-promoting rather than health-reducing by using multifactorial approaches. For instance, social relationships are more accurate predictors of mortality if researchers investigate them in a multifaceted way, e.g., by including both structural factors such as living arrangements or relationship status and social network inventories (Holt-Lunstad & Steptoe, 2022).

1.2 Social isolation and social loss

Bond formation is automatically accompanied by the "risk" of bond disruption or bond loss, which is considered one of the most painful experiences in life. Losing a loved one entails not only loss through death, but also permanent separation such as divorce and breakup, friendship dissolution or more temporary losses such as long-distance relationships, or children leaving their childhood homes. In the year of 2020, about 985,600 people died in Germany (Statistisches Bundesamt, 2022b), most of them of cardiovascular diseases (35.29%). Especially after the outbreak of the SARS-CoV-2 virus, (COVID-19), the number of deaths has risen in Germany (Statistisches Bundesamt, 2021). This holds true for the United States as well, where age-adjusted death rate increased by 0.7% between 2020 and 2021 (Ahmad et al., 2022). Moreover, divorce rates have significantly increased in the past 50 years from 76,520 (18.07%) in 1970 to 143,801 (38.25%) in 2020 (Statistisches Bundesamt, 2022a). On the other hand, according to a study in the United States, marriage seems to have become rarer but more stable with less divorces reported (Cohen, 2019).

Growing divorce and declining marriage rates may be one reason why Western society and especially the older population becomes increasingly affected by social isolation and loneliness (World Health Organization, 2021). Although social isolation is not equal to social loss, its causes and consequences might share common variance. For example, reactions to social isolation, such as loneliness, are fuelled by the discrepancy between perceived fulfilment of social connectedness and actual social connectedness (Baumeister & Leary, 1995; Peplau & Goldston, 1985). While this does not necessarily result from losing someone, social isolation could similarly be seen as a symptom of the feeling of disconnectedness or the missing of a close attachment figure. According to the belongingness hypothesis, human beings constantly strive for social belonging as well as for the maintenance of lasting positive and significant relationships (Baumeister & Leary, 1995). The non-fulfilment of the need to belong and feelings of disconnectedness, resulting in social isolation and loneliness, may in the long-term peak in greater risk for mortality and morbidity (Holt-Lunstad, 2018; Holt-Lunstad et al., 2010).

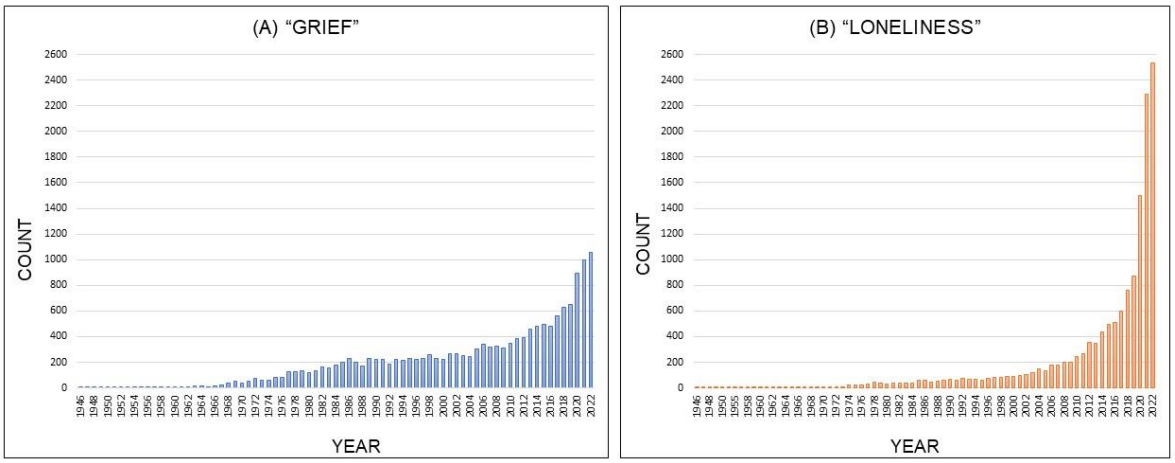
Although losing a loved one is most commonly associated with grief, other types of relationship dissolution also trigger severe disruptions; friendship endings (especially those that are accompanied by conflict or hurt feelings) (Vieth et al., 2022), homesickness and intimate

romantic breakups similarly trigger grief symptoms such as yearning (O'Connor & Sussman, 2014), loneliness (Vedder et al., 2022), psychological distress (Field, 2011; Hope et al., 1999), and psychiatric conditions such as depression, anxiety or substance use (Whisman et al., 2022). One study found higher activations in brain regions related to sadness in individuals grieving after a romantic breakup (Najib et al., 2004). On a physiological level, events such as partner loss, separation, and divorce have been independently associated with increased risk for stroke, heart disease and overall mortality (Cacioppo et al., 2015; Ong et al., 2016; Valtorta et al., 2016). Despite their close kinship, the similarities and differences between different types of losses are still highly understudied (Field, 2011; Robles & Kane, 2014).

In human social loss research, the term *loss* has a different meaning from the term *grief*: Whereas the first defines the loss event itself, the latter describes the subjective reaction to the loss with all its elements. *Bereavement*, on the other hand, is defined as the state of having suffered the loss of a loved one and entails the time after a loss during which grief is experienced (Zisook & Shear, 2009).

Figure 1

Total search count of the terms "grief" (A) and "loneliness" (B) according to PubMed.



Note. Figure 1 represents the total count of search results of the terms "grief "(A) and "loneliness "(B) according to *PubMed*. X axis depicts publication year, y axis represents search count.

Although grief has always been part of human life and history, it recently has received growing interest in research. The number of hits for the search term "grief" within *PubMed* has increased exponentially during the last 50 years (see Figure 1A) (https://pubmed.ncbi.nlm.nih.gov/?term=grief&timeline=expanded, retrieved January 03rd, 2023). Interestingly, during the time before (2019) and after (2021) the first year of COVID-19 pandemic, the number of publication entries rose 350 points. Similarly, search results of the

term “loneliness”, which represents one of the most important symptoms of social isolation, has even more exponentially risen within the past 50 years and reached about 2500 hits in the year 2022 (https://pubmed.ncbi.nlm.nih.gov/?term=loneliness&timeline=expanded, retrieved February 17th, 2023) (see Figure 1B). Even though the low hit rate at the beginning of the recordings may have been partly due to a lack of digitization, it can still be assumed that there is a growing interest in researching grief and loneliness. These data only give a first hint towards the increasing focus on important aspects in social isolation and loss, especially during times of extreme isolation and contact restrictions.

1.3 Theories on bond formation and bond disruption

Theories on bond formation and disruption improve the understanding of inter-individual differences in adjustment to isolation and loss and potential mechanisms through which they might impact long-term health. According to attachment theory, e.g., the so-called *attachment behavioural system* is described as a psychobiological regulatory system that provides a secure base, safety and intimacy and helps down-regulate physiological stress-responses after threat (Ainsworth & Bowlby, 1991; Bowlby, 1969; Bowlby, 1997/2005; Bretherton, 1992).

The formation and maintenance of a secure attachment is assumed to help maintain emotional balance and resilience during stressful situations and to provide the foundation for personal growth and mature autonomy (Shaver & Mikulincer, 2009). An insecure attachment style (anxious vs. avoidant), which results from unavailable or lost attachment figures, however, is assumed to reduce those psychological benefits (Mikulincer & Shaver, 2022). Attachment theory predicts that securely attached individuals adapt more easily to separation and loss compared to insecurely attached individuals. More precisely, anxiously, or avoidantly attached individuals should display higher and prolonged psychological grief reactions, as they lack general self-regulatory resources. They might suppress attachment needs or emotional reactions to a loss by denying the importance of the lost loved one (Mikulincer & Shaver, 2022). These assumptions have already been partly tested, not only regarding psychological distress, but also inflammatory activity and other somatic changes (Mikulincer & Shaver, 2022).

The psychobiological model of co-regulation, self-regulation and dysregulation expands on attachment theory (Sbarra & Hazan, 2008). According to this model, interpersonal relationships help regulate physiological stress systems by co-regulating them with the attachment figure. Potential mechanisms are thought to be oxytocin (OT) and endogenous opioid releases in response to pleasurable experiences, which down-regulate bodily stress responses (LeRoy et al., 2019; Sbarra & Hazan, 2008). Relationship dissolution is assumed to lead to a disorganization of this co-regulated system, which can be subdivided into an

organized and an attachment-specific disorganized reaction. The organized reaction represents the unspecific physiological stress-response ("fight-or-flight" response), which includes the cardiovascular system (e.g., heart rate, catecholamines) and the hypothalamic–pituitary–adrenal (HPA) axis (e.g., corticotrophin-releasing hormone (CRH)). The disorganized response is described as the loss of co-regulating joint behaviors, affections, and cognitions. To overcome this dysregulated response, the surviving individual must adapt to the new environment (self-regulation phase) (Sbarra & Hazan, 2008).

Robles and his colleagues add to the attachment theories by postulating that close attachment figures serve as social-cognitive and emotional regulators in stress-related physiology (Robles & Kane, 2014). According to their theory, attachment systems help regulate stressful situations by providing additional energy to the brain through physiological mediators such as HPA axis activation. Attachment is hypothesized to play not only a role in allostatic processes like inflammation, but also restorative processes such as sleep or skin repair. The authors postulate that the impact of relationship-related and non-relationship-related stressors on the physiological system is influenced by person-related factors such as attachment security (Brooks et al., 2011).

Within loss research, grief theories provide further insights into potential courses and important aspects of grief that influence long-term adaptation to loss. The potentially oldest model is the five stages of grief model which outlines the emotional stages of denial, anger, bargaining, depression and acceptance (Kübler-Ross & Kessler, 2005). The stages can vary in order and intensity, with repetitions and omissions. Thus, the grieving process remains highly individual, making it difficult to prove the five stages model empirically (Steinig & Kersting, 2015; Znoj, 2016). According to the dual process-model of coping, grief is moreover described as a dynamic process of oscillating between orientation towards the loss and orientation towards recovery (Schut, 1999). On the one hand, the grieving individual is challenged to process bond disruption by accepting the loss and dealing with intrusive reactions, denial, and avoidance. On the other hand, the surviving individual tries to focus his/her attention towards life changes, orienting to new scopes of action and exploring new roles and relationships (Stroebe & Schut, 2005; Stroebe et al., 2001). According to the dual process model, the more the individual can adapt to the loss, the better he/she manages to flexibly alternate between both processes.

Other than the above-mentioned grief models, Continuing Bonds (CB) theory is based on attachment theory. According to CB theory, the relationship with the deceased loved one does not end with his/her death, but rather transforms. CB theory predicts that the course and features of continuing relationships in part determine the adaptivity of grief pathways (Field & Filanosky, 2009; Klass et al., 1996). CB is defined as "the presence of an ongoing inner relationship with the deceased person by the bereaved individual" (Stroebe & Schut, 2005).

On the one hand, CB might serve as a grief-specific strategy helping the survivors to cope with the loss. The reminiscence and the ongoing feeling of a deep connection provides solace. If the deceased is represented as a role model and internalized secure base (internalized CB), CB is assumed to be adaptive. On the other hand, once the psychological proximity exceeds internal representation by inducing hallucinations, e.g., through the misperception of a stranger as the deceased, CB may become mal-adaptive (externalized CB) (Field, 2006a, 2006b). Ext. CB is hypothesized to be indicative of unresolved loss, as it shows the inability of the surviving individual to realize that the loss occurred and therefore hinders integration of the loss into their life (Field & Filanosky, 2009). In a long-term, ext. CB might result in a greater risk of developing chronic diseases or even higher mortality. In contrast, int. CB should facilitate adaptive grief, as it helps integrating the loss in one's life by nurturing the positive development of the surviving individual (Field & Filanosky, 2009).

A more recent theory of grief combines cognitive stress theory and attachment theory as it postulates grief as being a more unconscious and automated process (O'Connor & Seeley, 2022). Within this theory, bonding is assumed to continue (similarly to CB theory), as the lost person persists in one's memory "forever". It is hypothesized that the neural architecture of the bond supports the belief (or the semantic knowledge) that the other persists, despite any sensory evidence (O'Connor & Seeley, 2022). Adapting an earlier model of acute and chronic alterations in biomarkers after bereavement (O'Connor, 2019), this model predicts that pre-existing reward or learning history (e.g., having an anxious attachment style, or cognitive impairments) influences problems in "grief learning", and therefore, whether loss adaptation follows without complications (for a detailed description, see O'Connor & Seeley, 2022).

1.4 When grief does not dissolve – prolonged grief

Although most mourners adapt to the loss after a certain amount of time (Bonanno et al., 2005; Lundorff et al., 2017), bond disruption sometimes results in psychopathology. The fact that there is a proportion of people who exhibits grief beyond the short-term, acute response, has in parts fuelled international interest in the study of prolonged grief trajectories. *Complicated grief* (CG) is a condition that affects approximately 10% of bereaved individuals and is marked by intense longing and yearning for the deceased (Middleton et al., 1998; Prigerson et al., 1995; Prigerson et al., 2009). While the term CG is historically rooted in the attempt to distinguish bereavement complications from major depression (Shear et al., 2011; Zisook & Shuchter, 1993), *Prolonged Grief Disorder* (PGD) or *Persistent Complex Bereavement Disorder* (PCBD) represent a small diagnostic entity (Maciejewski et al., 2016; Prigerson et al., 2021; Prigerson et al., 2009). PGD has been newly included into the

International Classification of Disorders (ICD-11) (World Health Organization, 2018), whereas PCBD is just being discussed in detail for inclusion into the revised version of the fifth Diagnostic Statistical Manual of Mental Disorders (DSM-V; DSM-VTR) (American Psychiatric Association, 2013, 2022). Symptoms involve clinically relevant intense yearning for the deceased, preoccupation with thoughts of the deceased, maladaptive behaviours related to the death, social isolation, identity disruption, marked sense of disbelief about the death, intense emotional pain (e.g., anger, bitterness, sorrow), emotional numbness, amongst others, that occur either six- or 12-months post-loss (depending on the diagnostic system) (Maciejewski et al., 2016; Prigerson et al., 2021; Prigerson et al., 2009).

According to a representative study in Germany (*N* = 2498), the prevalence of PGD/PCBD is about 1.2-1.5% in the general population and 3.3-4.2% in the grieving population (*N* = 914) (Rosner et al., 2021). Based on a meta-analysis which included studies from Asia, Europe, Australia and the US, prevalence rate is at 9.8%, whereas higher rates are observed in older populations, in longitudinal studies and in self-report studies (Lundorff et al., 2017). Although only a small proportion of mourners develop prolonged grief symptoms, there might be a high number of unreported cases. Moreover, the inclusion of PGD and PCBD into the diagnostic manuals indicates the clinical significance of researching aspects of reactions to loss that might impair well-being of the individuals affected long-term (Maercker et al., 2013). For example, it has been demonstrated that PGD is associated with reduced quality of life, increased suicidality, depression, anxiety, and posttraumatic stress disorder (PTSD), as well as physical distress such as heart attack and high blood pressure (Vang et al., 2022). Likewise, the implementation of the new diagnostic category points out the existence of factors or circumstances that make grieving individuals suffer more severely than others.

1.5 Neurobiological changes as potential mechanisms for adverse health outcomes after bond disruption

During the past decades, research has been increasingly focusing on the neurobiological underpinnings of the formation and disruption of social bonds (Insel & Young, 2001). Collective knowledge about normative biological processes that follow social isolation and loss, might help researchers and practitioners better understand, diagnose, predict, and treat deviations from those trajectories, peaking in mental and physical illness. Attachment formation and maintenance is linked to neuroendocrine systems such as oxytocin (OT), arginine vasopressin (AVP), dopamine (DA), and corticotrophin-releasing-hormones (CRH) (Carter, 2017). More specifically, it has been shown that forming and maintaining pair bonds is associated with central-nervous release of the neurotransmitters or neuromodulators dopamine and OT in the reward system (Ditzen, Eckstein, et al., 2019; Insel & Young, 2001;

Kakarala et al., 2020; Zietlow et al., 2019). Those reactions then lead to the regulation of the autonomic nervous system in a cascade of further hormonal responses (Eckstein et al., 2014; Zietlow et al., 2019). OT has been shown to facilitate the formation of pair bonds and friendships as well as their positive effects (Pohl et al., 2019). As the hormone plays a role in attachment formation and maintenance, it might also do so in isolation and loss. Research on neurobiological underpinnings of human social isolation and loss is influenced by animal models and animal research where mostly monogamous prairie voles are used. In this species, the loss of a mate is associated with enormous stress reactions (Bosch et al., 2009), and it was shown that this stress is attenuated by the central nervous application OT (Grippo et al., 2009). Regarding the neurobiological response to social loss, dysregulation of the hypothalamic-pituitary-adrenal axis (Buckley et al., 2012) and the immune system are often investigated (Assareh et al., 2015; Schultze-Florey et al., 2012). At this point it is important to mention that the stress system as well as the immune system are regulated by central nervous OT mechanisms (Zietlow et al., 2019). Although research on OT in loss is scarce, animal studies suggest the role of OT in emotional dysregulation after partner loss (Hurlemann & Scheele, 2016). Within humans, OT has been associated with high relationship distress or missing relationships, although only in women (Taylor et al., 2006; Taylor et al., 2010). On the other hand, vasopressin seems to be elevated in men with high relationship distress (Taylor et al., 2010).

Investigating and summarizing neurobiological underpinnings of human social isolation and loss not only adds to the subjective, self-report level, but also helps close the link between social relationships and long-term impairments. In the long term, it might support researchers and practitioners in predicting and identifying subpopulations that are at risk for adverse health-trajectories.

1.6 Similarities and differences in loss types using a multifactorial approach

Just as the reasons and characteristics of forming and maintaining an attachment to someone might differ depending on the type of attachment, isolation and loss experiences might also vary. For example, while parents or siblings are not “self-chosen” and thus affection is not always mutual, romantic relationships and friendships are mostly voluntarily chosen, creating social support, closeness and intimacy on both sides (Flannery & Smith, 2021). This might strongly influence how a separation is experienced. It should also make a large difference, whether the loss was voluntary (e.g., deciding to dissolve a friendship or romantic relationship) or involuntary (being left by a friend or romantic partner), e.g., regarding feelings of responsibility. Additional important factors might be the type of loss, and whether the loss is temporary (being separated due to living long-distance from each other, being socially isolated)

or permanent (divorce, breakup, friendship dissolution or loss through death). Illuminating potential similarities and differences could help detect common underlying mechanisms and thus better understand the nature und (dys-)functionality of loss reactions.

To sum up, social relationships are highly variable and thus reactions to isolation and loss in humans differ depending on moderating factors. It is therefore important to aggregate both similarities and differences in the diverse stages or scenarios to better understand the underlying processes of grief and to deduce implications for risk groups and interventions. Furthermore, as social loss is an inevitable part of life, it might be important to explore the "positive" or healing aspects of grief, which adds to the understanding of grief and loss as an inevitable life event. Through the ongoing investigation of potential factors that could protect against strong reactions to isolation and loss, researchers will be able to gain an increasing understanding of the underlying processes. With this knowledge, preventive programs and interventions will be better able to adapt to the individual needs of the humans affected.

1.7 Aims of the present dissertation

The first aim of this dissertation is to analyse reactions to social isolation and social loss on both the neuroendocrine and the psychological levels, as well as to identify similarities and differences. The second aim is to synthesize psychological and contextual factors that are promoting vs. hindering adaptive reactions to social isolation and social loss. This might illuminate not only negative, but also positive or healing aspects of losing a loved one. Within this dissertation, I will address the above-mentioned issues using examples from different contexts. The aims are to 1) identify effects of temporal separation through social isolation in romantic relationships on loneliness and cortisol as neuroendocrine stress response, 2) systematically review neuroendocrine correlates of grief and moderating variables, and lastly, 3) assess how contextual factors of the loss, attachment style and different types of continuing the bond to a deceased loved one influence complicated grief and post-traumatic growth.

By addressing physiological, psychological, and contextual aspects using different research designs, I aim to shed a multi-modal light on social isolation and social loss and thus give impulses for future investigations.

2 Temporary separation through social isolation

2.1 Social isolation and physical and mental health

Within the past decades, research on the long-term effects of social isolation and loneliness on health has increased (Holt-Lunstad & Steptoe, 2022; Steptoe et al., 2013). Whereas loneliness is defined as a subjective distressing feeling of isolation or the perceived

discrepancy between actual and desired social involvement, social isolation is described as an objective indicator of being alone (Fried et al., 2020; Holt-Lunstad & Steptoe, 2022). Both social isolation and loneliness have been linked to increased risks for adverse physical and mental health outcomes (Creese, Khan, Henley, O'Dwyer, Corbett, Da Silva, et al., 2021; Leigh-Hunt et al., 2017), such as psychosocial stress (Beutel et al., 2017), depression (Erzen & Çikrikci, 2018), generalized anxiety (Beutel et al., 2017), cognitive decline (Lara et al., 2019), dementia (Kuiper et al., 2015), cardiovascular diseases (Ruwanpathirana et al., 2015; Steptoe et al., 2013; Valtorta et al., 2016; Xia & Li, 2018), chronic obstructive pulmonary disease (Barton et al., 2015), suicidal behaviour (Fässberg et al., 2012) and all-cause mortality (Heffner et al., 2011; Holt-Lunstad et al., 2015; Holt-Lunstad et al., 2010; Steptoe et al., 2013; Yu et al., 2020). Chronic loneliness might even hinder the formation of new social relationships by provoking negative cognitive biases such as interpersonal distrust (Lieberz et al., 2021).

Although most of the studies use observational designs only (Leigh-Hunt et al., 2017), thus prohibiting causal conclusions, research on potential underlying psychobiological mechanisms may reveal pathways through which loneliness and isolation effect health (Steptoe et al., 2004). It is assumed, e.g., that loneliness and isolation initiate declines in stress-protective hormones which lead to adverse effects on heart rate, blood pressure, neuroendocrine and immune system, and sleep rhythms (Cacioppo & Cacioppo, 2014; Cacioppo & Hawkley, 2003; Heffner et al., 2011; Uchino et al., 1996). Moreover, there is vast evidence on elevated cortisol levels (Adam et al., 2006; Doane & Adam, 2010; Lai et al., 2018), altered cortisol awakening responses (Doane & Adam, 2010; Lai et al., 2018) and increased inflammatory activity (Heffner et al., 2011) in loneliness and social isolation.

One structural proxy of social isolation is represented by single-living arrangements, which are a strong predictor for physical and mental health (Steptoe et al., 2013). According to a study conducted in Germany in 2016, above 30% of all households were one-person households (Klinenberg, 2016). More interestingly, in early adulthood (18 to 30 years), over 30% of German residents were living without their partner (*living apart together*) (*Zensus 2011: Vielfältiges Deutschland*, 2011). According to another survey conducted in Germany in 2018, about 27 to 39% of the individuals indicated that they had a long-distance relationship (Statista, 2018).Similarly, within the United States, the number of couples *living apart together* between the ages 23-70 rose from 6-7% in the late 90s to 13% 20 years later (Strohm et al., 2009). Moreover, long-distance relationships are common, especially among young students (Stafford et al., 2006).

Consistent with the model of co-regulation, dysregulation and self-regulation (Sbarra & Hazan, 2008), it has been previously hypothesized that even short separations from a partner might be perceived as disruptive, as they are accompanied by the loss of co-regulation (Diamond et al., 2008). Diamond and her colleagues investigated co-habiting couples

separating in everyday life due to job-related travels. They found significant changes in subjective stress and HPA axis activity, amongst others, especially in those who were left behind and who displayed high separation anxiety (Diamond et al., 2008). This is accordance with the attachment model, which predicts higher separation distress in individuals with high attachment insecurity (Mikulincer & Shaver, 2022). Furthermore, wartime or job-related separations, and especially novel and irregular separations from the partner, are associated with elevated depressive, anxiety, and physical symptoms, sleep disturbances and loneliness (Robles & Kane, 2014; Vormbrock, 1993). Likewise, separating at the airport is associated with elevated sadness levels and proximity-seeking behaviour, such as caregiving, contact seeking, and contact maintenance in couples (Fraley & Shaver, 1998). Long-distance relationships are additional challenges in romantic relationships (Hamilton & Meston, 2010; Sahlstein, 2004), and factors such as high relationship quality, might protect against potential breakups or conflicts (Kelmer et al., 2013; Yoder & Du Bois, 2020).

2.2 Loneliness and cortisol in divorced and isolated couples during Covid-19 lockdown (Paper I)

The COVID-19 outbreak during the beginning of 2020 led to rigorous lockdown regulations, especially in the beginning of the pandemic. Individuals were confronted with restrictions of unknown duration, which was linked to worries, particularly in those who were already burdened (Hopf et al., 2021). By being asked to stay at home, individuals were obliged to refrain from physical contacts other than those with whom they were living. Thus, COVID-related lockdown resembles an extremely unique situation, providing increased risk to cause or amplify social isolation and persisting feelings of loneliness. According to a recent statistic in Germany, in the year of 2020, 13.8% of the middle-aged and elder adults were feeling lonely, which is about 5% higher compared to 2014 and 2017 (Huxhold & Tesch-Römer, 2021). However, loneliness changes after lockdown onset seem to depend on moderators, such as sex (Creese, et al., 2021; Hansen et al., 2021), pre-lockdown levels of loneliness (Creese et al., 2021; van der Velden et al., 2021), distress and social support (Hansen et al., 2021).

To prevent long-term effects of loneliness and isolation, it is crucial to examine potential buffering factors and moderators. In accordance with the social buffer hypothesis (Cohen & Wills, 1985), meaningful social contacts such as romantic relationships can be protective in various contexts and populations (Ben-Zur, 2012; Ditzen, Germann, et al., 2019; Ditzen & Heinrichs, 2014; Högnäs, 2020). On the other hand, divorce or widowhood increases the risk for loneliness (Dahlberg et al., 2021), thus showing the adverse effects of the loss of a loved one. Moreover, it is rather the quality of a relationship and not only the fact of being in a relationship that explains differences in loneliness (Hawkley et al., 2008; Mund & Johnson,

2021; Pinquart & Sörensen, 2000). Lastly, being in a romantic relationship is associated with lower aggregated cortisol levels compared to being single (Chin et al., 2017), and affectionate couple interactions are linked to reduced cortisol levels (Ditzen, Germann, et al., 2019; Ditzen & Heinrichs, 2014).

As mentioned above, living with others might protect against loneliness (Greenfield & Russell, 2010), but also neuroendocrine stress responses (Stafford et al., 2013) as well as mortality risk (Tabue Teguo et al., 2016; Zueras et al., 2020). During strict lockdown due to COVID-19 pandemic, couples who were living apart from each other faced challenges that were comparable to couples who were living in a long-distance relationship. They were both temporarily separated from their partner and forced to keep physical contacts with their loved one to a minimum. We thus expected couples living apart from their partner to exhibit equally high burden levels compared to singles during lockdown.

Given the vast evidence on structural factors of social isolation and loneliness outside of COVID-19, the aim of our first study was to assess the role of both relationship status and living arrangements in the subjective perception of isolation (trait and state loneliness) as well as neuroendocrine stress-responses (cortisol levels) during COVID-19 lockdown (Hopf, Schneider, et al., 2022). We expected highest levels of loneliness in divorced and widowed participants, followed by singles and lastly, couples. Likewise, we assumed living alone as well as being single to be a risk factor for elevated loneliness and cortisol levels. Most notably, we hypothesized that the prohibition to visit the romantic partner represents temporary loss or separation and thus, individuals who were not living with their partner during lockdown, consequently showed loneliness levels comparable or higher to single individuals. Moreover, we expected that momentary loneliness would be positively linked to cortisol. We also hypothesized that living situation and relationship were moderators of this association. Finally, as found by previous investigations (Kelmer et al., 2013; Yoder & Du Bois, 2020), we assumed that high relationship quality buffered loneliness in individuals who were not living with their partner.

To test our hypotheses, we conducted an online survey with subsequent ecological momentary assessments (EMA) in every-day life in the beginning of first lockdown between April and July 2020 in Germany. The analyses reported in this dissertation are part of time-point 1 within a longitudinal mixed-method design, which consists of two time-points assessed in a one-year interval. *N* = 1054 participants (Age *M* = 36.32, *SD* = 14.75, *Range* = 18;81, 77.7% female) reported on demographics, living situation and levels of trait loneliness via the revised version of the German *University of California* (UCLA) *Loneliness Scale* (Russell et al., 1980). Participants who were in a romantic relationship additionally reported on their relationship quality via the *Partnerschaftsfragebogen* (Hahlweg, 2016). *N* = 247 of the participants who took part in the online study fully completed the EMA study by collecting six

saliva samples for cortisol extraction on two successive days and simultaneously answering questions on their current level of loneliness (visual analogue scale VAS from 0 to 100). Health behaviour variables were measured at each assessment time-point to control for sleep, food, drink, and drug consumption as well as physical activity, according to author consensus guidelines (Stoffel et al., 2021; Strahler et al., 2017). Results within the online study sample revealed highest mean trait loneliness in divorced and widowed participants, followed by singles and participants who were in a romantic relationship. This pattern was also found in the EMA sample, with singles displaying higher mean state loneliness levels compared to the participants who were in a romantic relationship.[2] This is consistent with research on romantic relationships as buffers for loneliness (Ben-Zur, 2012; Ditzen, Germann, et al., 2019; Ditzen & Heinrichs, 2014; Högnäs, 2020). More interestingly, subsequent interaction analyses showed that those who were living alone and apart from their partner displayed loneliness levels comparable to alone living singles. Furthermore, being in a relationship and living alone was associated with significantly elevated levels of state loneliness compared to being in a relationship and living with the partner or with others. On a hormonal level, we found significantly lower mean cortisol levels in those who were in a relationship compared to singles, but no differences with respect to the living situation. Thus, romantic relationships protected against neuroendocrine stress-responses as shown in previous literature. Additionally, in line with our hypothesis, participants who were in a relationship displayed weaker loneliness-cortisol associations compared to singles. One potential mechanism could be that participants who were in a romantic relationship have counter-regulated their physical stress-responses to loneliness through mechanisms that are specific to romantic encounters such as affectionate touch or intimacy. However, these mechanisms need to be directly addressed in future. Lastly, we found relationship quality to be negatively correlated with mean state loneliness in everyday life.

In summary, previous findings on divorce/widowhood as a risk factor and romantic relationships as buffers for loneliness were replicated, both on a trait and a momentary level. Moreover, direct associations of loneliness with neuroendocrine stress-responses were reduced in those with a partner, showing that there might be characteristics in a relationship that buffer short-term reactions to negative psychological states such as loneliness. However, this issue needs to be addressed in an experimental design directly measuring postulated mechanisms such as intimacy, positive interactions, or touch. The most fascinating finding is that temporary separation from the partner during lockdown was linked to higher degrees of loneliness in everyday life, nihilating the partner as social buffer and showing the strong link between physical isolation and mental health. Additionally, although it cannot be causally

[2] As in the EMA subgroup, only n = 4 divorced/widowed participated, we did not include them in the analyses.

interpreted, it indicates the importance of intimate contact or at least physical proximity for the health-promoting effects of romantic relationships. This has been partly shown in previous studies, e.g. with regard to cortisol responses (Ditzen, Germann, et al., 2019; Ditzen et al., 2008), electrodermal activity (Han et al., 2021), self-reported pain (Bourassa et al., 2019), and c-reactive protein (Jolink et al., 2023). Lastly, relationship quality protected against loneliness in couples, however, it did not reduce loneliness in those who were living apart together. Future research could address other mechanisms which buffer high loneliness in couples. For example, enduring vulnerabilities such as attachment insecurity, depression, emotion regulation strategies or neuroticism might play a role (Pietromonaco & Overall, 2022).

3 Permanent separation through social loss

Losing someone through death is one of the most critical life events, evoking emotional, cognitive, behavioural, and somatic changes in the surviving relatives. Amongst others, grief is characterized by yearning, sadness, crying, distress, anxiety, and depression (Biondi & Picardi, 1996; Kristensen et al., 2012). The intensity and duration of short-term reactions to loss moderate the development of chronic issues by influencing the vulnerability to psychiatric or psychosomatic diseases. Long-term consequences involve increased risks for developing cardiovascular diseases (Biondi & Picardi, 1996), Major Depressive Disorder (Assareh et al., 2015), and elevated mortality risk (Carey et al., 2014). Especially due to current discussions and the inclusion of PGD/PCBD into the diagnostic systems, it is important to study antecedents and factors that explain psychological and physiological adjustment to loss.

According to the model of co-regulation, dysregulation and self-regulation, the amount and longevity of short-term physiological stress-responses after bond disruption help improve predictions of long-term adaptation to loss and its effects on health (Sbarra & Hazan, 2008). Within physiology research, the neuroendocrine system plays a significant role, as it is directly activated after an internal or external stressor has occurred. The unspecific neuroendocrine stress-reaction takes place in the sympathetic adrenal medullary (SAM) system and the hypothalamic-pituitary-adrenal (HPA) axis. The SAM system provides a rapid and automated reaction to physiological and psychological stressors, mediated by catecholamines (Godoy et al., 2018). The SAM system eventually activates the HPA axis, resulting in the synthesis of corticotrophin-releasing hormones (CRH) and vasopressin (VP), hence stimulating the secretion of adrenocorticotrophic hormones (ACTH) into the peripheral circulation (Aguilera, 2012). Consequently, this leads to the release of glucocorticoids (e.g., cortisol) in the adrenal gland and to negative feedback inhibiting HPA axis SAM activation in the brain (Aguilera, 2012; Stephens & Wand, 2012). Provided that those systems are functioning well, the organism will quickly go back to normal (Wadsworth et al., 2019). However, if activation is prolonged due to

malfunctions or an ongoing stressor, the HPA axis gets chronically activated, engaging cardiovascular, metabolic, immunologic and central nervous activity (Wadsworth et al., 2019). Regarding the social stressor of losing someone, studying neuroendocrine changes thus helps researchers classify the magnitude and longitude of physiological reactions to loss and predict adaptation and long-term health impairments. Moreover, by examining potential moderators of neuroendocrinology, we get increasingly comprehensible insights into the extent and course of grief as well as into the mechanisms through which losses affect the surviving human beings.

3.1 Neuroendocrine reactions to social loss and contributing factors (Paper II)

Neurobiological changes after social loss have already been investigated, e.g., showing disruptions in HPA and SAM axis activity (Bosch & Young, 2017; Goodkin et al., 1998; Mason & Duffy, 2019), altered inflammatory responses (Knowles et al., 2019; O'Connor, 2012) and sleep disturbances (Lancel et al., 2020), amongst others. Beyond stress hormones, the neuropeptide OT might play a role as it is linked to social relationships and attachments. Within animal studies, social isolation has been linked to decreased OT concentrations (Grippo et al., 2009) and negative effects of isolation could be buffered through OT administration (Insel & Winslow, 1991). However, human research on the role of OT in grief is scarce. Likewise, there is no study summarizing moderators of neuroendocrine stress responses, although this might improve the understanding of different grief trajectories. Thus, the aim of study II was to systematically review literature on neuroendocrine reactions to social loss and to simultaneously identify moderators for grief trajectories. Due to the high heterogeneity of the methods used to assess the outcome measures, we decided not to conduct a meta-analysis, but to summarize and interpret the findings in a systematic way.

Within our review, we searched for all original studies that investigated any neuroendocrine markers (cortisol, epinephrine, norepinephrine, OT, insulin, prolactin, endorphin) in human adults aged 18 or older who have lost a loved one (Hopf et al., 2020). After systematic and careful selection, we finally included 26 articles, most of which investigated cortisol (saliva, blood, or hair) as primary outcome. Fewer studies investigated catecholamines, insulin, prolactin, and OT as primary outcomes after bereavement. The main and most robust findings were higher levels of cortisol and flattened diurnal cortisol slopes in bereaved compared to non-bereaved adults, which indicates a disrupted physiological stress response (Adam et al., 2017). As former studies have linked flattened day-slopes to adverse physical and mental health outcomes (Adam & Kumari, 2009; Adam et al., 2017), such as depression (Doane et al., 2013), anxiety, cancer, cardiovascular disease, or inflammation (Adam et al., 2017), the magnitude of disrupted HPA axis activity could be an indication for future mental or physical health impairments after loss. Furthermore, compared to normally

grieving subjects, individuals with CG showed significantly lower morning and overall cortisol levels, as well as flattened diurnal cortisol slopes. Five years after loss, individuals with CG displayed significantly higher cortisol morning responses and overall cortisol responses compared to the time directly after the loss. All in all, results indicate higher HPA axis dysregulation in prolonged grief (Holland et al., 2014). Regarding peripheral OT concentrations, one study compared circulating OT levels in individuals with CG, to individuals with non-CG and to non-bereaved patients with major depressive disorder (Bui et al., 2019). The authors found significantly higher OT concentrations in participants with CG compared to the other two groups, which indicates previously assumed involvement of the OT and the attachment system in prolonged reactions to loss. Elevated OT levels in individuals with prolonged grief might mirror their difficulties to integrate the loss into their life as their bond to the lost loved one is still strong. This is in accordance with neuroscientific evidence on the attachment- and reward-system being more actively involved in CG participants while yearning lost loved ones (McConnell et al., 2018).

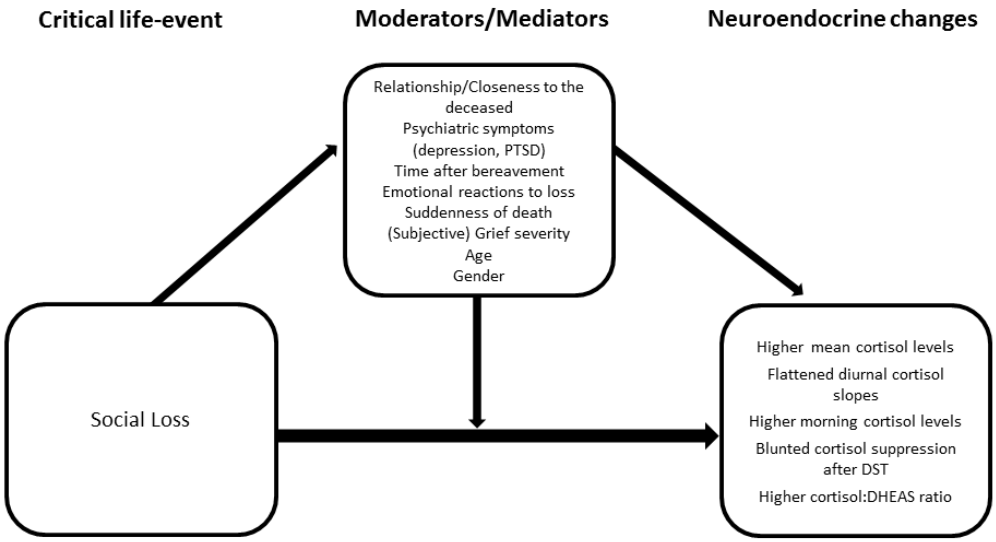
Most importantly, neuroendocrine stress reactions depended on numerous moderators (see Figure 2). For example, the more deaths an individual has experienced, the higher cortisol levels were found. Interestingly, participants experiencing longer death forewarning displayed higher levels of cortisol compared to participants who had experienced a shorter forewarning. One reason might be that stress exposure was prolonged due to a longer preparation period, which overall resulted in higher cortisol levels. Affective states also play a role in neuroendocrine grief reactions. For example, men suffering from emotional numbness six months post-loss, showed higher cortisol levels twelve months after death, compared to men who did not suffer from emotional numbness. However, this did not hold true for women, indicating sex specific reactions. Another important moderator was grief intensity: Higher scores in grief severity were associated with lower morning cortisol levels.

Whereas most of the studies within the review assessed basic neuroendocrinology after loss, only a limited number of studies investigated changes in neuroendocrinology after psychosocial interventions. One article found reduced cortisol levels after a bereavement support group (Goodkin et al., 1998). Another study discovered that epinephrine levels predicted psychopathology after CG treatment and moderated the effectiveness of the treatment (O'Connor et al., 2013). Additionally, pre-loss intervention elevated cortisol levels and reduced prolactin levels in surviving relatives, supporting the hypothesis that preventive measures “pre-activate” grief and thus promote mourning, which as a consequence helps advance the grieving process (Theorell et al., 1987). This is interesting in the way that neuroendocrinology and HPA/SAM axis activation might have different long-term effects depending on timing. Early HPA axis activation could prevent from prolonged grief in that it

"prepares" the body for the upcoming loss. On the other hand, prolonged activation, or hyper-activation over a longer time might foster the development of chronic health impairments.

Figure 2

Moderators of neuroendocrinology after social loss.



Note. This Figure stems from Paper II (Hopf et al., 2020) and summarizes the results of the studies investigating neuroendocrine mechanisms of grief. DHEAS, dehydroepiandrosterone-sulphate; DST, dexamethasone suppression test; IGF, insulin-like growth factor; OT, oxytocin; PTSD, post-traumatic stress disorder.

The quality of the studies, which was assessed with the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Heart Lung and Blood Institute, 2017), was average low to moderate. This is due, in part, to the lack of measuring pre-bereavement hormonal levels, which makes it difficult to rule out intraindividual variance in the outcomes of interest. Furthermore, although it has been previously shown that grief experiences differ largely between persons (Rosenblatt, 2017), comparisons were mainly done between groups of grievers and non-grievers, without accounting for subjective grief severity.

To sum up, studies on neuroendocrine reactions to social loss have mostly focused on changes in cortisol levels depending on the length of time since the death has occurred. Other variables such as adrenocorticotrophic or oxytocinergic reactions are highly understudied and should be focused on in future research. Nevertheless, the past decades of research show, that post-loss neuroendocrinology depends on moderators that could be separated in factors related to the death itself, environmental or person-related characteristics before the death, and psychological states after the death event. To capture sustained neuroendocrine grief

reactions and their long-term effects on health, future research could accompany grieving relatives over a longer timeframe, starting with pre-loss assessments with both person-related and state-related predictors, followed by assessments directly after the loss and continuous measurements afterwards. Lastly, the assessment of prolonged grief via questionnaire or standardized interview might help to evaluate the adaptivity of grief trajectories.

3.2 Continuing bonds after bereavement: effects on complicated grief and post-traumatic growth (Paper III)

As mentioned in section 1.3, social ties do not directly disappear after the loss of a loved one, they rather change in quantity and quality (Field & Filanosky, 2009; Root & Exline, 2014). Although the deceased person is no longer physically available, he or she remains in inner-cognitive and emotional representations as well as in behaviour and memory. Surviving relatives continue their relationship by thinking or reminiscing about their deceased (Marwit & Klass, 1995), telling stories (Nickman et al., 1998), dreaming (Black et al., 2021) or keeping possessions (Nickman et al., 1998). Moreover, the deceased loved one remains present through influencing the surviving person's character, lifestyle, and beliefs in everyday life (Foster et al., 2011; Nickman et al., 1998). According to CB theory, internalizing the bond is assumed to be adaptive as the grieving person integrates the lost loved one into an internal representation and uses him/her as a secure base. This has been in part shown since int. CB is associated with higher levels of post-traumatic growth (Field & Filanosky, 2009; Lipp & O'Brien, 2022; Scholtes & Browne, 2015; Tedeschi et al., 2017). According to the theory of post-traumatic growth, people often see growth following adversity or crisis, e.g., through their relationships, worldview, or other personal areas (Tedeschi & Calhoun, 1996). Personal growth after a traumatic event is assumed to occur when the individual successfully overcomes challenges associated with the loss, such as managing everyday-life stress on their own, but also reorienting one's own goal horizons (Tedeschi & Calhoun, 1996). Externalized CB, on the other hand, is assumed to be maladaptive, as it describes the grieving person's problems of accepting the loss and his/her failure to internalize the attachment figure (Field, 2006a, 2006b). Thus, ext. CB is hypothesized to lead to higher symptoms of unresolved grief such as CG (Field & Filanosky, 2009). Additionally, moderators might influence the associations of CB subtypes with grief. For example, finding peace and meaning in the loss could predict a better adaptation to the loss and therefore, higher int. CB scores (Neimeyer et al., 2006). Individuals who suffered a sudden or violent loss as well as individuals who feel responsible for the death, are also assumed to show higher ext. CB scores compared to those who do not feel responsible (Field & Filanosky, 2009). Furthermore, int. CB seems to rise with increasing closeness to the deceased, as a closer relationship is likely to be followed by a greater

disruption after loss (Field & Filanosky, 2009). Lastly, attachment style might contribute to the intensity of CB. According to attachment theory, avoidance is associated with the suppression (or hypo-activation) of the attachment system. Individuals with highly avoidant attachment style ought to remain distant from and minimize importance of close relationships (Mikulincer & Shaver, 2010). On the other hand, anxious attachment style is assumed to be linked to a hyperactivation of the attachment system. It has been hypothesized that insecure (both high-anxious or high-avoidant) attachment style is associated with higher ext. CB as it implicates greater difficulties to adapt to or internalize the loss (Field & Filanosky, 2009; Ho et al., 2013).

As CB could be one psychological indicator of the adaptivity of grief trajectories, it could in part explain why a proportion of grieving individuals develop CG and others do not. Therefore, having a reliable and valid measure of CB is essential to understand its associations with long-term adaptation to loss. So far, CB measures only exist in very few languages. The so-called *Continuous Bonds Scale* (CBS) is applied mostly in English-speaking populations (Field & Filanosky, 2009; Field et al., 1999; Scholtes & Browne, 2015; Stroebe et al., 2012) and has been validated only in Italian (De Luca et al., 2016) and Chinese (Ho et al., 2013). Thus, the primary goal of study III was to validate the current English version of the CBS of Field and Filanosky (2009) in a German sample and to investigate their relationship to CG and posttraumatic growth. The secondary goal was to replicate the above-mentioned findings on contributing risk and protective factors for unresolved CB (Hopf, Eckstein, et al., 2022). We used the latest version of the CBS for psychometric validation, which was originally developed by Field and his colleagues (Field et al., 1999). This version is the first to introduce the two subscales ext. CB and int. CB (Field & Filanosky, 2009). and consists of 16 items with ten items representing int. CB and six items representing ext. CB. Two native speakers translated the English items into German, a third person back translated it and finally the two native speakers reviewed it until reaching consensus regarding the wording. Between May 2020 and October 2020, we recruited adult German-speaking participants via online grief portals, grief funeral homes, bereavement groups, and hospices from all over Germany. Our final sample consisted of N = 364 participants with a mean age of M = 48.16 (SD = 13.32). Most of the participants were female (89.9%) and the majority had lost a child (35.4%), followed by a parent (24.5%). The most frequently reported cause of death was an acute disease (27.5%), with a mean time since death of M = 7 years (SD = 7.08). The three most frequently reported time ranges were 5-10 years (22.5%), followed by 10-20 years (20.9%) and 2-5 years (19.5%).

Following the procedure of the original validation study, we conducted an exploratory factor analysis (EFA, principal axis analysis with oblimin rotation) to determine the optimal number of factors. We subsequently calculated confirmatory factor analysis (CFA) to examine whether a two-factor-model (10 items for the int. CB and six items for the ext. CB) showed a good fit to the data. According to EFA, both scree plot and parallel test justified a two-factor-

solution, which accounted for 42% of the total variance. Discriminative power of all items was medium to high (.43 - .69) and internal consistency of the subscales and the total scale was satisfying (Cronbach's α = .78 – .88). Although EFA indicated solutions that were consistent with CB theory, CFA could not fully confirm this exploratory approach, as the fit-indices of the two-factor-solution demonstrated only a fair fit to the data (*TLI* = .84, *CFI* = .86, *RMSEA* = .08, *SRMR* = .07). In accordance with our hypotheses, analyses of covariance revealed that violent deaths, closer relationship, and feelings of responsibility, were associated with significantly higher scores of ext. CB, but not int. CB scores. Thus, those features of the relationship as well as the loss event itself represent risk factors for ext. CB. Unfortunately, we did not assess subjective relationship quality but rather ranked the closeness of the relation. Although the relationships to the own child is assumed to be particularly strong (d'Epinay et al., 2010), having a low relationship quality might reduce the risk for prolonged or severed grief reactions (Amato & Hohmann-Marriott, 2007). In contrast, finding peace in the loss was positively associated with int. CB scores, although this correlation was non-significant. Nevertheless, the tendency indicates that accepting the loss reflects a resource in grief and helps integrate the deceased loved one into the internal representation of a secure base. Contrary to our predictions, we did not find a significant correlation between ext. CB and insecure attachment style, which was measured through the *Experiences in Close Relationships* scale (ECR-R) - short version (Ehrenthal et al., 2021). Regardless of the fact that null-effects were also found elsewhere (Ho et al., 2013), this could be due to statistical range restriction, as our sample did not display high levels of ext. CB in general. Likewise, traumatic losses might result in greater ext. CB compared to less subjectively traumatic or natural losses. As our sample mostly consisted of non-violent losses, it may have not adequately represented traumatic aspects of loss. Moreover, insecure attachment style was positively correlated with CG symptoms, assessed via the *Inventory of Complicated grief* (ICG-D) (Lumbeck et al., 2013). Although not hypothesized, this is consistent with attachment theory postulating that individuals with anxious or avoidant attachment styles have greater difficulties to cope with the loss due to the lack of self-regulatory resources and thus show higher risk for developing prolonged grief (Mikulincer & Shaver, 2022).

We additionally found differences depending on sex, with women reporting significantly higher ext. CB scores compared to men. Moreover, ext. CB was significantly and highly correlated with CG symptoms in women. This is in line with prior research, e.g., showing higher levels of traumatic grief, depressive and anxiety symptoms in females compared to males (Chen et al., 1999; Shulla & Toomey, 2018). One reason for the sex differences could be that men and women exhibit different grief trajectories. For example, it has been revealed that men express prolonged grief as an acute, decreasing reaction, whereas women tend to show extended, mounting grief (Lundorff et al., 2020). Alternatively, differences between men and

women regarding self-reported reactions to loss could be rooted in social, historical, or cultural differences such as distinct traditional roles or emotion expression (De Boeck et al., 2018). Lastly, the small number of male participants might also have contributed to the non-significant results.

Regarding post-traumatic growth, which was assessed with the *Posttraumatic Personal Growth Inventory* (PTPGI) (Maercker & Langner, 2001; Tedeschi & Calhoun, 1996), we found the expected small to medium positive associations with the int. CB subscale. More interestingly, correlations with the ext. CB were equally high, which was not consistent with our hypotheses. One reason could be that CB subtypes do not directly translate into everyday coping or that there are other important factors explaining or predicting posttraumatic growth that haven't been investigated yet (Yu et al., 2016). Alternatively, both subtypes could develop differently over time: the immediate reaction to the loss might be a shock initially and thus promote ext. CB, but later transform into int. CB.

To sum up, the results provide additional evidence on the role of continuing the bond to the deceased loved one in grief and grief coping. They also strengthen the assumption that differential aspects of the loss event as well as the relationship to the deceased, influence adaptation to loss by affecting post-traumatic growth and complicated grief. However, as our study is only cross-sectional and retrospective, we cannot make causal conclusions about the factors investigated. Both CFA and validation analyses revealed a less clear picture regarding the differentiation between ext. and int. CB. According to our data, both types of CB seem to play a role in both adaptive and mal-adaptive indicators of grief. Future research should investigate under which circumstances ext. CB is adaptive vs. mal-adaptive. By using a longitudinal design, potential factors could be frequently measured over the course of the grief process to display the complex nature and intraindividual variation of CB. Additionally, it could be interesting to examine to what extent the failure to transfer the externalized attachment figure into an internal representation, results in more unfavorable grief trajectories.

Although our study contains several limitations such as unequal sample sizes, cross-sectional design, and range restriction, it contributes to a clearer understanding of CB and its role in grief. Future intervention studies might help the grieving participants to foster "positive" aspects of continuing attachment and to shift the ext. CB to a more internalized, secure base. Subsequent grief research could therefore consider including int. and ext. CB as well as factors associated with the loss itself (violence, finding peace, feelings of responsibility) and relationship-related characteristics (closeness to the deceased) into their design.

4 General discussion

4.1 Summary of the results

The aim of the present dissertation was to analyze and compare responses to different types of losses using a multifactorial approach. On a physiological level, I focused on neuroendocrinology, as it is one of the central systems affecting various other structures within the body. On a psychological level, I concentrated on loneliness and subjective grief responses. By using different research designs, aspects of social isolation and social loss were assessed both on a state level in every-day life (Paper I) and on a trait level (Papers I, II and III). Starting with temporary separation through social isolation, I analyzed loneliness and diurnal cortisol levels as neuroendocrine stress response in couples living together vs. separated. Next, I systematically reviewed neuroendocrine stress responses to permanent loss and their moderators. Finally, different types of continuing bonds and their prediction in complicated grief and post-traumatic growth were investigated with further examination of contextual, attachment-related, and relationship-related moderators.

Data gathered during initial COVID-19 lockdown (Paper I) revealed higher levels of trait loneliness in divorced and widowed participants, compared to singles and individuals who were in a relationship. In everyday life, single individuals displayed higher levels of cortisol and state loneliness, compared to those who were in a relationship. This is in accordance with earlier studies demonstrating the stress-buffering effect of romantic relationships (Ben-Zur, 2012; Beutel et al., 2017; Robles & Kiecolt-Glaser, 2003). Most interestingly, the buffering effect of a romantic partner was not present anymore when individuals were living alone and apart from their partner. Although within this context, we investigated social isolation and not social loss, even the temporary separation from the partner during lockdown was experienced as psychologically aversive, but only if the individual was living alone. However, we did not directly measure underlying mechanisms and the analyses were made in an ecologically valid environment, thus limiting interpretation to correlations only. Despite our expectations based on previous studies showing that physical contact and intimacy with the partner are one key factor modulating physiological stress-responses (Diamond et al., 2008; Ditzen, Germann, et al., 2019; Ditzen et al., 2008), cortisol levels did not differ depending on living arrangements in couples. Lastly, state levels of loneliness were associated with cortisol in individuals who were in a relationship, indicating that emotional states might be directly related to the neuroendocrine stress response.

The review of neuroendocrine reactions occurring in bereaved adults after losing a loved one through death (Paper II) revealed disrupted HPA axis activity, SAM activity, as well as elevated circulating OT levels. HPA axis dysfunction after loss is also found in research on

trauma (Daskalakis et al., 2016; Morris et al., 2016) and loneliness (Brown et al., 2018; Hackett et al., 2012; Hopf, Schneider, et al., 2022; Schutter et al., 2017; Steptoe et al., 2004) which represent individual aspects or consequences after bereavement and stress-related neuroendocrine dysregulation. Moreover, neuroendocrine disruptions were moderated by closeness to the deceased, psychiatric symptoms (depression, PTSD), affective reactions (grief severity, emotional numbness, yearning, complicated grief), loss-related factors (time after bereavement, suddenness of death, number of experienced losses), and lastly, characteristics of the surviving person (age, sex, use of social support, increasing separation anxiety). The results are in line with the model of co-regulation, dysregulation, and self-regulation (Sbarra & Hazan, 2008), which postulates that the loss of a close attachment figure is accompanied by an organized physiological stress response. Results on relationship-related factors such as closeness to the deceased influencing neuroendocrinology, are consistent with literature on PGD symptomatology: Losing a child or partner is associated with highest PGD-symptoms compared to loss of a parent or close relationship (Shear, 2012; Tang & Xiang, 2021). To sum up, results from study II indicate that neuroendocrine disruptions can prevail even years after loss and that those changes are non-linear and influenced by many moderators. In the long term, neuroendocrine changes could influence psychopathology, in that they either foster quicker adaptation to loss or facilitate mal-adaptive reactions to loss.

Lastly, I validated a self-report questionnaire measuring the ongoing relationship to the deceased loved one (ext. and int. CB) via the CBS (Paper III). I continued with analyzing the influence of person- and relationship-related features in CB and the associations between CB and CG as well as post-traumatic growth. Although results indicate a fair fit of the two-factor solution, items were highly reliable. Contrary to our expectations, both ext. CB (e.g., hallucinations of the deceased), and int. CB (integrating the lost loved one into inner representation and using its relationship as a secure base) were positively associated with CG. This means that a stronger ongoing inner or outer bond to the deceased loved one might be a risk factor for prolonged CG. Interestingly, associations between CG and ext. CB were only significant in women, indicating that continuing attachment might have differential effects depending on sex. Post-traumatic growth was significantly positively associated with both int. and ext. CB, implying that even when having externalizing thoughts of the deceased, the surviving individual's personality showed growth and could find "positive" meaning in the loss. Regarding moderators, violent losses, closer relationships to the deceased and feelings of responsibility for the death were significantly associated with higher ext. CB., but not int. CB scores. Thus, disadvantageous factors of the death event itself and of the relationship play a role in adverse CB outcomes. Contrary to our predictions, attachment style was not associated with either type of CB. However, higher anxious and avoidant attachment style were positively associated with CG symptoms. This is in accordance with extended attachment theory

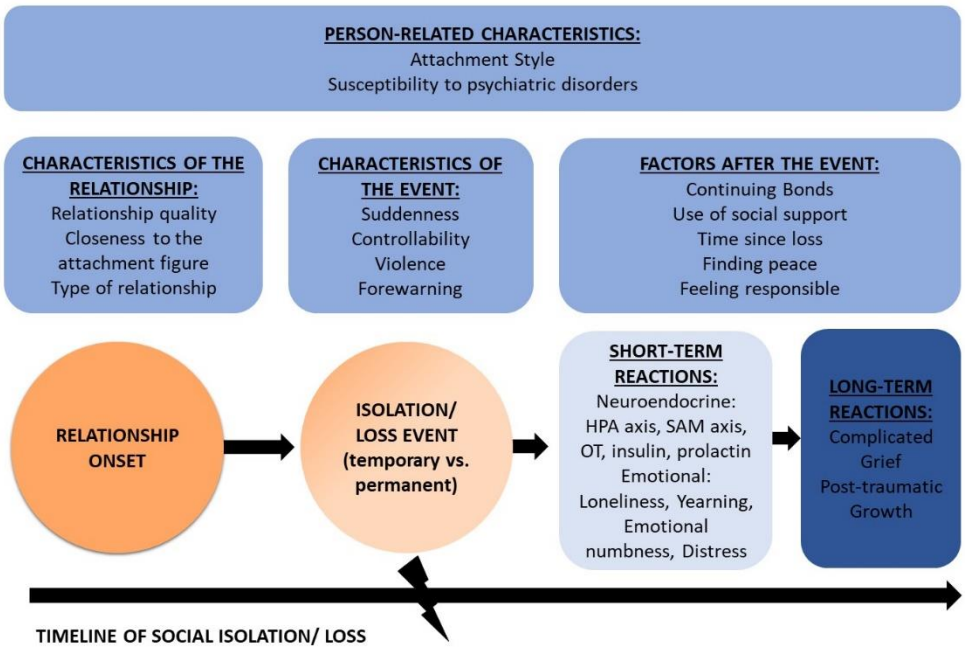
postulating that higher insecure attachment-style might lead to greater difficulties to adapt to a loss (Mikulincer & Shaver, 2022).

4.2 Joint interpretation of the results

When taking a step back, one might notice that social isolation and social loss share similarities: in both situations, one or more social attachment figures are somehow missing (either temporarily or permanently). Both social isolation and loss are directly associated with emotional reactions, such as, e.g., loneliness, yearning, emotional numbness, and negative affect. Furthermore, they both represent an objective state rather than the perception or reaction of the person affected. There is high variation in the subjectivity of the responses as well as in the long-term consequences. Thus, it is important to include psychological self-report measures when conducting research on social isolation and loss. Within Figure 3, the results gathered during this dissertation, are summarized, and thematically arranged to get an overview of the factors investigated and to take them into context.

Figure 3

Summarized results of the dissertation.



Note. This figure shows factors influencing the course of social isolation and/or loss; all results depicted here have been gathered within this dissertation.

First, relationship-related aspects such as relationship quality, closeness to the attachment figure and type of relationship exert influence on bond formation, maintenance and social isolation or loss. Secondly, aspects of the loss event itself might affect subsequent

reactions. Moreover, external factors, such as suddenness of the loss, violence, or controllability, are objective aspects of the loss event itself, but might be important moderators in post-loss trajectory. Post-loss factors could affect long-term reactions, such as time since the loss occurred, CB to the lost loved one, but also subjective feelings of responsibility or finding peace in the loss. Reactions to the loss can be separated into short-term responses (which can also prevail over a longer time), to long-term or prolonged reactions such as CG (which per definition occurs at least 6 months after the loss event) and post-traumatic growth. Lastly, person-related factors are supposed to influence the whole course of a relationship, from bond formation to bond maintenance, temporary separation, and loss.

It is crucial to mention that for the most part, evidence within this dissertation was gathered in the context of social loss through the death of a loved one. Thus, comparisons between different types of losses can only be put together for a few overlapping elements. Regarding subjective reactions, loneliness is one important psychological aspect we investigated both in widowhood and temporary separation. Loneliness plays a crucial role in mental health, and everyone who experiences feelings of disconnectedness might also be at risk of feeling lonely (Vedder et al., 2022). Although loneliness is not included in the ICD-11, it is stated as a symptom of grief within the DSM-V system (criterion C); however, it is still unclear which role it may play in prolonged grief (Vedder et al., 2022). Within this dissertation, loneliness is elevated both in widows/divorced individuals, in individuals living alone, and in those who were living apart from their partner during temporary isolation due to COVID-19 lockdown. Moreover, participants who had a partner and simultaneously reported on low relationship quality, displayed higher loneliness levels compared to participants who reported on a higher relationship quality. This mirrors previous findings on relationship distress or disruptions and health (Robles et al., 2014). Overall, these results indicate that loneliness is a subjective affective state or trait that is common in various stages of social disconnectedness. Loneliness and prolonged loneliness after bereavement may hence be an indication for difficulty to adjust to social distress, social disconnection, or social loss.

As to neuroendocrine stress responses, temporary separation from the partner (Paper I) did not influence cortisol levels in everyday life, implying that short-term isolation might not suffice to induce statistically different physiological reactions in couples compared to singles. Another reason could be that the couples knew that the separation was only temporary and not self-imposed. Alternatively, conflicts within partnership or between roommates might have been potentiated during lockdown, leading to higher cortisol levels in general, overshadowing the buffering effects of a romantic relationship. However, we replicated previous findings on romantic relationships as neuroendocrine stress-buffers, influencing long-term health. Within temporary separation, it was rather the subjective perception of social isolation, in this study represented by loneliness, that was associated with higher neuroendocrine stress-responses

in those who were in a romantic relationship. Thus, feeling subjectively lonely within a relationship during extreme social isolation, was directly linked to physiology, showing that it is rather the subjective feeling within a social situation that impacts physiology. These findings mirror results in neuroendocrinology of social loss: Subjective reactions such as emotional numbness or severity of CG symptoms moderated neuroendocrine stress responses to an extent.

Relationship-related characteristics within social loss, e.g., closeness to the deceased being related to neuroendocrine stress reactions, might be a parallel to relationship quality being linked to neuroendocrine stress responses during temporary isolation. Furthermore, closeness to the deceased was associated with externalized CB symptomatology. Thus, pre-loss closeness could not only be directly linked to basic physiology but also to psychological adaptation after the loss (in this case greater difficulty to integrate the loss into an internal representation).

Within social loss research (Papers II and III), we additionally found positive associations between CG and both subtypes of insecure attachment style. Similarly, in our review, one study found that rising separation anxiety over the course of hospitalization, was associated with higher cortisol levels. These similarities indicate that attachment and separation-related anxiety and avoidance booster both neuroendocrine and psychological grief trajectories. The findings are in line with attachment theory and the role of attachment styles in psychobiology, which predicts insecurely attached individuals to anticipate earlier and react more intensely to relationship-related stressors (Bowlby, 1973; Robles & Kane, 2014). As to external, loss-related characteristics, interestingly, sudden losses were associated with lower neuroendocrine disturbances compared to longer care for the terminally ill. This “weaker” body response does not necessarily indicate that subjective reactions to the loss are smaller or less strong. It could rather be a result of the fact that there was no prolonged stressor (e.g., taking care of the loved one). In contrary, the surviving individual might be able to develop a feeling of peacefulness more easily, as he or she knew about the upcoming loss earlier und thus had more time to psychologically prepare for the event. Feeling peaceful regarding the loss has also been investigated in Paper III, where individuals who did feel peaceful showed marginally significantly higher levels of int. CB. This might in the long term even affect the development of prolonged grief symptoms. These potential paths (anticipating the loss → finding meaning and peace → internalizing the bond → complicated grief, moderated by neuroendocrine stress responses) could be directly addressed in the future.

It is important to note that Figure 3 only resembles a small collection of evidence found within this dissertation and does not at all describe the whole picture regarding loss and loss-related factors. Research expands on pre-loss factors such as resilience (Bonanno et al., 2005), other relationship qualities such as interpersonal closeness (Vieth et al., 2022) or

gender and socio-cultural factors (Stelzer et al., 2020). For example, if relationship quality is low or relationship distress is high, relationship dissolution might be perceived as higher relief, leading to more positive psychological consequences and higher well-being (Amato & Hohmann-Marriott, 2007). As for gender and cultural differences, men and women might express their grief differently due to traditional gender roles or because emotions such as guilt or shame are experienced differently (De Boeck et al., 2018). Thus, it is important to comprehensively integrate other potential factors such as cultural background into grief research.

4.3 Strengths and limitations

The biggest strength of this dissertation is that it uses a multifactorial approach. By including contextual (Paper I, II, and III), subjective (Paper I, II, and III) and neuroendocrine factors (Paper I and II), reactions to social isolation and loss were looked at from different angles. Furthermore, assorted designs and statistical methods made it possible to implement differential operationalizations of isolation and loss. Another positive aspect is the use of EMA within Paper I which led to highly ecologically valid data. By integrating various outcome measures in different contexts, this dissertation adds to a more holistic understanding of factors that are involved in social isolation and loss adaptation. On the other hand, however, the variety of methods makes it difficult to statistically compare the results and to make them generalizable (external validity). Another limitation is that I did not jointly investigate social isolation and social loss (expect for Paper I), which limits interpretation and comparability. Moreover, within Paper II, many studies did not assess grief severity on a continuum, thus limiting the interpretation of the results to the comparison with non-bereaved controls only. Additionally, due to the use of cross-sectional and observational designs only, causal conclusions about the expected mechanisms are prohibited. Cross-sectional data ignore the complexity of the course of reactions to social isolation and loss as well as their inter- and intraindividual variability. For example, timing has been previously suggested as a key factor in psychopathology. According to a recent systematic review, loneliness trajectories in bereavement usually go from highest directly after the death, to gradual declines, with a few deviating trajectories prolonging in a high range over a longer time (Vedder et al., 2022). Furthermore, in the early years after breakup, the risk of developing psychiatric disorders seems to be highest (Chatav & Whisman, 2007; Whisman et al., 2022). Despite the difficulties in the recruitment and maintenance of a grieving sample, future research should therefore implement longitudinal methods and accompany grieving individuals over a longer timeframe with assessments of pre- and post-loss neuroendocrinology whenever possible.

4.4 Implications and future research

The results imply that subjective emotional reactions are important measurement endpoints when analyzing objective stressors such as social isolation or social loss. Likewise, neuroendocrine stress responses include unspecific HPA axis dysregulation, which in long-term might affect long-term adaptation to loss, such as CG (O'Connor et al., 2013). On the other hand, research on the role of other neuroendocrine parameters, such as OT, is still limited. OT has already been studied within research on stress-buffers, but it remains open, how specific OT alterations are to social loss. According to Taylor et al., OT is postulated as being a specific marker of social relationships/relationship distress and having discriminant validity to stress itself (Taylor et al., 2006). In loss research, elevated levels of circulating OT were found in those who exerted higher levels of CG (Bui et al., 2019). This is in accordance with an animal study that found elevated plasma OT levels in socially isolated prairie voles (Grippo et al., 2007). One hypothesis for hyperactivation could be that the deceased individual leaves a social gap within the surviving loved one leading to an implicit “urge” to release OT to counterbalance the gap. However, the direction and mechanisms underlying the process of disrupted relationships are not yet fully understood. Within animal research, e.g., it has been proposed that k opioid receptors might play a role and that the effects of OT activity depend on timing (Bales & Rogers, 2022). This model, however, is difficult to test within human loss research. To sum up, neuroendocrine disruptions are unspecific and do not always mirror subjective reactions to social isolation or loss. It is important, however, to measure their long-term trajectories as they represent the quantity of physiological stress reactions, which as a result, might affect long-term adaptation to loss.

As mentioned in the beginning, findings gained within this dissertation, especially regarding moderators, could help researchers develop models to predict long-term effects on health and reveal implications for adaptive and personalized interventions to prevent undesired effects. For example, future grief therapy may well guide the bereaved individuals in establishing a continuous bond with the deceased loved one and in gradually shifting the quality of the bond from externalized to internalized elements (Yu et al., 2016). Results of Paper I also indicate that loneliness occurs not only in living alone or single/divorced/widowed individuals, but also within couples, families, or individuals who have a large a social network, for example if the perceived quality of their relationship is low. Keeping that in mind, education or counselling programs could therefore also target troubled families or couples who struggle despite having a large social network. Moreover, objective factors of the loss event itself could alert advisors and psychotherapists to vulnerable groups that are at special risk of developing long-term problems in adjustment to loss. Counsellors should especially reach out to individuals suffering from a sudden, uncontrollable, or violent loss, as well as to those who feel

responsible for the death and who had an especially close relationship to the deceased loved one. Additionally, neuroendocrine disruptions occurring over a longer time, might be addressed through relaxation-targeted interventions. Finally, individuals with high attachment anxiety or avoidance, might have greater problems adapting to the loss and thus represent another risk group.

Beyond the psychological and neuroendocrine processes of social isolation and social loss, neuroimaging findings may help to better understand the underlying mechanisms and develop interventions that target specific subgroups who are especially vulnerable to long-term health impairments. It has been recently hypothesized, e.g., that prolonged grief is characterized by brain activations that differ from grieving individuals who do not fulfil prolonged grief criteria (Kakarala et al., 2020). Furthermore, PGD or CG might develop and be maintained because the lost loved one still acts as a reward or a source of pleasure (Kakarala et al., 2020; O'Connor et al., 2008). One fMRI study, e.g., found activations in pain-related brain regions for both CG and non-CG participants, whereas reward-related brain areas (nucleus accumbens) were activated only in those with CG while looking at pictures of the deceased loved ones (O'Connor et al., 2008). However, those findings have yet to be replicated. Simultaneously, activations in the amygdala and reward-related brain regions were found when individuals with PGD were presented with a deceased-related cue (Arizmendi et al., 2016). Within another study, higher yearning scores in bereaved individuals anticipating viewing pictures of their loved ones predicted higher activation in the subgenual anterior cingulate cortex (sgACC), an area that is also associated with reward (McConnell et al., 2018). Additionally, eliciting grief before the actual loss activates brain areas related to social pain, which predicts lower grief symptoms (Jain et al., 2019). Thus, although initially being experienced as aversive, anticipating the loss might shape or “prepare” for subsequent grief and foster adaptation to loss in a long-term. Sensitive pre-bereavement interventions could thus help anticipate the loss. In sum, despite their overall small sample sizes, fMRI data support the understanding of the processes that maintain intense grieving and craving the loved one, potentially leading to prolonged grief.

4.5 Conclusion

Notwithstanding the above-mentioned limitations, the results within this dissertation indicate that both social isolation and social loss are objective states that can be followed by psychological consequences and neuroendocrine disruptions, although those processes are not always interrelated. Although isolation and loss are not the same, they still share the important similarity that the subjective reaction to it, rather than the objective situation per se is an important determinant for adverse health outcomes. Moreover, the way social isolation

or social loss are perceived depends on moderating factors that can be either relationship-related, person-related, or event-related. Furthermore, short-term moderators, such as neuroendocrine disruptions or continuing bonds, might predict or affect long-term adaptation to social isolation or loss. However, to test this hypothesis, experimental or longitudinal designs should be implemented that allow for causal conclusions.

Finally, regarding positive aspects after social loss, continuing the inner bond to the deceased loved one can foster personal development, showing that growth might result even after a painful experience such as the loss of a loved one.

Appendix I: Paper I

Hopf, D., Schneider, E., Aguilar-Raab, C., Scheele, D., Morr, M., Klein, T., Ditzen, B., & Eckstein, M. (2022, September). Loneliness and diurnal cortisol levels during COVID-19 lockdown: the roles of living situation, relationship status and relationship quality. *Scientific Reports, 12*, 15076. https://doi.org/10.1038/s41598-022-19224-2

Hopf's contribution according to the contributor roles taxonomy (CRediT) author statement (Allen et al., 2019): Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, resources, software, validation, visualization, writing—original draft.

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Loneliness and diurnal cortisol levels during COVID-19 lockdown: the roles of living situation, relationship status and relationship quality

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Loneliness and social isolation have become increasing concerns during COVID-19 lockdown through neuroendocrine stress-reactions, physical and mental health problems. We investigated living situation, relationship status and quality as potential moderators for trait and state loneliness and salivary cortisol levels (hormonal stress-responses) in healthy adults during the first lockdown in Germany. *N* = 1242 participants (mean age = 36.32, 78% female) filled out an online questionnaire on demographics, trait loneliness and relationship quality. Next, *N* = 247 (mean age = 32.6, 70% female) completed ecological momentary assessment (EMA), collecting twelve saliva samples on 2 days and simultaneously reporting their momentary loneliness levels. Divorced/widowed showed highest trait loneliness, followed by singles and partnerships. The latter displayed lower momentary loneliness and cortisol levels compared to singles. Relationship satisfaction significantly reduced loneliness levels in participants with a partner and those who were living apart from their partner reported loneliness levels similar to singles living alone. Living alone was associated with higher loneliness levels. Hierarchical linear models revealed a significant cross-level interaction between relationship status and momentary loneliness in predicting cortisol. The results imply that widowhood, being single, living alone and low relationship quality represent risk factors for loneliness and having a partner buffers neuroendocrine stress responses during lockdown.

The recent Corona virus (COVID-19) pandemic has been occupying mental and physical health facilities for 2 years now. Hard lockdown regulations in almost all countries early during the pandemic (April until June 2020) to prevent further spreading of the virus entail increased social isolation. The steady and massive health threat from the virus in combination with the missing social buffering effect of everyday social encounters lead to or amplified psychosocial problems that could have long-term consequences for mental and physical health[1–4]. E.g., loneliness, as the subjective and emotional component of social exclusion, is a highly topical and public health issue in modern societies, where social isolation and anonymity become increasingly prevalent[5,6]. It has been previously defined as a psychological aversive state that entails a perceived lack of intimacy or social companionship and the subjective feeling that social relationships are deficient in either quality or quantity[7], which forms the basis of recent research on the topic[8]. By contrast, social isolation is defined as the objective state of being alone[7,9]. According to the belongingness-hypothesis, loneliness is rooted in the human need to socially belong, or the pervasive drive to form and maintain lasting positive and significant social relationships[10]. It has been shown that the sense of belonging in early adolescents is mainly achieved through the acceptance by peers, whereas in late adolescence and adulthood, it is achieved especially by romantic relationships, marital status

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and close friends[11]. On the other hand, lacking feelings of belonging are assumed to be associated with loneliness and negative physical and mental health outcomes in a long-term[10]. Both loneliness and social isolation are significantly related to indices of physical and mental health, such as psychosocial stress[12], depression[13], generalized anxiety[6], cardiovascular diseases[14], chronic obstructive pulmonary disease[15], and mortality[8,9,16–19]. Chronic loneliness may hamper the formation of new social relationships by inducing negative cognitive biases such as interpersonal distrust[20]. Furthermore, loneliness is associated with neuroendocrine parameters, like elevated cortisol levels[21–23] and altered cortisol awakening responses[23,24]. As one of the main effector hormones of the hypothalamus–pituitary–adrenal (HPA) axis, the steroid cortisol is secreted in response to external and internal stressors in order to re-establish homeostasis[25]. Previous studies suggest that cortisol may serve as a potential short-term correlate of loneliness, predicting poor physical or mental health outcomes in the long-term[21,22].

According to the social buffering hypothesis[26], social relationships play a beneficial role in physical and mental health[26–29]. Among the most intense social relationships are romantic relationships, as they serve as the primary source of support, fulfilling needs such as intimacy, attachment, and emotional support[30]. Supportive and affectionate interactions with the partner reduce stress, pain, and psychological distress. They even influence the immune system, wound healing or mortality rates[31–35]. Being in a relationship has been found to be associated with lower loneliness levels, compared to never-married, divorced, and widowed individuals[36–38]. Especially in the middle and higher age, romantic relationships become important buffers for loneliness[39]. Additionally, romantic relationships directly affect physiological stress responses, such as cortisol secretion. Individuals who are in a close relationship, show lower aggregated cortisol levels than singles[40] and affectionate couple interaction can reduce cortisol levels[41,42]. On the other hand, the loss of a partner, for example due to breakup or death, is considered one of the most stressful life events in adulthood, being associated with reduced mental and physical health outcomes[43]. Divorced and widowed individuals show significantly higher loneliness scores than married individuals[44–46]. Moreover, partner loss is accompanied by altered HPA axis functioning, resulting in elevated cortisol levels and flattened diurnal cortisol slopes[47].

Although being in a relationship protects against feelings of loneliness, couples can also experience higher levels of loneliness. As one important factor, relationship quality has been shown to be negatively associated with loneliness[48–53]. In times of extreme social isolation, relationship quality might become an important moderator, especially if couples do not live together and thus are unable to see their partner and potentially have to rely on non-physical relationship qualities. Living alone has become increasingly prevalent, with one-person households accounting for more than 40% of all households in Scandinavian nations, more than 33% of all households in France, Germany, and England; and more than 25% of all households in the United States, Russia, Canada, Spain, and Japan[54]. In Germany, in the young adult age of 18 to 30 years, more than 30% live without a partner[55]. An important distinction in this context is between partnerships with and without a common household (the latter being called "living apart together"). In general, living alone has been seen as a risk factor for poor physical and mental health[54,56]. For instance, the living situation predicts mortality risk[57,58] and people who are living alone show higher loneliness levels[59]. Cross-sectional studies suggest that during the pandemic, being married served as a protective factor against loneliness[60], whereas being divorced or widowed increased the risk of loneliness[61]. Furthermore, living with others has been found to protect against loneliness[62], even when controlling for relationship status[63] and loneliness during lockdown predicted psychological distress[64]. However, it has not been investigated yet, whether relationship status and living situation during lockdown affected biological, specifically neuroendocrine, health parameters, such as cortisol levels. In previous studies, living alone had been positively correlated with cortisol levels[65]. Likewise, the buffering effect of living situation and relationship status with regard to psychobiological outcomes during stress-exposure (i.e. the world-wide considerable psychological stress through COVID-19) has not been examined yet. Previous research suggests that the separation from a partner is linked to elevated feelings of loneliness and cortisol levels in general[66–68]. In adolescents, significant correlations between self-reported loneliness and cortisol awakening responses during COVID-19 lockdown were found[69]. Nonetheless, moment-to-moment associations of loneliness and cortisol have not been investigated in adults yet. Furthermore, it is still elusive if relationship status and living situation moderate these associations. Lastly, the effect of psychological variables such as relationship satisfaction, on the association between living arrangements and loneliness during lockdown has not yet been addressed.

Study objectives. The purpose of this study was to investigate relationship status and living situation as potential moderators for trait and state loneliness as well as momentary cortisol levels during the COVID-19 pandemic and during lockdown. We aimed to replicate findings about the association between relationship status and trait loneliness, showing that being in a relationship is associated with lowest levels of loneliness, followed by singlehood and divorce/widowhood (Hypothesis 1). In order to explore state loneliness and cortisol in every-day life, we used an ecological momentary assessment (EMA) approach. Secondly, we expected that the current living situation and relationship status have an impact on momentary (state) loneliness (Hypothesis 2) and cortisol levels (Hypothesis 3). Based on previous studies[59–69], we assumed that being in a relationship and living with others are associated with lower loneliness and cortisol compared to being single and living alone. Additionally, we hypothesized a positive association between momentary (state) loneliness and momentary (state) cortisol levels (Hypothesis 4) and expected the relationship status and living situation to moderate this association (Hypothesis 5). Specifically, we hypothesized that being in a relationship and living with others buffers the effects of momentary loneliness on cortisol levels. Lastly, we hypothesized that relationship quality moderates the association between living situation and momentary (state) loneliness levels in individuals being in a relationship (Hypothesis 6). More precisely, we expected that the negative effect of living apart together on loneliness is buffered through high relationship quality.

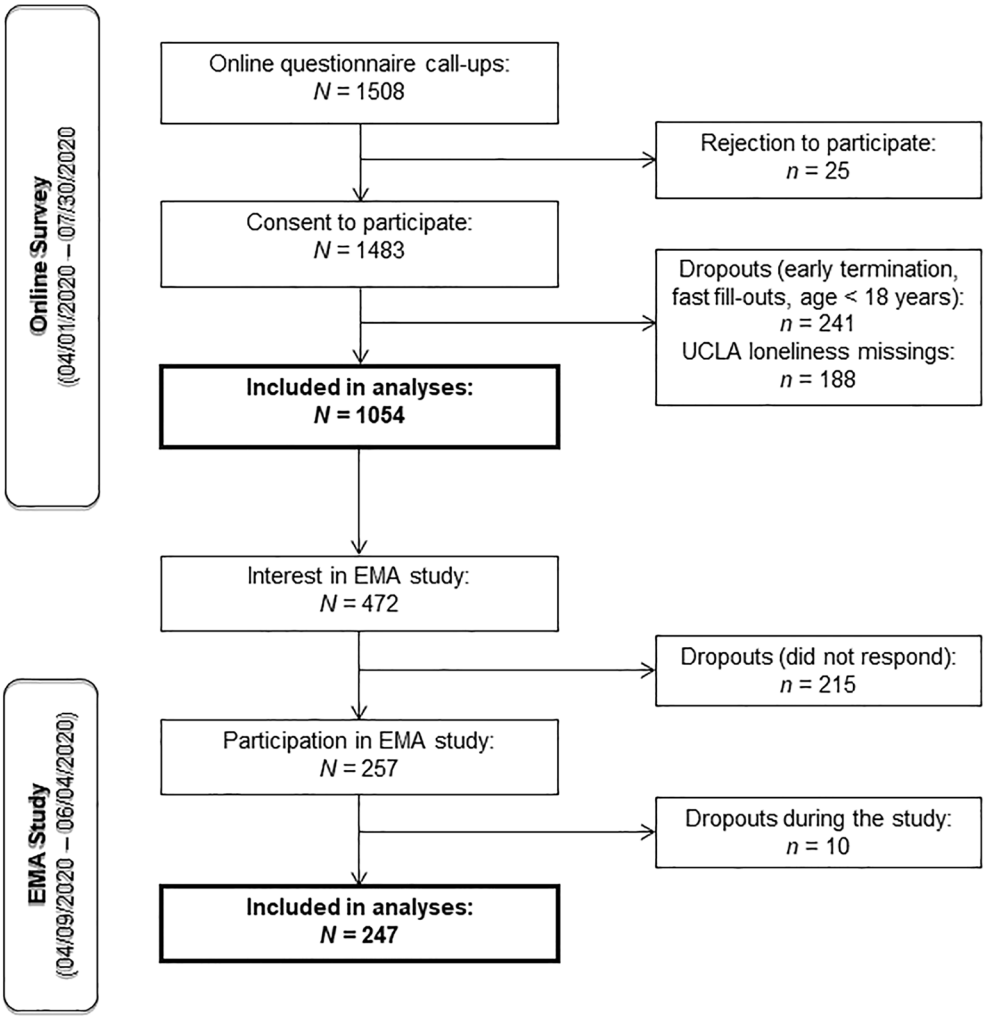

Figure 1. Flowchart of the recruitment process. *Note.* Participants were recruited between April 1st and July 30th 2020 via online media and local newspapers. Inclusion criteria were: Fluency in German, minimum age of 18 years and willingness to participate voluntarily. In total, 1483 individuals agreed to participate, from which 1054 participants filled out the questionnaires of interest.

Methods

Participants. This study was approved by the Heidelberg Medical Faculty's Ethics Committee (Heidelberg University, approval no. S-214/2020) and performed in accordance with the Declaration of Helsinki. All participants signed an informed consent and were recruited between April 1st and July 30th 2020 via online media and local newspapers. Inclusion criteria were: Fluency in German, minimum age of 18 years and willingness to participate voluntarily. In total, 1483 individuals agreed to participate, from which 1054 participants filled out the questionnaires of interest (see Fig. 1). The mean age of the participants was $M = 36.32$ years ($SD = 14.75$, $Range = 18; 81$), with 77.7% being female ($n = 819$). Demographic characteristics are displayed in Table 1.

Of the participants in the online survey, 472 showed interest in the EMA with the salivary sampling. Of those 472 participants, 54% ($n = 257$) took part in the EMA study. After excluding individuals who did not react to our messages and dropouts during data collection ($n = 10$), the remaining 247 cases were included in the analyses. The participants' mean age was $M = 32.6$ years ($SD = 13.12$, $Range = 18; 78$), with 70% being female ($n = 173$). Demographic characteristics of the EMA study sample are displayed in Table 2.

Measures. *Loneliness.* To measure trait loneliness in the online survey, we employed the German version of the revised 20-item University of California at Los Angeles (UCLA) loneliness scale[70,71]. Within our study, the scale displayed high internal consistency (Cronbach's $\alpha = .91$). Participants are asked to answer, how often they felt a certain way during the past two weeks, on a 4-point Likert scale with higher scores indicating more loneliness. Exemplary items are 'I feel isolated from others.' or 'I do not feel alone.' (negatively scored item). In order to assess momentary levels of loneliness in the EMA study, we used a single item measure ("Do you feel lonely at the moment?") with a visual analogue scale (VAS; 0—not at all, to 100—very lonely).

	Categories	*n* (%)
Gender	Female	819 (77.7)
	Male	227 (21.5)
	Diverse	4 (.4)
	Non-responders	4 (.4)
Occupation	At school/training/college/university	368 (34.9)
	Employed/civil servant	502 (47.6)
	Self-employed	100 (9.5)
	Unemployed	40 (3.8)
	Pensioner/housewife/househusband	98 (9.3)
Relationship status	In a relationship	655 (77.7)
	Single	329 (31.2)
	Divorced/widowed	70 (6.6)

Table 1. Demographic characteristics of study 1 (online survey). This table depicts total and relative sample sizes split in different groups (gender, occupation and relationship status) of the Online-Study. Total $N = 1054$. Participants in the singles group are those who were never-married.

	Categories	*n* (%)
Sex	Female	173 (70)
	Male	74 (30)
Relationship status	In a relationship	171 (69.2)
	Single	71 (28.7)
	Missing	5 (2)
Living situation	Living alone	52 (21.5)
	Living with others	194 (78.5)
Relationship status × living situation	Single—living alone	26 (10.5)
	Single—living with others	45 (18.2)
	In a relationship—living alone	26 (10.5)
	In a relationship—living with others	70 (28.3)
	In a relationship—living with partner	75 (30.4)
	Missing	5 (2)

Table 2. Demographic characteristics of the EMA study. This table depicts total and relative sample sizes split in different groups (gender, relationship status, living situation and relationship status depending on living situation) of the EMA study. Total $N = 247$. Participants in the singles group are those who were never-married.

Salivary cortisol. Saliva samples for determination of cortisol concentrations were collected at the same times as EMA. Sampling times were adapted to the individual wake-up time. Samples were taken at six time-points on two consecutive days: directly after awakening, 30 min, 45 min, 2½ h and 8 h after awakening and immediately before going to sleep. Participants stored the samples in their freezer until collected on dry ice and stored at − 80 °C until analysis. Analyses were conducted in the biochemical laboratory at Heidelberg University Hospital's Institute of Medical Psychology using commercial enzyme-linked immunosorbent assay (ELISA, Demeditec Diagnostics, Germany) procedures with reported detection limit of .019 ng/mL. Intra- and interassay variability for cortisol were 2.95% and 7.51% respectively. Log-transformed (ln) momentary as well as mean cortisol levels were used as outcome measures.

Relationship quality. Relationship quality was assessed via the short version of the *Partnerschaftsfragebogen* (PFB)[72]. It consists of 9 items that can be answered on a 4-point Likert scale. In our sample, the internal consistency of the PFB was very good (Cronbach's $\alpha = .85$). We used the global PFB score by adding up all items. The total score ranges between 0 and 36.

Control variables. For both trait and state loneliness as outcome, we included age and sex as control variables (CVs), as they have been previously shown to influence loneliness during the lockdown[73]. For momentary cortisol as outcome, CVs were assessed on both the momentary level and the trait level, based on expert consensus guidelines[74,75]. The following CVs were assessed on a momentary level: sleep duration, sleep quality, sleeping problems, sleep medication, forced awakening, brushing teeth, eating behaviour, drinking behaviour, medication, alcohol consumption, nicotine consumption, caffeine consumption, and physical activity (with respect to the last sample), assessment time-point (1 variable for the rise from time-point 1 to 2, and 1 variable for the fall

from time-point 2 to 6), and day (1 vs. 2). Trait level control variables were age, sex, and body mass index (BMI). As the momentary level CVs were of a high number and we wanted to reach a somewhat parsimonious model, we first determined, which of the theoretically included CVs had an impact on cortisol at all. We thus run an initial hierarchical linear regression with momentary cortisol levels as outcome and all CVs as predictors. The variables that had no significant association with cortisol levels ($p > .05$) were excluded from our final analyses. Significant CVs for cortisol as outcome were: eating, drinking, alcohol consumption, caffeine and physical activity (yes/no). As the results of the more parsimonious model and the full model were identical, we decided to report on the parsimonious model for easier interpretation. However, both models are included in Appendix B.

Procedure. The study was part of a large-scale longitudinal study that aims to investigate long-term consequences of COVID-19 lockdown on psychobiological health. Results within this paper entail data from time-point 1 (first lockdown in Germany). The online survey as well as the EMA were both conducted with the platform *soscisurvey.de* and participation was completely anonymous. After completing the online survey, participants were asked whether they wanted to take part in the EMA. Those who were interested, were contacted via email. The responders received Salicap® tubes for saliva collection with additional informational documents via mail and specific instructions via phone. The assessment of the saliva samples took place between April 9th and June 3rd 2020. On two consecutive days, the participants received the respective link via SMS to a short online survey including instructions for saliva sampling six times per day. Participants were asked to refrain from food or caffeine before they provided three saliva samples which were stored in the freezer. Then, they were asked to answer further questions about their sleeping behaviour, consumption behaviour, and physical activity. Commitment was constantly monitored online: if the participants have not yet accessed the link 5 min after it was sent, they were reminded by phone to do so. After completion of the two sampling days, data were stored on an institute-internal data server and saliva samples remained in the participants' home freezer until collection.

Data processing and statistical analyses. Hypotheses 1–3 focused on between-person effects and only included level 2 predictors (relationship status and living situation). Thus, these hypotheses were tested with analyses of covariance (ANCOVA). For hypothesis 1, family status (married/in a romantic relationship vs. single vs. divorced/widowed) served as independent variable (IV) and UCLA loneliness scores as dependent variable (DV). Post-hoc contrasts coding was conducted in order to analyse the linear trend of the means. For hypotheses 2 and 3, relationship status (single vs. in a relationship) and living situation (alone vs. with others) served as IVs. In this step we were interested in overall loneliness and cortisol in every-day life, thus the aggregated momentary loneliness and cortisol levels were used as DVs. As the distribution of the cortisol data was positively skewed, we natural-log-transformed the data in order to normalize their distribution. In case the assumptions of conducting an ANCOVA were violated, we used bootstrapping estimates ($n = 1000$) in order to achieve more robust results[76]. To test pairwise differences in momentary loneliness scores between the living situation and relationship status groups (in case the main effects were significant), we calculated Tukey Honestly Significant Differences (HSD) with Bonferroni-corrected p values adjusted for multiple comparisons. We further calculated partial η^2 in order to receive the effect sizes, with $\eta^2 \geq .01$ indicating a small, $\eta^2 \geq .06$ a medium, and $\eta^2 \geq .14$ a large effect.

As hypotheses 4 and 5 included a cross-level interaction, we conducted multilevel modelling (MLM) regression analyses, which enabled us to assess the within- and between-person effects of momentary loneliness on momentary cortisol levels. By using MLM we were able to represent the hierarchical structure of the data, which was necessary in order to depict the multilevel-predictors. The individual levels of loneliness were centred on the person's mean in order to test the within-person effect on cortisol levels. In order to assess the between-person effects, we centred the individuals' mean loneliness levels on the grand mean. For hypothesis 5, relationship status (single vs. in a relationship) and living situation (living alone vs. living with others) were included as dichotomous moderators in order to assess their interaction with level 1 loneliness scores (the exact formulas for hypotheses 4 and 5 are displayed in Appendix A in the supplement). For hypothesis 6, we conducted an ANCOVA with the sub-dataset of participants in a relationship, using living situation (alone vs. not alone), grand-mean-centred relationship quality (PFB) and their interaction as predictors, as well as age and sex as covariates. ANCOVA analyses were conducted with SPSS Statistics Version 27 ©, whereas MLM analysis were conducted via R Version 4.0.3.

Results

In the following, we will report results from all hypotheses separately. Descriptive statistics of the outcomes of interest are shown in Tables 3 and 4, respectively.

Trait loneliness depending on family status (Hypothesis 1). On average, participants had a loneliness score of $M = 38.95$ ($SD = 10.89$; $Range = 20–77$). There was a significant effect of family status on trait loneliness after controlling for sex and age ($F(1, 1035) = 26.67$, $p < .001$, $\eta^2 = .049$). Sex was significantly related to self-reported loneliness, with women showing higher loneliness scores than men ($F(1, 1035) = 6.39$, $p = .012$, $\eta^2 = .006$). The subsequently planned contrasts revealed a significant linear trend ($F(2, 1035) = 26.67$, $p < .001$, $\eta^2 = .049$), indicating that married people/people in a relationship displayed the lowest loneliness scores, followed by singles and divorced/widowed individuals.

Association of relationship status and living situation with loneliness in every-day life (Hypothesis 2). Participants in the EMA study reported an overall loneliness of $M = 27.36$ with highly varying scores ($SD = 20.94$).

Results indicate significant associations of both living situation ($F(1, 234) = 12.93$, $p < .001$, partial $\eta^2 = .05$) and relationship status ($F(1, 234) = 8.57$, $p = .004$, $\eta^2 = .04$) with mean loneliness levels. People living alone reported

Groups	Trait loneliness (UCLA loneliness scale)	
	M	*SD*
Family status		
Married/in a relationship	37.2	9.75
Single	41.09	11.91
Divorced/widowed	45.42	12.03
Sex		
Male	37.18	10.15
Female	39.33	10.95

Table 3. Means and standard deviations of the UCLA loneliness scale (online survey). This table depicts means (*M*) and standard deviations (*SD*) of trait loneliness, measured by the UCLA loneliness scale, in the different subgroups of the online-study.

Groups	State loneliness (VAS)	
	M	*SD*
Living situation		
Living alone	37.55	23.44
Living with others	24.63	19.42
Relationship status × living situation		
Single—living alone	39.29	25.6
Single—living with others	32.32	23.28
In a relationship—living alone	35.74	21.35
In a relationship—living with others	23.09	18.99
In a relationship—living with partner	21.42	15.99

Table 4. Means and standard deviations of momentary loneliness levels (EMA study). This table depicts means (*M*) and standard deviations (*SD*) of momentary (state) loneliness, measured by a single-item measure with a VAS scale (0–100), in the different subgroups of the EMA study.

significantly higher loneliness than people living with others. Also, individuals who were in a relationship reported significantly lower loneliness levels than singles. A third ANCOVA yielded a significant interaction between living situation and relationship status on mean loneliness ($F(1, 233) = 7.27$, $p < .001$; $\eta^2 = .11$). Post-hoc Tukey's HSD test indicated significant differences for the following pairwise comparisons (see Fig. 2): in a relationship living alone versus in a relationship living with partner ($p = .016$), single living with others versus in a relationship living with partner ($p = .028$), single living alone versus in a relationship living with partner ($p = .001$), in a relationship living alone versus in a relationship living with others ($p = .056$), and single living alone versus in a relationship living with others ($p = .005$).

Association of relationship status and living situation with cortisol in every-day life (Hypothesis 3). Descriptive statistics of the variables of interest are displayed in Table 5. Mean cortisol levels in the entire EMA-sample were $M = 8.6$ ng/mL ($SD = 2.22$). Results show a significant effect of relationship status on mean cortisol levels ($F(1, 219) = 4.58$, $p = .034$, partial $\eta^2 = .02$), with singles having significantly higher mean cortisol levels than individuals with a partner. Living situation did not have a significant effect on mean cortisol levels ($F(1, 219) = .04$, $p = .840$). Furthermore, BMI had a significant effect on cortisol, with higher BMI levels predicting higher cortisol levels ($F(1, 219) = 15.16$, $p < .001$).

Association of momentary loneliness, relationship status, and living situation with cortisol levels (Hypotheses 4 and 5). The Intraclass Correlation Coefficient (*ICC*) within the empty MLM was .007, indicating that .7% of the variance in cortisol levels was accounted by between-person differences and 99.3% by within-person differences. As 22 cases had missing values on level 2 variables, a total of 225 cases and 1722 data points were included in the analyses. The random intercept and slopes model (with level 1-loneliness set as random predictor) showed a better fit to the data compared to the random intercepts-only model, ($\chi^2(2) = 7.52$, $p = .020$), therefore we report results from this model. There was a non-significant within-person effect of self-reported loneliness on cortisol levels ($b = .002$, $t(1487) = 1.34$, $p = .179$). Importantly, we observed a significant interaction between relationship status and momentary loneliness levels ($b = -.004$, $t(1487) = -2.88$,

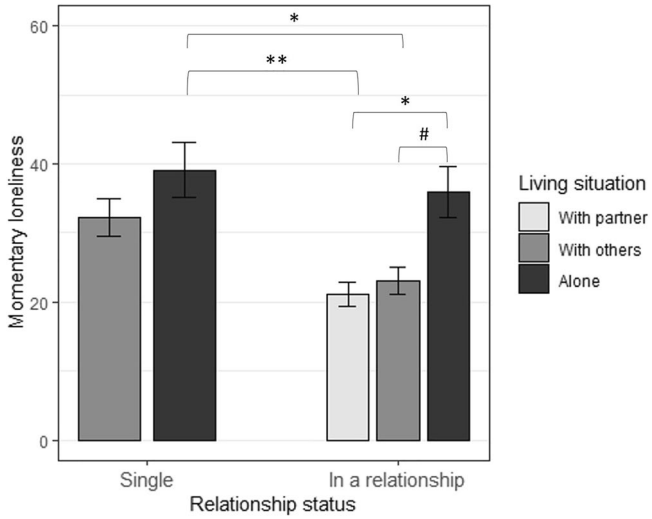

Figure 2. State loneliness levels (visual analogue scale) as a function of relationship status and living situation in the EMA study. *Notes.* Results of the Tukey's HSD test assessing differences in mean loneliness levels of the EMA sample as a function of relationship status and living situation. ** represents $p < .001$, * represents $p < .05$, and # represents $p < .1$. Error bars depict confidence intervals based on the *t*-distribution.

Groups	Cortisol (ng/mL)	
	M	*SD*
Relationship status		
In a relationship	8.44	6.13
Single	8.98	6.31
Living situation		
Living alone	8.64	2.31
Living with others	8.61	2.19

Table 5. Means and standard deviations of salivary cortisol levels (EMA study). This table depicts means (*M*) and standard deviations (*SD*) of momentary cortisol levels, measured by a single-item measure with a VAS scale (0–100), in the different subgroups of the EMA study.

$p = .004$). Therefore, the association between a person's momentary loneliness levels and momentary cortisol levels was smaller for participants who were in a relationship than for those who were single. Pseudo R^2 for this interaction was .1315, showing that the amount of unexplained variance in cortisol levels was reduced by 13.15%. The interaction between living situation and momentary loneliness levels was not significant ($b = .002$, $t(1487) = .96$, $p = .361$). Results of the reduced model (with significant CVs only) and the full model (with all CVs) are shown in supplementary Tables 1–4 in Appendix B in the supplements.

Relationship satisfaction as moderator of the associations between living arrangements and loneliness (Hypothesis 6). In the subsample of participants who were in a relationship, participants displayed self-reported mean relationship quality of $M = 20.22$ ($SD = 4.87$; *Range* = 6–27). ANCOVA revealed a significant association between relationship quality and self-reported mean state loneliness levels ($F(1, 149) = 5.02$, $p = .03$, $\eta^2 = .03$)). Furthermore, participants who were living alone, showed significantly higher state loneliness levels compared to participants who were living with others ($F(1, 149) = 9.77$, $p = .002$, $\eta^2 = .06$). However, the interaction between relationship quality and living situation was not significant ($F(1, 149) = 1.97$, $p = .16$, $\eta^2 = .01$), indicating that relationship quality did not moderate the association between living situation and loneliness.

Discussion

This study examined the (separate and joint) associations between structural (relationship status and living situation), psychological factors (relationship quality) and loneliness and cortisol during COVID-19 lockdown.

All in all, our results provide further evidence for the belongingness-hypothesis, showing that romantic relationships, as a source for meaningful interactions and intimacy, as well as living with others protect against loneliness and neuroendocrine stress-responses, in this case diurnal cortisol levels[36–38,54,59]. Moreover, divorced/widowed participants showed the highest trait loneliness, followed by singles (never-married). Thus, the loss of previously experienced positive relationship aspects such as romantic support, solace, and physical proximity,

may be associated with feelings of loneliness. Furthermore, individuals who were in a relationship and living alone ("living apart together"), were lonelier than those who were living with their partner, but did not differ in their momentary loneliness levels compared to singles living alone. Being in a relationship and living with others was associated with similar levels of loneliness compared to being single and living with others. This indicates that, during extreme physical isolation and contact restrictions, having a partner per se does not protect against loneliness, but rather living with others becomes an increasingly important buffer for loneliness. As during hard lockdown, intimacy and physical closeness are lacking in couples who are living apart, these important stress-buffering factors in the romantic relationship are suddenly missing, which is experienced as aversive[68]. Contrary to this finding, Greenfield and Russel found higher loneliness levels in couples who were living apart but with others[59]. One explanation for these conflicting findings could be that during lockdown, there were no alternatives for direct social interactions outside the apartment and thus the co-habitants became an especially important substitute for any direct contact with the romantic partner. We further found that higher relationship quality predicted lower momentary loneliness levels, which is in line with cognitive approaches to loneliness assuming that quality rather than quantity of social relationships buffers short-term psychological burden. However, relationship quality did not moderate the association between living situation and loneliness. Thus, the protective effect of living together during the COVID-19 lockdown was evident irrespectively of the relationship quality. In the online survey, female participants reported significantly higher trait loneliness levels than male participants. This adds to numerous studies revealing female gender as a risk factor for loneliness[77,78]. Interestingly, however, recent neuroimaging studies indicate that loneliness-associated neural effects may be more pronounced in high lonely men than women[79,80].

Although the results support our hypotheses about the importance of structural and psychological factors for self-reported loneliness, there are many other potential psychological mediators explaining these associations. It is important to keep in mind that romantic relationships buffer against negative mental and physical health consequences only under certain circumstances, for instance if marital functioning is perceived as positive[33]. Moreover, social dimensions such as perceived social proximity, knowing that there is someone you can count on, as well as actually perceived support, may be important underlying mechanisms influencing psychobiological health[29].

On a neuroendocrine level, being in a relationship buffered momentary cortisol levels and their association with loneliness. This is also in line with theoretical and empirical literature indicating that having a romantic partner serves as a biological *zeitgeber*. It has been suggested that social interactions on a regular and high frequent basis help regulating optimal physiological stimulation levels by modulating arousal to be medium high and attenuating maladaptive stress[81]. These results show us that romantic relationships have a direct impact on neuroendocrine stress responses, which in a long-term may have a positive effect on health-related outcomes[21,22]. Contrary to our hypothesis, living arrangements by themselves neither affected cortisol levels nor moderated the association between momentary loneliness and cortisol levels. One reason why these associations were only found with relationship status, could be, that there may be operators that are unique in relationships. For instance, feelings of connectedness[82], intimacy[41] or affective touch[83] are specific driving factors in romantic relationships. As they are not characteristic for other relationships such as co-habitants, they only come into use when romantic relationships are investigated.

This study adds to previous research on social buffering[17,26,27,29] in the context of enduring stress and extreme physical isolation. As lockdown-related long-term psychological health problems are increasingly revealed, it is important to study structural and psychological factors that might influence those consequences. Likewise, short-term neuroendocrine responses during lockdown could help unravel the neurobiological mechanisms underlying detrimental effects of loneliness and social isolation for mental health. Using a psychobiological EMA design, we were able to assess not only trait loneliness levels, but also moment-to-moment variations in loneliness and salivary cortisol in a naturalistic setting. The every-day life assessments took place in the individuals' personal environments, which yielded highly ecologically valid data. Moreover, as the participants' current loneliness levels were directly assessed, reporting errors due to retrospective assessment could be reduced. In order to represent the hierarchical structure of the data, MLM was used, enhancing statistical power of the analyses. Moreover, due to the close supervision of the participants, we were able to keep their commitment high and thus collect high-quality data. Another strength of this study is the wide range of the participants' age, making the sample more representative for every age group. The collection of saliva samples in the participants' every-day life enabled us to integrate psychobiological measures and provide a multi-level view on stress experiences during COVID-19.

This study has several limitations that need to be addressed. First of all, sample sizes differed between relationship subgroups due to recruitment of a convenience sample, reducing statistical power of the analysis and potentially biasing the results. As widowers/widows and divorced individuals are on average older and less technically involved than singles, they are more difficult to recruit for an online survey. To address this problem, we analyzed the data using bootstrapping and non-parametric test. Both analyses revealed comparable results. Noteworthy, sensitivity analyses show that only medium but not small effect sizes could have been reliably detected within our sample. Thus, the results should be interpreted with caution. Another limitation is the cross-sectional design of the study, which makes it impossible to draw causal conclusions on long-term (mental) health outcomes. Furthermore, there is no baseline assessment of the variables of interest before lockdown, therefore we were not able to control for the participants' pre-lockdown levels of loneliness and cortisol. Thus, our results can only be seen as a "snapshot" of the current situation. In addition, the data collection during this specific phase of lockdown in which the majority of participants worked from home hampers generalization of our data to other situations.

There are several aspects that could be addressed in future research. Although we found main effects of relationship status, living situation, and relationship quality, they only explained a small amount of variance in the outcomes. This indicates that there are additional predictor and moderator variables influencing the outcomes. For example, previous research has shown that level of education of the own partner has an influence on mental and physical health[84]. Additionally, the stress-buffering effects of close relationships is not restricted to romantic

relationships. For example, having meaningful relationships with close friends or relatives[38] could be one protective factor. In addition, longitudinal assessments with repeated within-person measurements of loneliness and cortisol over a longer period of time could be implemented, in order to probe long-term psychological and physiological consequences of COVID-19 and strict lockdowns.

All in all, our study reveals further evidence for romantic relationships as a protective factor against trait and state loneliness, both on a structural level (alone vs. in a relationship) and a psychological level (relationship quality), as well as momentary cortisol levels during the ongoing stress of the pandemic and social isolation. Additionally, living with others during lockdown protects against loneliness in every-day life. The fact that individuals who were living apart from their partner displayed similar levels of loneliness compared to singles, implicates that especially in times of social isolation, the lack of direct physical contact to the partner makes a difference when it comes to psychological burden. This joint role of partnership and living situation should be taken into account when analysing structural factors for negative mental health outcomes, but also identifying resources for resilience. Moreover, it is especially important to consider not only relationship status, but also relationship quality as an important psychological aspect of romantic relationships and a buffering factor for loneliness in couples, potentially counter-balancing the negative effects of living alone. This is in line with previous epidemiological research suggesting that rather than being married, it is the satisfaction with the relationship (e.g., the amount of support or criticism from a partner), which influences health-related outcomes[85]. In the context of clinical interventions, the results implicate that especially singles and divorced individuals, women, couples with low relationship quality as well as alone living residents (whether single or in a relationship) should be offered psychosocial support in order to prevent them from long-term negative health consequences. More importantly, on the one hand, individuals who are living apart from their partner, could profit from interventions to enhance their perceived relationship quality, on the other hand, alone living single individuals should be offered help in re-establishing meaningful social bonds with their close friends in order to counter-regulate their feelings of loneliness. Finally, public health campaigns should address and sensitize the society towards loneliness and mental health symptoms in those different groups to empower individuals to actively approach social offers and use them as resource.

Data availability

The datasets generated during and/or analysed during the current study are openly available online (https://doi.org/10.11588/data/SYVQMM).

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Competing interests

The authors declare no competing interests.

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Appendix II: Paper II

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EDITOR INVITED REVIEW

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Neuroendocrine mechanisms of grief and bereavement: A systematic review and implications for future interventions

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Abstract

Bereavement is associated with many negative behavioural, psychological and physiological consequences and leads to an increased risk of mortality and morbidity. However, studies specifically examining neuroendocrine mechanisms of grief and bereavement have yet to be reviewed. This systematic review is a synthesis of the latest evidence in this field and aims to draw conclusions about the implications of neurobiological findings on the development of new interventions. PRISMA guidelines for systematic reviews were used to search for articles assessing neuroendocrine correlates of grief. Findings were qualitatively summarised. The National Heart, Lung, and Blood Institute Study Assessment Tool was used to assess the quality of the included studies. Out of 460 papers, 20 met the inclusion criteria. However, most were of fair quality only. As a neuroendocrine marker, the majority of the studies reported cortisol as the outcome measure and found elevated mean cortisol levels, flattened diurnal cortisol slopes and higher morning cortisol in bereaved subjects. Cortisol alterations were moderated by individual differences such as emotional reaction to grief, depressive symptoms, grief severity, closeness to the deceased and age or gender. Research on neuroendocrine mechanisms of grief is still in its early stages regarding grief measures and the use and timing of neuroendocrine assessments. Most of the studies focus on cortisol as outcome, and only limited data exist on other biomarkers such as oxytocin. Future research might consider assessing a broader range of neuroendocrine markers and use longitudinal designs with a focus on the psychobiological reactions to loss. Based on this, individually tailored psychosocial interventions, possibly in the palliative care context, might be developed to prevent prolonged grief disorder.

KEYWORDS

bereavement, cortisol, grief, hypothalamic-pituitary-adrenal-axis, oxytocin, stress, trauma

1 | INTRODUCTION

1.1 | Social loss and its consequences

The loss of a loved person is one of the most devastating experiences in life and is associated with psychological, behavioural and physiological changes in the surviving close persons. The term *loss* is referred to the actual loss event, whereas *grief* entails the subjective reactions that are associated with loss. Although grief also occurs after a separation, in this review, we focus exclusively on grief after an actual loss of a loved one through death. *Bereavement* is defined as the state of having suffered the loss of a loved one and entails the time after a loss during which grief is experienced.[1] Physiological reactions to bereavement include neuroendocrine, immunological and somatic changes.[2] Psychological consequences include insecurity, anxiety, aggression and depressive and (psycho-) somatic symptoms,[3] which result in a greater vulnerability to somatic or psychiatric problems, such as cardiovascular diseases[4] or clinical depression.[5,6] Some studies even associate loss with increased mortality among the survivors,[7-10] highlighting the massive effects of this experience. More recently, for example, systematic research revealed that social loss triggers the development of Takotsubo cardiomyopathy, or "Broken Heart Syndrome". This syndrome is a reversible, stress-induced cardiomyopathy that mimics acute myocardial infarction and occurs after intense emotional or physical stress.[11] Above this, patients with Takotsubo cardiomyopathy have a higher prevalence of neurological or psychiatric disorders than those with an acute coronary syndrome.[12]

The previously described non-pathological mourning process is an adaptive response and usually has no long-term negative effects.[13] If, however, grieving continues and symptoms occur, that are beyond typical grief, *Prolonged Grief Disorder* (PGD) or *Persistent Complex Bereavement Disorder* (PCBD) can be diagnosed. PGD is characterised by longing for and preoccupation with the deceased, along with emotional distress and significant functional impairments that persist beyond 6 months after the loss of a significant other.[14] Approximately 10%-20% of mourners develop PGD/PCBD.[15-18] The diagnosis has only recently been added to the latest versions of the International Classification of Diseases (ICD-XI, PGD) and the Diagnostic Manual for Psychiatric Disorders (DSM-5, PCBD),[19] and led to debate about the defining criteria and consequences.[7,16,20,21] The term *Complicated Grief* (CG), which was originally developed to distinguish grief from depression,[22] does not represent the official diagnosis but, instead, comprises a larger category with diagnostic disordered grief encompassing a smaller group.[23] This distinction has to be kept in mind when interpreting empirical studies on grief. In the following, we employ the original terms used in the studies in each case.

1.2 | Psychobiological models of pair bond formation and bond disruption

The death of a loved one goes along with several psychosocial consequences: loneliness, a disruption in daily routines, a substantial loss of coherence, impaired sleep, and, most centrally, being separated from the loved person. All of these factors individually have been associated with poor health outcomes. For example, loneliness enhances the risk of morbidity and mortality,[24] elevates cardiovascular activation,[25] leads to cortisol dysregulation[26-28] and is associated with a greater utilisation of health care institutions.[29] A lower level of sense of coherence is associated with increased burden in caregivers of patients with chronic illness.[30] Additionally, poor sleep quality is associated with blunted cortisol awakening responses.[31] As the above mentioned psychosocial consequences all come together in grieving survivors, it can be assumed that those neuroendocrine and psychological changes may be even more pronounced in those who suffer intensely from the loss.

In this context, attachment and attachment disruption theories give important indications towards a better understanding of grief and its role in physical and mental health. Sbarra and Hazan[32] postulated that understanding the functionality and cause of human adult attachment could give us deeper insights into human coregulation and biobehavioural reactions to loss. According to their model,[32] relationships function as interpersonal regulatory systems. Interpersonal regulation means that couples co-regulate their emotional and behavioural responses, which serves as an adaptive mechanism that is less effortful and more automatic than individually regulating them.[32,33] The disruption of a relationship ends these regulatory benefits and leads to stress-related grief responses (dysregulation). The main task in coping with loss would be to manage dysregulation by using behavioural, emotional or cognitive strategies (functional *self-regulation*), which then attenuate the physiological consequences. According to the model, the initial reaction to loss not only involves psychological, but also physiological changes accompanied by psychological reactions.[32] Therefore, it is important to know the associated biological mechanisms of grief to predict negative psychological changes and to prevent grieving persons from long-term negative effects such as PGD/PCBD.

On the neuroendocrine level, grief might be primarily associated with an unspecific neuroendocrine stress-reaction, especially hypothalamic-pituitary-adrenal (HPA) axis activity. HPA axis activation leads to the synthesis of corticotrophin-releasing hormones (CRH) and vasopressin (VP), stimulating the secretion of adrenocorticotrophic hormones (ACTH) into the peripheral circulation.[34] As a result, ACTH induces glucocorticoid (e.g., cortisol) release in the adrenal gland, leading to a negative-feedback inhibiting HPA axis activation in the brain.[34,35] Cortisol secretion normally reaches its peak 30-45 minutes after awakening (cortisol awakening response [CAR]), followed by a subsequent decline during the day and reaching its lowest point between midnight and 5.00 AM[36,37] Besides its stress-dependence, a healthy HPA axis function shows strong diurnal patterns, and deviations from the typical decline throughout the day provide valuable information regarding the role of the axis in disease processes. Cortisol can be measured in several ways. Basal urinary free cortisol is often used to interpret aggregated cortisol levels. Hair or nail samples indicate hormone secretion over weeks or even months.[36] Recent studies have started to examine the

circadian rhythm of cortisol by evaluating a strong CAR and daily pattern of pronounced cortisol decreases during the day as indicators of a highly functional feedback-sensitivity of the HPA axis.[37]

As an additional neuromodulator, oxytocin (OT) is a hypothalamic neuropeptide that, after secretion from the paraventricular nucleus of the hypothalamus (PVN) and supraoptic nucleus (SON), is stored in the posterior pituitary lobe[38] and released into the peripheral blood circuit and into central-nervous brain areas, as parts of the pain network and the reward-system,[39] OT interacts with the HPA axis system by accompanying its response to a given stressor and exerting stress-reducing effects, for example heart rate, blood pressure and cortisol level decrease.[40-42] OT plays an important role in the formation and maintenance of social relationships.[43,44] In turn, the OT system is also altered after the disruption of a relationship.[45]

1.3 | Neuroendocrine changes after social loss in animals

In the history of research on neurobiological changes after social loss in humans, researchers often relied on animal models of separation and loss. More specifically, they began to examine neurobiological factors of social loss in the prairie vole (*Microtus ochraster*), which serves as an animal model of human social loss. In these monogamous rodents, the loss of a companion is associated with the activation of the HPA axis with higher basal plasma corticosterone concentrations[46-48] and adrenal hypertrophy.[49]

Vole mothers show significant increases in the corticotrophin-releasing factor (CRF) mRNA expression in the PVN,[46] when separated from their pups. Interestingly, the stress response to separation can be reduced through the peripheral, subcutaneous application of OT.[50,51] The separation from an adult attachment figure in voles leads to decreased OT mRNA expression in the PVN[49] and increased density of OT-immunoreactive cells in the PVN and the SON. The latter has been interpreted as a consequence of a decreased release and limited OT receptor activity in reaction to loss.[48] Furthermore, OT fibres signalling to the NAcc show decreased activation after loss in voles.[44]

Translating these effects of OT to human attachment, one can assume that the OT system is also involved in social loss in human beings. Neuroendocrine mechanisms involving OT have already been discussed with relevance for different mental disorders.[52] Although they might only serve as one of many response domains after the death of a beloved person, they could be a key mediator in the relationship between grief and the development of psychiatric disorders such as PGD or PCBD.[32] Deviations from functional neuroendocrine stress responses have already shown to be involved in response to trauma[53-55] and could possibly serve as a prognostic indicator for the development of grief-related psychopathology. Furthermore, important implications could be derived regarding preventive psychosocial interventions before the death of the close person in order to enhance co-regulation, as well as the awareness of the upcoming relationship disruption.

To date, a number of articles exist reviewing literature on the neuroendocrine mechanisms of grief, although they either exclusively focus on animal studies[44,45] or on prolonged grief in the context of only one neuroendocrine marker.[56] Therefore, the aim of the current work is to extend the existing literature by systematically reviewing studies investigating neuroendocrine mechanisms in the early stage of grief with potential predictive value for long-term pathological reactions to loss.

2 | MATERIALS AND METHODS

2.1 | Search strategy and eligibility criteria

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[57] A Boolean search was used to find the wide range of studies reporting neuroendocrine mechanisms of grief. The search terms were (grief OR bereavement OR bereaved OR "bond disruption" OR "social loss" OR "bond loss" OR sorrow OR mourning) AND (neuroendocrine OR endocrine OR neurobiol* OR psychobiol* OR psychophysiol* OR biomarker*). The initial search was performed in 22 March 2019 and updated on 23 April within four large databases including *Web of Science* (http://webofknowledge.com), *CINAHL* (https://www.ebscohost.com/nursing/products/cinahl-databases), *PubMed* (https://pubmed.ncbi.nlm.nih.gov) and *PsycINFO* (http://www.apa.org/psycinfo). The authors repeated the search on 13 November 2019 by adding more specific neuroendocrine words (oxytocin OR OXT OR OT OR cort* OR insulin OR prolactin OR endorphin OR catecholamin*) to find all the relevant articles concerning specific neuroendocrine changes after bereavement. Additionally, reference lists of relevant reviews, primary studies, and theoretical frameworks were searched for potential articles.[6,17,32,43-45,58-62] Two independent readers (DH and HM) screened the article abstracts and read the selected full-text articles in order to decide whether to include or exclude the articles according to predefined criteria. Non-consistent decisions were discussed until consensus was reached. The eligibility criteria for the studies were:

Inclusion criteria:

- Original study.
- Neuroendocrine markers (cortisol, epinephrine, norepinephrine, OT, insulin, prolactin, endorphin) investigated.
- Population: human adults (> 18 years) who lost a beloved person (partner, family member, close friend).
- Article available in English.

Exclusion criteria:

- Experimentally induced grief.
- Grief reactions did not occur as a result of death (eg, grief related to depression or post-traumatic stress disorder (PTSD); grief after divorce or break up).

- Article not available in English.
- No neuroendocrine markers assessed.
- Child or adolescent population (< 18 years).

2.2 | Data extraction

Relevant data of the incorporated studies, including publication date, study design, sample characteristics, grief assessment tools, neuroendocrine measure and results, were extracted for qualitative data analyses. Study quality was assessed independently by three authors (DH, ME and CAR) using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[63] This tool consists of 14 items (including 18 sub-items) assessing key issues of the study's internal validity; for example, population recruitment, statistical power considerations, assessment of exposure and outcome variables and consideration of confounding variables. The criteria can be met, not met, cannot be determined, are not applicable or not reported. The raters discussed their ratings to resolve discrepancies and come to a final decision. Studies were rated as "good", "fair" or "poor" to describe the risk of bias. A "good" quality rating indicates the least risk of bias. We decided to rate studies as "good" if they met more than 2/3 of the criteria. A "fair" rating indicates that the study shows higher risk of bias but not enough to invalidate results. Studies were rated as "fair if they met at least half of the criteria. A "poor" rating indicates high risk of bias that could significantly compromise the accuracy of the results. Studies were rated as "poor" if they met less than half of the criteria.

3 | RESULTS

In total, 677 papers were found during the systematic search (Figure 1), from which 469 articles remained after removing duplicates. After screening the abstracts, 39 articles remained for full-text eligibility search. Six articles were excluded because there was no full-text available online,[64-69] one study was excluded because it exclusively examined heart rate variability and cytokine production system,[70] one other study investigated receptor genes only[71] and five studies investigated early parental loss in childhood and

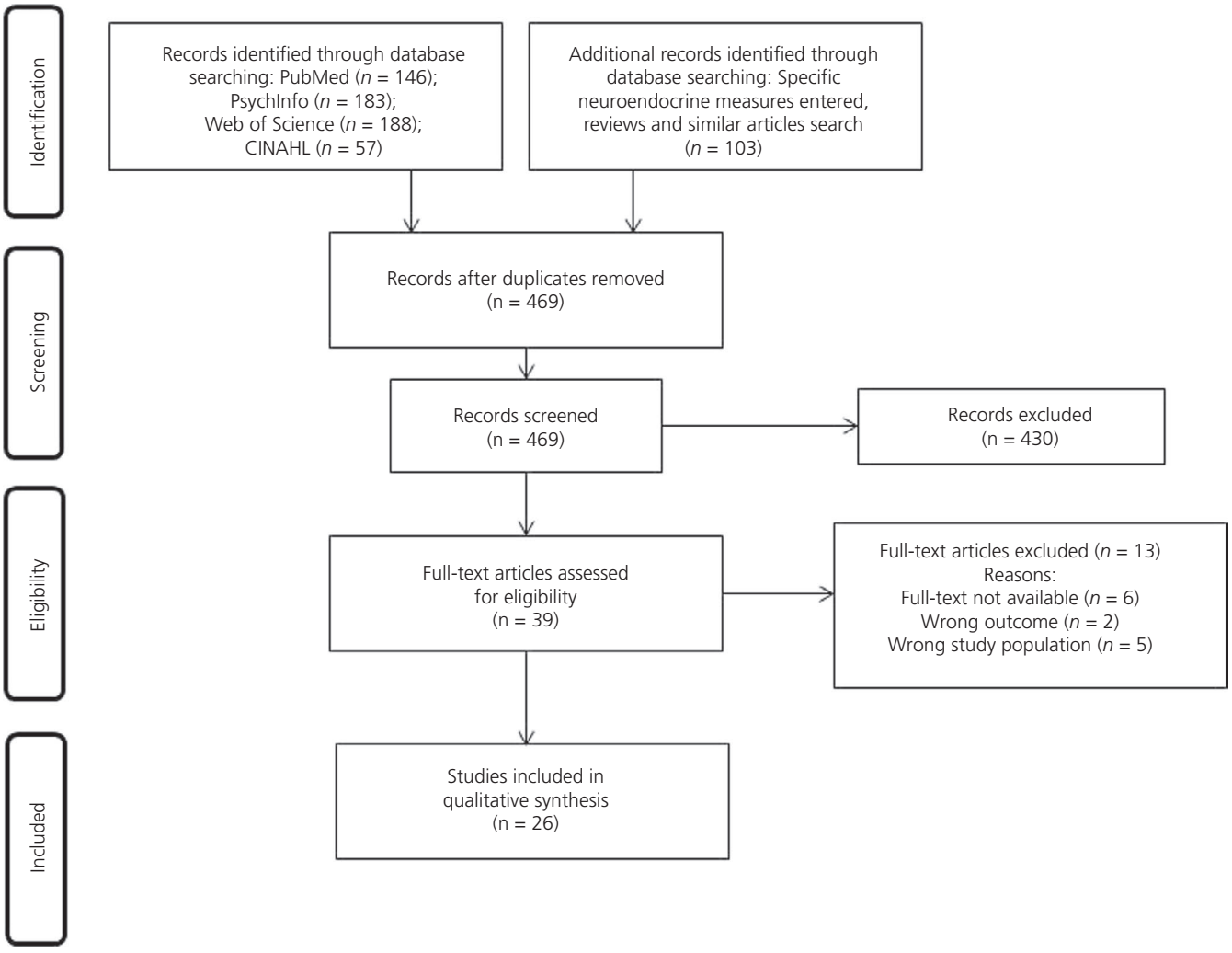

FIGURE 1 PRISMA flowchart on the study selection process

were therefore excluded.[72-76] The final sample consisted of 26 articles published between 1986 and 2019. According to the Quality assessment ratings, five studies showed good quality,[77-81] whereas 21 studies showed fair quality.[82-102] The results are shown in Table 1.

3.1 | Mean cortisol level

Five studies examined the association between bereavement and mean cortisol levels. Jacobs et al[84] compared 56 bereaved with non-bereaved spouses, both 1 and 2 months after hospitalisation of their spouse. It was hypothesised that adults with rising separation anxiety and distress during bereavement would show higher cortisol levels than those with lower anxiety. They collected 24-hour urinary free cortisol on three separate days in the week before the second interview and averaged the daily values of cortisol. Participants with high separation anxiety showed higher cortisol levels than those whose anxiety level fell from 1 to 2 months after hospitalisation. There was no difference in cortisol levels between the bereaved and the anticipatory bereaved.[84] Irwin et al[92] assessed cortisol weekly over 1 to 2 months in 28 recently bereaved, anticipatory bereaved, or non-bereaved women. They found significantly higher cortisol levels in the bereaved compared to the other controls. Spratt and Denney[93] examined the effect of sudden child death on cortisol levels in 18 bereaved vs non-bereaved parents. They report no differences in cortisol levels between the two groups. One further study compared cortisol levels between 260 bereaved and 262 non-bereaved men and women at the same time as controlling for depressive symptoms. Levels were assessed at one time-point after the psychiatric interview. No significant differences between the two groups were found.[79] Minton et al[96] investigated changes in physiological stress 11, 12 and 13 months after loss in 47 widows. They compared mean morning and evening cortisol levels and hypothesised that during the first anniversary after their loss, physiological stress level would be the highest. However, no significant differences in cortisol levels were found. The authors suggest that the anniversary does not represent an immediate stressor, not being sufficiently salient to change neuroendocrine stress levels.[96] Andersen et al[97] investigated the psychological and physical health effects of repeated loss among university students after clustered peer deaths. Cortisol was measured via hair samples 3 months after the loss. A significant association of prior bereavement experiences with hair cortisol level was found, as well as a significant negative relationship between the number of bereavement experiences and cortisol levels. The latter finding is interpreted in the way that people with prior bereavement maintain average levels of cortisol across the extended period of loss, whereas those with no prior experience display dysregulated cortisol levels.[97]

3.2 | Morning/evening cortisol

Two studies investigated bereavement in the context of morning cortisol. Buckley et al[80] assessed morning cortisol in 62 bereaved and 50 non-bereaved men and women 2 weeks and 6 months post-loss by taking one sample each morning. They found significantly higher cortisol morning levels in the bereaved compared to the controls at both time-points.[80] The second study examined whether overnight basal urinary free cortisol 12 months after loss depended on gender, the emotional reaction to loss (emotional numbness) and circumstances of spousal bereavement (prolongation) which were assessed 6 months post-loss. It was hypothesised that longer forewarning of death ("How long before your spouse's death did you realise that s/he was going to die?") and higher emotional numbness would be associated with higher cortisol dysregulation (higher cortisol levels).[78] As expected, prolonged forewarning was significantly associated with elevated cortisol levels. During 6-12 months, cortisol levels increased in widowers and decreased in widows. Bereaved men with emotional numbness at time 1 had higher cortisol levels at time 2 compared to men without emotional numbness. This association was not found in women.[78]

3.3 | Diurnal patterns of cortisol

Four studies examined diurnal cortisol patterns. Ong et al[90] compared morning cortisol, CAR and cortisol slopes across the day between 22 bereaved and 22 non-bereaved adults. They hypothesised that affect moderated the relationship between bereavement and HPA axis dysfunction.[90] Significantly lower cortisol wake-up levels and flatter diurnal cortisol slopes were found in the bereaved compared to the non-bereaved adults. The results were also partly in line with the mediation hypothesis: pre- to post-loss changes in positive affect accounted for 29% of the effect of spousal loss on diurnal cortisol slopes.[90] Similar results were found in a small sample ($n = 12$) of study participants suffering from CG.[81] Only participants with CG showed flattened diurnal cortisol slopes, whereas participants experiencing normal grief did not. It was proposed that only individuals experiencing a prolonged reaction to loss might develop permanent HPA axis dysregulation.[81] By contrast, Holland et al[82] found dysregulated HPA axis function independent of grief level. They compared diurnal cortisol levels between 56 depressed controls and depressed bereaved men and women with or without elevated PGD symptoms. Significantly lower cortisol wake-up levels and flatter diurnal slopes were found in the depressed bereaved PGD group compared to the depressed controls. The differences in cortisol levels between the depressed bereaved with PGD and the depressed bereaved without PGD were not statistically significant. On a descriptive level, men and women who had lost a spouse showed greater cortisol dysregulation than those who lost someone else than their partner.[82] It was suggest that, according to the results, the loss of a loved one is predictive of more dysregulated cortisol, irrespective of one's level of PGD symptoms. Peréz et al[77] investigated diurnal cortisol levels both 2 years and 5 years post-loss in CG sufferers compared to normal grieving men and women and controls in a population-based sample of 2084 adults. Significantly lower morning cortisol and overall cortisol levels (represented by the area under the curve) were found in the CG group compared to the healthy grievers at time 1. No significant differences were found regarding the diurnal slope.

TABLE 1 Results of the qualitative systematic review grouped by outcome

Study	Study design	Sample characteristics		
		Grief types/groups	Loss relation (%)	N/n per group (% female)
Mean cortisol level				
Jacobs et al (1987)[84]	Longitudinal: two time-points: first interview 1 month after hospitalisation of partner (1), second interview 2 months after hospitalisation (2)	2 × 2 groups Bereaved vs anticipatory bereaved Rising separation anxiety vs declining separation anxiety from (1) to (2)	Spouse	*N* = 56 *n* (bereaved) = 40 *n* (anticipatory bereaved) = 16 (50)
Irwin et al (1988)[92]	Longitudinal: weekly assessment of cortisol in a 1-2 month period < 6 months post-loss	(1) Recently bereaved women vs (2) women with terminally ill husbands vs (3) women with healthy husbands	Spouse	*N* = 28 *n* (1) = 9 *n* (2) = 11 *n* (39 = 8 (100)
Spratt & Denney (1991)[93]	Longitudinal: four time-points: 2, 4, 6 and 8 months post-loss (sudden loss)	Suddenly bereaved (1) vs non-bereaved (matched to bereaved)	Child	*N* = 18 *n* (1) = 9 (66)
Andersen et al (2013)[97]	Cross-sectional	Undergraduate students who experienced repeated peer deaths	Friends classmate	*N* = 122 (61.48)
Cohen et al (2015)[79]	Cross-sectional (part of a larger biomarkers study): in average 1.04 years post-loss	Bereaved (1) vs non-bereaved (2)	NR	*N* = 529 *n* (1) = 260 (50)
Morning/evening cortisol				
Buckley et al (2009)[80]	Prospective controlled cohort study, longitudinal: two time-points: 2 weeks and 6 months post-loss	Bereaved (1) vs non-bereaved (2)	Spouse (94) Child (6)	*N* = 112 *n* (1) = 62 *n* (2) = 50 (66)
Minton et al (2009)[96]	Exploratory longitudinal correlational study 11, 12 and 13 months post-loss	Widows	Partner (100)	*N* = 47 (100)
Richard-son et al (2015)[78]	Prospective multi-wave study, longitudinal Three time-points (only 1 and 2 used in biomarker analysis): 6 months (1), 18 months (2) and 48 months (3) after the death	Bereavement vs no bereavement	Spouse	Widowers: n (1) = 64 n (2) = 61 controls: *n* = 1545 (only subsample used) (NR)

Age (mean/ range or SD)	Grief assessment	Dependent neuroendocrine measure	Results	QA rating
62.6 (NR)	SA	24-hour urinary free cortisol Assessment times: three separate days in the week before time-point (2)	Group, in which separation anxiety rose from (1) to (2) had sig. higher cortisol levels than group in which SA diminished or dropped sig. Higher cortisol levels were found both for the bereaved and the anticipatory bereaved subjects	Fair
52.2 (3.4)	None	Plasma cortisol	sig. Higher mean plasma cortisol levels in group (1) compared to group (3) Not significant: Plasma cortisol level in group (2) and (3)	Fair
(1) = 49 (38-61)	None	Plasma cortisol Assessment time: between 9.30 AM and noon) at the four defined time-points	No significant differences in plasma cortisol between the two groups	Fair
20.13 (1.14)	None Other variables: relationship to the deceased media exposure to deaths mental health history prior adverse experiences distress responses to peer deaths	Hair cortisol assessment times: once 3 months after the loss experience	Prior bereavement experiences (eg, death of friend or family member) are significantly associated with hair cortisol level sig. negative relationship between number of bereavement experiences and cortisol levels during the period of peer deaths single most important predictor of cortisol response is whether or not a student had previously experienced the loss of a friend or family member	
(1) = 54.27 (11.72) (2) = 53.23 (11.05)	One/two questions: Had someone close died since Project 1? - if yes, number of persons close to the participant who had died since the last interview	Urinary cortisol Assessment times: after interview during 2-day visit	No significant differences in urinary cortisol between the two groups [a]sig. association between number of bereavements and levels of cortisol	Good
(1) = 65.2 (33-84) (2) = 61.6 (36-87)	None	Plasma cortisol Assessment time: morning	sig. higher morning cortisol levels in group (1) compared to group (2) at time-point 1 and 2 Not significant: cortisol levels and depression Higher alcohol intake is associated with higher cortisol levels	Good
74.1 (6.3)	None	Morning and evening salivary cortisol (each averaged over 3 days) Assessment time: 45 minutes after awakening and 12 hours later three consecutive days	No significant differences in cortisol levels between months 11, 12 and 13	
Bereavement group: 70 (6.25) no bereavement group: NR	None	Overnight basal urinary free cortisol Assessment time: morning	Cortisol levels increased from (1) to (2) in widowed men and decreased in widowed women Prolonged forewarning as sig. predictor of cortisol levels Bereaved men who reported emotional numbness at (1) had higher cortisol levels at (2) compared to bereaved women	Good

(Continues)

TABLE 1 (Continued)

Study	Study design	Sample characteristics		
		Grief types/groups	Loss relation (%)	N/n per group (% female)
Cortisol diurnal pattern				
Ong et al (2012)[90]	Cross-sectional: in average 17.5 months post-loss	Bereaved (1) vs non-bereaved (2)	Spouse	*N* = 44 n (1) = 22 (86)
O'Connor et al (2012)[81]	Cross-sectional: up to five years post-loss	CG vs NG	Mother (NR) Sister (NR)	*N* = 24 *n* (CG) = 12 (100)
Holland et al (2014)[82]	Cross-sectional: in average 3.1 years post-loss	(1) Depressed nonbereaved vs (2) depressed bereaved without elevated PGD vs (3) depressed bereaved with elevated PGD symptoms	Spouse/ partner (33) Parent (16.7) Sibling (12.5) child (4.2)	*N* = 56 *n* (1) = 32 *n* (2) = 15 *n* (3) = 9 (60.7)
Peréz et al (2017)[77]	Population-based cohort study (1) two years post-loss (2) between two and five years post-loss	CG vs NG vs no grief	Partner (NR) Child (NR) Parent (NR) Brother/ sister (NR) Others (NR)	*N* = 2084 *n* (NG) = 131 *n* (CG) = 31 *n* (no grief) = 1922 (55)

Age (mean/ range or SD)	Grief assessment	Dependent neuroendocrine measure	Results	QA rating
65.8 (48-80)	None	Salivary cortisol Assessment times: three to 6 months after questionnaire assessment on four successive days awakening, 30 minutes after awakening, before lunch, at bed- time	Sig. lower average wakeup levels of salivary cortisol in group (1) compared to group (2) sig. flatter diurnal cortisol slope curve among group (1) compared to group (2) Not significant: effect of spousal loss on CAR response Pre- to post-loss changes in positive emotion accounted for 29% of the effect of spousal loss on diurnal cortisol slopes *mediating effect of positive emotion, even if controlling for confounding factors	Fair
CG = 42.67 (10.54) NG = 46.91 (9.32)	Interview for Complicated Grie	Salivary cortisol Assessment times (Diurnal pattern): waking, 45 minutes post waking, 4.00 PM and 9.00 PM	sig. slope differences between CG and NG groups: diurnal slope of the CG group was lower in the morning and higher in the evening --> flatter slope Sig. lower cortisol level 45 minutes post-wake in CG compared to NG Sig. higher cortisol levels at 4.00 PM in CG compared to NG	Good
69.9 (7.6)	Prolonged Grief Disorder Scale (PG-13)	Salivary cortisol Assessment times: awakening - 5.00 PM - 9.00 PM Two consecutive days (combined for analysis) log-transformed values as independent variable	Sig. lower levels of log-cortisol levels at wake and flatter diurnal slopes in group (3) compared to group (1) Not significant: differences between group (2) and (3), although descriptively flatter profile in group (3) compared to group (2) Bereavement independently of its strength is associated with dysregulated cortisol levels Subsidiary analysis: Those who most recently lost a spouse showed sig. greater cortisol dysregulation (higher log-levels at wake and flatter slope) than those who lost someone else than the partner Not significant: continuous PG did not predict log-cortisol	Fair
64.9 (5.5)	Inventory of Complicated Grief (ICG), Dutch version	Salivary cortisol Assessment times: awakening - 30 minutes after awakening - 5.00 PM - bedtime	(1) Sig. lower levels of morning cortisol in CG vs NG Sig. lower overall diurnal cortisol levels (AUCg) in CG vs NG Sig. lower levels of morning cortisol in CG vs control Not significant: slope difference between CG and NG Not significant: cortisol differences between NG and controls (2) [a] Sig. AUCg and cortisol morning response differences between CG (2-5 years) and CG (< 2 years) [a] Sig. higher scores in ICG are associated withlower morning cortisol	Good

(Continues)

TABLE 1 (Continued)

Study	Study design	Sample characteristics		
		Grief types/groups	Loss relation (%)	N/n per group (% female)
Cortisol:DHEAS ratio				
Khanfer et al (2011)[89]	Cross-sectional: within 2 months post-loss	Bereaved (1) vs non-bereaved (2)	Close family member (NR) Friend (NR)	*N* = 48 *n* (bereaved) = 24 *n* (non-bereaved) = 24 (67)
Vitlic et al (2014)[85]	Cross-sectional 2 x 2 design	Young bereaved (1) vs young non-bereaved (2) vs old bereaved (3) vs old non-bereaved (4)	Spouse (65 for (1) and 9.5 for (2)) Close relative (35 for (1) and 91.5 for (2))	*N* = 93 n (1) = 31.8 n (2) = 20 n (3) = 26 n (4) = 26 (58)
DST/CRH stimulation test				
Roy et al (1988)[86]	Cross-sectional: CRH stimulation test	Bereavement complicated with depression (1) vs uncomplicated bereavement (2) vs depressed controls (3) vs healthy controls (4) Sample (3) and (4) are used from earlier study	Spouse (25) 1st degree relative (75)	*N* = 92 *n* (1) = 9 *n* (2) = 19 *n* (3) = 30 *n* (4) = 34 (41)
Petitto et al (1992)[102]	Cross-sectional: assessment of adults with affective disorder who had experienced loss earlier in life DST	Patients with affective disorder Early loss (<= 19 years) vs late loss (> 20 years) Only first loss examined	Mother (20) Father (60) Sibling (20)	*N* = 45 *n* (early loss) = 22 *n* (late loss) = 23 (58)
Gerra et al (2003)[88]	Longitudinal: 3 time-points: 10 days (1), 40 days (2) and 6 months after stress-full life event DST administered	Bereaved vs controls	Parent (57) Son (14) Spouse (29)	*N* = 28 n (bereaved) = 14 n (control) = 14

Age (mean/ range or SD)	Grief assessment	Dependent neuroendocrine measure	Results	QA rating
73 (5.3)	None	Blood cortisol Cortisol:DHEAS ratio	[a] Sig. higher cortisol:DHEAS ratio in group (1) compared to group (2) Not significant: Differences in cortisol level between group (1) and (2), although higher mean values in group (1)	Fair
(1) = 31.8 (9.03) (2) = 31.7 (8.41) (3) = 71.3 (5.79) (4) = 72.6 (5.72)	Core Bereavement Items (CBI) IES	Venous blood samples, Cortisol, DHEAS, cortisol:DHEAS-ratio	Sig. lower DHEAS, higher cortisol and higher cortisol:DHEAS ratio in (3) compared to (4) No significant differences in these outcomes between (1) and (2) Those with higher CBI - scores showed higher cortisol:DHEAS ratios Those with higher social support reported lower cortsiol:DHEAS ratios	Fair
(1) = 47.6 (14) (2) = 41.5 (13.7) (3) = 42.3 (13.1) (4) = 29.4 (5.1)	DSM-III assessment of complicated vs non-complicated bereavement (with vs without depression) Texas Inventory of Grief (128)	Plasma ACTH and cortisol after CRH administration (1-µg/kg) Assessment times: 30 minutes, 50 minutes, 60 minutes, 75 minutes, 105 min135 min and 165 minutes after injection of needle	Sig. higher basal cortisol levels in group (1) compared to group (2) and (4) No significant differences in ACTH-levels Sig. smaller ACTH responses to CRH in group (1) compared to group (2) and (4) Sig. greater cortisol responses to CRH in group (1) compared to groups (2) - (4) No significant differences in ACTH responses to CRH between groups (1) and (2)	Fair
44.7 (14.1)	None	Blood cortisol Assessment times: 4.00 PM and 11.00 PM 1 day after dexamethasone application 11.00 PM day before)	Among the affective disorder patients of the early loss group, younger age at first loss significantly[a] correlated with higher 4.00 PM cortisol levels First loss as strongest predictor for HPA axis functioning Late loss predicts higher cortisol levels at 11.00 PM	Fair
38 (17-75)	None Degree of stress (Social Adjustment Scale)	Blood cortisol blood ACTH DST Assessment of blood samples: between 9.00 and 11.00 PM at times (1), (2) and (3)	Sig. higher cortisol plasma levels after DST in time (1) compared to time (2) and (3) [a] Sig. higher cortisol plasma levels after DST in time (1) in bereaved group compared to control Sig. higher mean basal ACTH concentrations in bereaved subjects in time (1) compared to (2) and (3) Sig. higher mean basal ACTH concentrations in bereaved subjects compared to controls in time (1) Sig. higher plasma cortisol concentrations in response to dexamethasone in high responders compared to low responders in the bereavement group Sig. correlations between HRSD and cortisol levels at time (1)	Fair

(Continues)

TABLE 1 (Continued)

Study	Study design	Sample characteristics		
		Grief types/groups	Loss relation (%)	N/n per group (% female)
Pfeffer et al (2009)[91]	Longitudinal: two time-points: one after study entry and one within 6 months after entry	(1) Bereaved (as a result of a traumatic event - terror attack at 09/11/2001) vs (2) non-bereaved	Spouse	*N* = 45 *n* (1) = 23 (96)
Catecholamines				
Jacobs et al (1986)[83]	Cross-sectional: 2 months after hospitalisation/death of the partner	Bereaved (1) vs anticipatory bereaved (2)	Spouse	*N* = 59 *n* (1) = 39 *n* (2) = 20 (51)
Jacobs et al (1997)[87]	Longitudinal: six time-points after hospitalisation over the course of 25-months follow-up: 1st time-point (1): directly after intake 2nd time-point (2): 1 month after intake 3rd time-point (3): 2 months after intake 4th time-point (4): between 2 and 13 months after intake 5th time-point (5): 13 months after intake 6th time-point (6): 25 months after intake 2nd time-point: baseline symptom assessment 3rd time-point: defensive and neuroendocrine assessment 5th and 6th time-point: outcome assessment	Bereaved/anticipatory bereaved	Spouse	*N* = 67 (50)
Insulin				
Cankaya et al (2009)[98]	Cross-sectional (part of a larger investigation of stress, individual differences, and health in a middle-aged and older primary care sample)	Sudden unexpected loss (linear or ordinal) Natural vs unnatural death	NR	*N* = 75 (100)

Age (mean/ range or SD)	Grief assessment	Dependent neuroendocrine measure	Results	QA rating
(1) = 41.79 (6.52) (2) = 41.12 (6.46)	None	Basal and post-dexamethasone cortisol Assessment times: 30 minutes after awakening, 7.00 PM , 4.00 PM , 9.00 PM on four consecutive days Dexamethasone administration: on day 3 in the evening	Sig. higher AM - cortisol in group (1) compared to group (2) PM - cortisol tended to be higher in group (1) compared to group (2) Sig. less afternoon cortisol suppression in group (1) compared to group (2) Not significant: group differences in cortisol suppression during AM assessment Sig. higher PM cortisol suppression in bereaved with accompanied PTSD compared to bereaved without any psychiatric disorder	Fair
61.9 (NR)	Emotional Distress associated with loss	24-hour urinary catecholamines (epinephrine and norepinephrine) Assessment times: three successive day	Higher outputs of catechloamines in (1) compared to (2) - not in a range associated with adrenal medullary disease No significant difference in norepinephrine or epinephrine in (1) compared to (2) Sig. negative correlation between norepinephrine and depression score	Fair
62 (0.9)	Unresolved grief/separation distress (as outcome variable)	As predictors: mean 24-hour urinary free cortisol at time-point (3) Mean 24-hour urinary free epinephrine at time-point (3) three samples	No significant difference between bereaved and non-bereaved in neuroendocrine functioning No sig. correlations between neuroendocrine measures and separation distress, depression, anxiety and demoralisation High mean cortisol predicted better self-rated health at time (5) High mean epinephrine predicted higher hopelessnes/helplessness scores at time (5) Mean cortisol was inversely correlated with symptoms of hopelessness and helplessness at time (6) Mean epinephrine was positively correlated with symptoms of hopelessness/helplessness at time (6)	Fair
52.07 (9.67)	None Traumatic Life Events Scale 1) Lifetime history of any sudden unexpected loss 2) Number of lifetime sudden losses 3) Type of sudden loss	IGF-1 assessed in blood assessment times: between late morning and late afternoon after the interview	Sig. lower IGF-1 levels in women who had experienced a sudden unexpected loss compared to women without a history of sudden loss Number of sudden losses is significantly associated with IFG-1 levels: the greatest decrease in IGF-1 was shown in the group with the most losses (> 5 sudden losses) No significant differences between those who lost someone as a result of an unnatural event vs a natural event	

(Continues)

TABLE 1 (Continued)

Study	Study design	Sample characteristics		
		Grief types/groups	Loss relation (%)	N/n per group (% female)
Oxytocin				
Bui et al (2019)[99]	Cross-sectional pilot study loss occurred at least 6 months prior to the study	Bereaved with primary diagnosis of CG (1) vs Major Depressive Disorder (MDD) (2) vs bereaved controls (3)	Parent (25.6 in (1), 40 in (2), 42.9 in (3)) Spouse (41 in (1), 12 in (2), 8.6 in (3)) Other (33.3 in (1), 48 in (2), 48.6 in (3))	*N* = 139 *n* (1) = 47 (70.21) *n* (2) = 46 (69.57) *n* (3) = 46 (69.6)
Prolactin				
Lane et al (1987)[100]	Cross-sectional bereaved sample, 8 weeks after death of the spouse	Widows/widowers with low (1), moderate (2), or high (3) developmental level of object representation (DLOR)	Spouse	*N* = 26 (46)
Intervention studies				
Theorell et al (1987)[101]	Intervention study (activation program)	Anticipatory bereaved and bereaved men and women who are about to lose/who lost a close relative (1) Activation programme Group (2) Comparison Group	Close female relatives (wives, sibling or child-ren)	*N* = 72 (100) *n* (1) = 36 *n* (2) = 36
Goodkin et al (1998)[94]	Randomised, controlled intervention study; longitudinal: Baseline (before intervention), 10 weeks (right after intervention), 6 months follow-up 10 months bereavement support group vs standard care control about 6 months post-loss	Bereaved HIV + homosexual men (1) vs bereaved HIV- homosexual men (2)	Close friend (NR) Partner (NR)	*N* = 119 *n* (1) = 45 (0)
O'Connor et al (2013)[95]	Part of a larger randomised clinical trial. longitudinal: Pre-Post Complicated Grief Intervention mean time post-loss = 87 months	Complicated Grief (continuously measured)	Close friend (NR) Spouse (NR) Parent (NR) Child (NR) Sibling (NR)	*N* = 16 (88)

Abbreviations: AUCg, area under the curve with respect to the ground and the slope; NR, not reported; QA, Quality Assessment.

ACTH, adrenocorticotrophic hormone; CAR, cortisol awakening response; CBI, Core Bereavement Items; CG, complicated grief; CRH, corticotrophin-releasing hormone; DHEAS, dehydroepiandrostheron-sulphate; DSM-III, Diagnostic and Statistical Manual of Mental Disorders III; DLOR, developmental levels of the survivors' object representation; DST, dexamethasone suppression test; HRSD, Hamilton Rating Scale for Depression; ICG, Inventory of Complicated Grief; IES, Impact Event Scale; IGF, insulin-like growth factor; MDD, major depressive disorder; NG, normal grief; OT, oxytocin; PG, prolonged grief; PGD, Prolonged Grief Disorder; PRL, prolactin; PTSD, post-traumatic stress disorder; SA, separation anxiety. sig.,significant.

Age (mean/ range or SD)	Grief assessment	Dependent neuroendocrine measure	Results	QA rating
(1) = 49.49 (12.87) (2) = 49.33 (13.27) (3) = 48.64 (12.7)	Inventory of Complicated Grief (ICG) Structured Clinical Interview for Complicated Grief (SCI-CG)[99]	Overall plasma levels of OT, measured through one simple blood collection	Sig. higher plasma OT levels for group (1) compared to group (2) No significant OT differences between (1) and (3) ICG symptom severity explained only 2% of the variation in plasma OT levels Secondary analysis: a primary or probable CG diagnosis is positively associated with plasma OT levels	
58.9 (26.4)	None DLOR (high vs moderate vs low)	Serum prolactin assessment times: before and after semistructured interview pre-to post interview prolactin change	Sig. larger mean PRL change in women compared to men Sig. negative correlation between PRL change and DLOR in women Sig. positive correlation between PRL change and DLOR in men	
(1) = 51 (24-77) (2) = 52 (21-77)	None Others: Depression Anxiety Mental Exhaustion	Serum prolactin serum cortisol assessment times: during treatment period before death 1 month after death 2 months after death	Increasing degree of mental exhaustion during the treatment period is associated with increasing cortisol levels and decreasing prolactin levels Sig. increased cortisol levels 1 month after death compared to the last observation before death Sig. lower prolactin levels during treatment in the activation programme compared to group (2) no significant differences in cortisol or prolactin levels from 1 to 2 months after death	
38.3 (9.5)	None	Plasma cortisol at all three time-points	sig. decrease of plasma cortisol levels in the intervention group compared to the control group Group (1) intervention subjects showed a decrease in cortisol levels from time 1 to time 3, whereas group 2 intervention subjects showed an increase in cortisol levels from time 1 to time 3 Sig. effect of intervention on cortisol levels (time 1 and 3 included) when controlling for baseline cortisol levels	Fair
64 (4.3)	Inventory of Complicated Grief (ICG)	Blood catecholamines: epinephrine, norepinephrine, dopamine Assessment times: up to 4 weeks before first therapy session between 10.00 AM and 3.30 PM	[a] Sig. prediction of post-treatment ICG score by pre-treatment epinephrine Not significant: pre-treatment dopamine and epinephrine in predicting post-treatment CG score	Fair

At time 2, significant higher cortisol morning responses and overall cortisol responses were found in the CG group compared to the same group at time 1. Furthermore, higher scores in grief severity were associated with lower morning cortisol levels.[77]

3.4 | Cortisol:DHEAS ratio

Two studies investigated the association between bereavement and the cortisol:dehydroepiandrostheron-sulphate (DHEAS) ratio. DHEAS is a sulfated steroid-hormone that is associated with HPA axis activity. By contrast to cortisol, which has immunosuppressive effects, DHEAS enhances the immune response. Studies have shown that DHEAS can buffer the suppressive effects of cortisol on neutrophil function.[89] Additionally, an increased cortisol:DHEAS ratio, which represents an imbalance between those biomarkers, appears to be a contributing factor to the process of age-related immunosenescence. Khanfer et al[89] hypothesised that ageing and stress had an additive and deleterious effect on immunity and that bereaved older adults should have higher cortisol:DHEAS ratios than non-bereaved older adults. They used the cortisol:DHEAS ratio as an indicator of neutrophil function and assessed cortisol levels in bereaved and non-bereaved older adults. Although cortisol levels were slightly higher in the bereaved group, a higher cortisol:DHEAS ratio was found in the bereaved compared to the non-bereaved subjects.[89] Vitlic et al[85] compared cortisol:DHEAS ratios between younger and older bereaved vs non-bereaved adults and found significant lower DHEAS, higher cortisol and higher cortisol:DHEAS ratios in the older bereaved compared to the older non-bereaved. These differences were not shown in the young groups.[85] Although the younger bereaved showed higher psychological effects of loss than the older subjects, these changes were not reflected in neuroendocrine outcomes. Finally, those with stronger grief symptoms showed higher cortisol:DHEAS ratios, whereas those with higher levels of social support showed lower ratios.[85]

3.5 | Dexamethasone suppression test (DST)/CRH stimulation test

The DST is applied to assess HPA axis feedback sensitivity.[103] By applying the corticosteroide dexamethasone, which mimics the effects of cortisol, cortisol release should be suppressed in healthy individuals. Non-suppression is considered an indicator of hypercortisolism. The CRH stimulation test was designed to test HPA axis dysregulation by stimulating the ACTH response.[103] After the administration of CRH, a rapid rise in ACTH and cortisol is expected, followed by a gradual decrease.

Four studies investigated DST/CRH results in bereaved individuals. Roy et al[86] applied the CRH stimulation test in bereaved men and women with or without depression and hypothesised that depressed bereaved would show similar reactions to CRH stimulation as depressed non-bereaved. The non-depressed women appear to have "normally" blunted responses to CRH stimulation, which may reflect their normal reaction to the negative feedback of hypercortisolism that is often found in depressive patients.[86] ACTH and cortisol were assessed in 92 participants after receiving the DST. Higher cortisol and lower ACTH levels were found in the depressed bereaved compared to the non-depressed bereaved and the healthy controls.[86] Petitto et al[102] examined the relationship between loss experience and HPA axis function in subjects with an affective disorder. They compared cortisol levels after DST in 45 men and women who had a loss experience at the age of 17 years or earlier with those who had a loss experience at the age of 18 years or later and included major depressive disorder as a control variable. Depressed men and women showed lower cortisol levels than the non-depressed. Among the affective disorder patients of the early loss group, younger age at first loss significantly correlated with higher afternoon cortisol levels. Furthermore, in the afternoon, men in the early loss group showed significantly higher cortisol levels than women. Late loss significantly predicted higher cortisol levels in the morning.[102] Gerra et al[88] compared ACTH, cortisol levels and immune markers after DST in 28 bereaved vs non-bereaved men and women 10 days, 40 days and 6 months after loss. They found higher cortisol levels in the bereaved, compared to the non-bereaved. ACTH levels were significantly higher in the bereaved group at time-point 1 only. Interestingly, cortisol and ACTH levels were highest in the early stage of bereavement. Furthermore, the effect of temperament was investigated: they found non-suppression of dexamethasone in subjects with high depression and harm avoidance compared to subjects with low depression and harm avoidance 6 months after bereavement.[88] Pfeffer et al[91] examined basal and post-DST cortisol in 23 traumatically bereaved participants over two time-points following the 9/11 terror attacks. Bereaved spouses showed higher morning basal cortisol and less afternoon post-dexamethasone suppression than non-bereaved subjects. Additionally, bereaved subjects with PTSD showed significantly greater afternoon post-dexamethasone suppression than bereaved subjects without PTSD, indicating higher glucocorticoid receptor sensitivity in the bereaved with PTSD.[91]

3.6 | Catecholamines

Two studies examined the association between bereavement and catecholamines as outcomes of sympathetic adrenal medullary function (SAM). Jacobs et al[83] investigated 24-hour urinary free epinephrine and norepinephrine on three successive days in 59 bereaved and anticipatory-bereaved subjects and found higher catecholamine outputs in the bereaved compared to the anticipatory bereaved; however, these differences were not significant. Norepinephrine was inversely correlated with depression scores and positively correlated with age. The latter finding is in line with past research showing that the SAM system in older adults adapts more slowly to stress.[83] Jacobs et al[87] examined the predictive effect of adrenal function on depression, anxiety, hopelessness, or unresolved grief. They assessed 24-hour urinary cortisol, epinephrine

and norepinephrine in bereaved and anticipatory-bereaved individuals. The neuroendocrine markers were assessed three times at time-point 3 (2 months after hospitalisation), at which 63% of the subjects were widowed. The psychological variables were assessed at time-points 2, 3, 5 and 6 (1, 2, 13 and 25 months after intake.) The neuroendocrine markers did not differ between the two groups. Epinephrine and cortisol only predicted hopelessness at time-point 5 in the bereaved subjects, although they did not predict any other psychological outcomes. Additionally, higher mean cortisol levels (average of the three assessments) at time-point 3 predicted better self-rated health at time-point 5. Mean cortisol measures were inversely correlated and mean epinephrine levels were positively correlated with hopelessness scores at time-point 6. The results indicate that adrenal function may serve as a mediator between social loss and health-related outcomes.[87]

3.7 | Insulin

Cankaya et al[98] investigated associations of interleukin (IL)-6 and insulin-like growth factor (IGF)-1 with the sudden death of a loved one in 75 females in an urban primary care setting. IGF-1 is posited as a protective factor in ageing-related diseases and is negatively correlated with immune markers such as IL-6. It was hypothesised that a prolonged exposure to stress and a sudden death would result in greater insulin changes than shorter exposure and a less sudden death. Significantly lower IGF-1 levels were found in women who had experienced a sudden unexpected loss compared to women without a history of sudden loss. The number of sudden losses was significantly associated with IGF-1 levels, meaning that the greatest decrease in IGF-1 was shown in the group with the most losses.

3.8 | Oxytocin

Bui et al[99] investigated peripheral plasma OT levels in men and women with CG. They compared a single assessment of OT levels of participants with a primary CG diagnosis to participants suffering from depression as primary diagnosis and bereaved control participants with no comorbid diagnosis. They found significantly higher OT levels in the CG group compared to the depressed group. There were no significant differences between the CG group and the group of non-pathological grief.[99] Secondary analyses revealed that a primary or probable CG diagnosis was positively associated with plasma OT levels.

3.9 | Prolactin

Lane et al[104] investigated sex differences in prolactin (PRL) changes during mourning in 26 spouses. Amongst others, PRL plays a role in the stimulation of maternal care, acts as an endogenous anxiolytic agent and regulates oxytocin neurones.[104] They assessed serum PRL before and after a semi-structured interview. The aim was to examine sex differences in the association between the developmental levels of the survivors' object representation (DLOR). The DLOR represents the verbal description of a person and the level of cognitive complexity of that description.[100] The results show a significant larger mean PRL change in women compared to men. A negative correlation between PRL change and DLOR was found in women, whereas a positive correlation was found in men.[100]

3.10 | Effects of bereavement interventions on neuroendocrine stress markers

Three studies examined the effects of bereavement interventions on stress-related neuroendocrine markers. In the first study, the effect of an activation programme on plasma cortisol and prolactin levels was examined in 72 close female relatives of cancer patients.[101] Plasma cortisol and prolactin, as well as anxiety, depression and mental exhaustion, were assessed during the intervention, right before the death of the relative and 1 and 2 months after loss. The results show that an increasing degree of mental exhaustion during the treatment period is significantly associated with increasing cortisol levels and decreasing prolactin levels. Furthermore, significantly higher cortisol levels were found 1 month after death compared to the last assessment before death. Also, lower prolactin levels during treatment were found in the activation group compared to the control group.[101] In the second study, the effects of a short-term bereavement support group intervention with 119 widowed men infected with HIV on immune variables and cortisol levels were assessed.[94] Recently bereaved HIV seropositive (HIV+) and HIV seronegative (HIV–) men were randomly assigned to either a bereavement support group intervention or a standard care group. Plasma cortisol was assessed pre, post and at 6-month follow-up. Significantly lower cortisol levels were found in the intervention group compared to the control group 6 months after the intervention. HIV + men in the intervention group showed significant decreases in cortisol levels from pre-assessment to follow-up, whereas HIV– men in the intervention group showed increased levels of cortisol within the same time-period.[94] The third study assessed predictive effects of catecholamines as moderators of a bereavement intervention and CG treatment outcomes after bereavement.[95] Sixteen bereaved individuals provided information on the Inventory of Complicated Grief (ICG) pre- and post-psychotherapy and blood epinephrine, norepinephrine and dopamine were assessed 4 weeks before the intervention. The post-treatment ICG-score was significantly predicted by pre-treatment epinephrine levels. SAM activity and autonomous function in the participants showed impaired CG outcomes after therapy.[95]

3.11 | Summarized results of good-quality studies

In summary, the results of "good quality" studies suggest the following neuroendocrine changes after the loss of a loved one:

- The more deaths of loved ones someone experiences, the higher his/her the cortisol levels.[77]
- Morning cortisol levels are significantly higher in bereaved compared to non-bereaved 2 weeks and 6 months after bereavement.[80]
- The longer the forewarning of someone's death, the higher the cortisol levels after bereavement.[80]
- Bereaved men suffering from emotional numbness 6 months after loss show higher cortisol levels 12 months after death compared to bereaved men who do not suffer from emotional numbness.[78]
- Compared to non-pathologically grieving subjects, people with CG show flattened diurnal cortisol slopes, suggesting that HPA axis dysregulation is more pronounced in prolonged grief.[79] People with CG show significantly lower morning and overall cortisol levels compared to non-pathological grievers 2 years after loss.[77]
- People with CG show significant higher cortisol morning responses 5 years after loss compared to two years after loss.[77]
- Higher scores in grief severity 5 years after loss are associated with lower morning cortisol levels.[77]

4 | DISCUSSION

The loss of a loved one can be associated with neuroendocrine alterations and dysfunction both in the early and late stage of bereavement. This systematic review summarises original articles examining neuroendocrine correlates of social loss. Of the original studies included in this review, most focused on HPA axis (eg, cortisol) or SAM-related hormones (epinephrine, norepinephrine) as primary outcomes. These studies not only suggest elevated mean cortisol levels and flattened diurnal cortisol slopes, but also increased epinephrine and norepinephrine levels after social loss. In general, flattened diurnal cortisol slopes have been associated with negative health outcomes in different study populations.[104] Individuals suffering from CG show flattened diurnal cortisol slopes[70,77] as well as lower morning and mean cortisol levels,[77] than those showing non-complicated grief. Furthermore, both closeness to the deceased[82] and grief severity[79] play an important role in the development of neuroendocrine dysregulations. The closer the relationship and the more or enduring the subjective impairment is articulated, the more endocrine dysregulation is pronounced. Particularly, higher grief levels and lower social support are associated with higher cortisol levels.[85] In addition, specific stressors, as well as psychological and demographic factors, partially account for HPA axis alterations. For example, increases in separation anxiety in the course of bereavement were associated with higher levels of cortisol[84] and having a longer forewarning before death lead to higher cortisol levels than experiencing an unexpected loss.[78] Sudden, unexpected losses, as well as a rising number of losses, are associated with lower insulin levels, showing that those context variables influence health-reducing neuroendocrine alterations after bereavement.[98] A positive affect was inversely correlated with cortisol levels,[90] whereas rising emotional numbness in men during the course of bereavement enhanced cortisol levels,[78] suggesting again that psychological variables are important when examining neuroendocrine changes after loss. Regarding gender differences, one study revealed that men showed decreasing cortisol levels, whereas women showed increasing cortisol levels during the course of bereavement.[78] Older men and women showed stronger alterations in their neuroendocrine stress responses than younger cohorts,[85,89] indicating that high age may have an additive effect on loss consequences. Furthermore, changes in stress-related alterations were shown, especially in the early stage of bereavement, although there is inter-individual variability.[88] In the latter study, however, almost no direct correlations between psychological and biochemical reactions were found. Neuroendocrine alterations were not only found directly after bereavement, but also months after loss experience.[97] Interesting results evolved with regard to psychiatric diseases: especially depressive symptoms were associated with higher cortisol levels[86,102] and higher cortisol non-suppression[88] in bereaved subjects. Furthermore, individuals suffering from PTSD after a traumatic loss showed higher cortisol levels than those with no trauma-related psychiatric diagnosis.[80] The same study suggests that trauma-related psychopathology may foster a prolonged neuroendocrine response to social loss up to 8 years after the event. One study investigated OT as a biomarker of grief and found higher OT levels in people suffering from CG.[99] Regarding prolactin changes, women have higher prolactin levels than men after having been interviewed about the deceased partner. Interestingly, women who have a more complex insight into the deceased person also show higher prolactin levels, whereas the opposite association is observed in men.[100]

In summary, these studies suggest that not only bereavement by itself, but also bereavement-associated psychopathology in particular is associated with stress-related neuroendocrine alterations. This is in line with research on trauma,[53,54] loneliness[26-28,105] and disrupted attachment,[44] which can all be individual psychosocial aspects of bereavement and separately serve as causal factors of stress-related neuroendocrine dysregulation. Bereavement can have health-impairing and fatal consequences for the surviving individual[4,6,9,106] and, as a consequence, interventions have been designed and evaluated to buffer these effects. The available studies on the effects of these interventions found the intervention to reduce cortisol levels.[94,95] Furthermore, epinephrine levels predicted psychopathology-related treatment outcomes suggesting that pre-treatment stress levels moderated the effectiveness of the intervention.[95] In line with this, catecholamines were correlated with helplessness and hopelessness in the course of bereavement,[87] and thus can serve as endocrine markers of subjective burden and treatment effects. An intervention before the partners' death was found to elevate cortisol levels and reduce prolactin levels, especially right before death.[101] The latter finding is consistent with the hypothesis that grief is activated by an intervention and that the active mourning may have a prophylactic value to the relative's grief reaction.[101]

The results indicate that, even years after loss, bereavement might be associated with neuroendocrine changes. These changes are

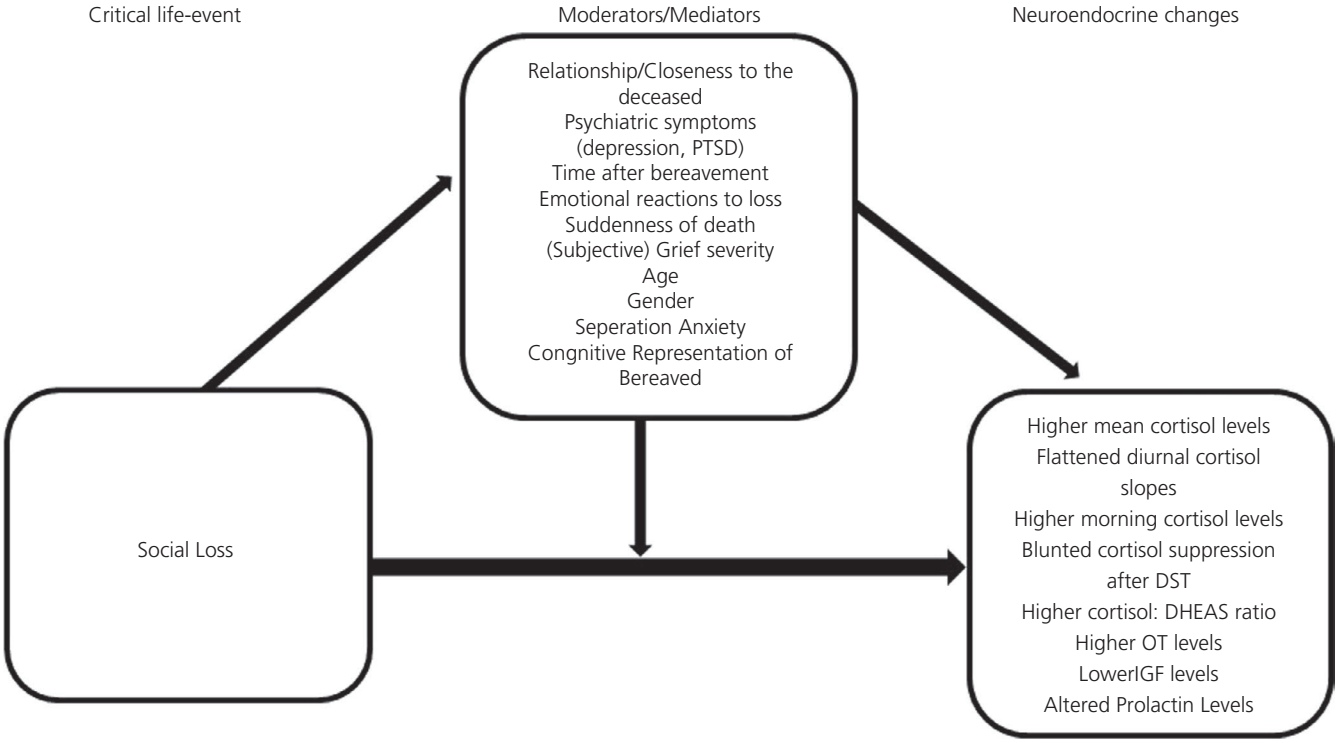

FIGURE 2 Model with summarised results (including potential moderators/mediators) of the studies investigating neuroendocrine mechanisms of grief. DHEAS, dehydroepiandrostheron-sulphate; DST, dexamethasone suppression test; IGF, insulin-like growth factor; OT, oxytocin; PTSD, post-traumatic stress disorder

moderated by grief severity, psychiatric state and psychological reactions to loss, as well as age and gender. On a psychobiological level, neuroendocrine responses may serve as moderators between the loss-event and long-term psychological outcomes (Figure 2). However, because of the methodological difficulties and contradictory results of the studies, these conclusions must be treated with caution.

For example, Ong et al[90] found that prolonged forewarning of death was associated with higher cortisol levels. They argue that a longer duration of care is associated with more stressful experiences, and thus leads to stronger physiological stress reactions.[90] Research on the development of PGD/PCBD shows that suddenness of death is a risk factor,[107] which initially appears to contradict the findings of Ong et al[90]. In this context, it is important to note that PGD/PCBD symptoms are not only characterised by physiological distortions such as elevated cortisol levels, but also by emotional and behavioural symptoms such as intense yearning, longing or emotional pain.[108] The contradictory findings may indicate that there are moderator variables between instant physiological reactions and the development of PGD/PCBD that foster the maintenance of an abnormally high cortisol level. It is not clear, yet, whether high cortisol levels or flattened diurnal slopes are risk factors of the development of PGD/PCBD. So far, only correlative conclusions can be drawn about HPA axis dysfunction and PGD/PCBD. To obtain a better understanding of what role HPA axis function may play in PGD/PCBD, it would be essential to measure cortisol levels in regular intervals over a longer time span after bereavement at the same time as measuring moderator variables.

There are further inconsistent study results regarding morning and mean cortisol. Buckley et al[80] found significantly higher morning cortisol levels in the bereaved, whereas Perez et al[77] found lower morning cortisol levels in people with CG. This discrepancy might be because of the different methods and timeframes investigated. Cortisol levels might be differentially affected depending on the time since loss. Furthermore, Buckley et al[80] compared grieving with non-grieving people, whereas Perez et al[77] compared people with CG and non-CG. Additionally, two studies found significantly elevated cortisol levels in bereaved and anticipatory bereaved,[86,92] whereas two other studies did not.[79,93] One reason for the conflicting results could be their methodological diversity, using different measurements of cortisol, different time-frames and different measurement foci. Furthermore, the study populations were somehow different. For example, Spratt and Denney[93] only examined suddenly bereaved parents, whereas Jacobs et al.[87] and Irwin[92] had participants with a longer history of end-of-life care.

4.1 | Limitations

The studies included in this systematic review reveal some limitations – one of them is the overall small sample size, which limits the statistical power of the results. Although 21 studies were of fair-quality and only five studies were rated as high-quality studies, the results must be interpreted with caution. For one thing, most of the studies considered the loss event as the exposure

variable without assessing continuous levels of subjective grief. According to some results, grief severity and subjective appraisal of loss have a stronger influence on neuroendocrine reactions than the loss experience itself.[77,78,84,85,90] Based on this, grief levels should be measured continuously to enhance the validity of the study. Furthermore, many studies took place years after the loss event. Potential confounding factors could have occurred within this time frame, which makes it difficult to disentangle the effect of bereavement from other factors influencing long-term endocrine changes. Another important fact is that many studies do not report whether the survivors made use of social support or psychosocial bereavement interventions, although social support can buffer the loss reaction. In the studies underlying this review, grief severities, as well as neuroendocrine outcomes, were assessed differently, which hampers their comparability or calculation of effect sizes using meta-analytic methods. More importantly and as a result of the unpredictability of death, neuroendocrine markers were not assessed before the loss of a loved person, and thus provide limited information on stable predictors only.

Despite the limitations mentioned, the findings of elevated cortisol and flattened diurnal slopes are relatively reliable, which suggests that they seem to be robust.

It has to be noted that, so far, only cortisol has been examined more extensively and research on other neuroendocrine measures, such as OT, ACTH or catecholamines, is still scarce.[99] The only study examining OT in the context of bereavement[97] has some methodological flaws, as the authors measured OT in the periphery. The assessment of peripheral OT levels is criticised because of its lack of association with central-nervous OT levels,[109] and ongoing methodological discussion about the reliable measurement of OT in the periphery even.[110] These points make it is difficult to draw reliable conclusions, especially with respect to neuroendocrine grief reactions in the human central nervous system. Based on the findings of animal studies on social loss as well as human studies with healthy couples, however, it can be assumed that the painful experience of a close person's death might also involve the OT system. The rewarding, stimulating effect of a well-functioning relationship is eliminated and the OT system remains under-stimulated.[111] This under-stimulation could in the long run even be related to the symptoms of PGD/PCBD. Additionally, studies investigating neural correlates of social loss indicate grief-related altered activation in brain areas such as the NAcc[112] and the ACC,[113] which are associated with the reward-system and high OT receptor densities. However, endogenous OT mechanisms in the central nervous system cannot be measured in the human living brain so far, which limits the possibilities to test for direct involvement of OT in the grieving process. Therefore,[44] animal models can be helpful to better understand those mechanisms. Moreover, human and animal studies can complement each other in a meaningful way because their methods lead to context-dependent results: experimental settings are artificial and may lead to different reactions than real-life events.[45] Above this, animal models cannot give us sufficient insights into the psychological reactions to loss. On the other hand, so far, the highly individual human grief-reaction cannot be investigated in a standard procedure or related to specific neuroendocrine changes in the living brain. Despite the lack of transferability, animal research can give us important hints as to where to start in human research and what hypotheses to establish. Therefore, the combination of knowledge from animal and human research can provide a broader picture on this complex topic.

Finally, some limitations should be mentioned regarding the recruitment of bereaved individuals. First, bereaved people are in an altered state of mind, with some describing numbness and a genuine loss of interest in daily matters. They might be difficult to reach with broad recruitment tools. For those who are, the reason for participating might be the hope for psychological support, meaning a rather vulnerable and selective subgroup might agree to participate. As to working with a bereaved sample, it can be challenging to maintain the motivation of the participants to remain in the study. Also, because the time of death most often occurs unforeseen, there usually are no individual baseline measures before the loss. To obtain pre-bereavement measurements, participants should be recruited before the death of their close one, treating them with the highest sensibility and psychological supervision.

4.2 | Future research and implications for psychosocial interventions

To help establish a comprehensive model of the neuroendocrine factors underlying the psychobiological reactions to social loss, in addition to the neuroendocrine stress response, future research can benefit from a focus on further and interacting neuroendocrine systems. Animal research on social loss suggests that, for example, the OT system interacts with the HPA axis and might be involved during grief reactions. Both CRH and OT have been shown to interact with the dopamine) system, which regulates reward and is involved in depressive disorders and addiction. In both animals and humans, dopamine appears to play a role in the formation of a romantic relationship; for example, reward-associated brain regions are highly activated in association with positive attachment interactions,[114-116] and it is assumed that this system could also be affected after loss by remaining under-stimulated.[111] Indeed, human studies already indicate activations in brain-regions with high OT and dopamine receptor density.[91,92] In line with this, withdrawal from drug abuse has been associated with similar activation patterns compared to separation from a partner.[46,111]

In addition, longitudinal studies assessing subjective and neuroendocrine markers before and after loss could minimise confounding inter-individual variations and thereby improve statistical power and long-term predictive power. Although necessarily in such studies, loss would always be predicted by a lethal illness, thereby limiting the range of different possible events to trigger grief.

Initial studies investigating neuroendocrine alterations after a bereavement intervention show promising effects and suggest that, beside subjective measures, neuroendocrine and stress-related outcomes can serve as meaningful indicators of treatment success.[94,95,101]

In this context, it is important to keep in mind that subjective and objective measures often diverge in research on stress, and thus it is important to reveal the differences between these measurements. This leads to the next step of exploring the reasons why these differences occur and what they mean for treatment success. However, to better interpret the meaning and importance of neuroendocrine measures for therapeutic success, more research is necessary. Furthermore, the assessment of neuroendocrine measures is associated with some hurdles. For example, the assessment of blood, urine or saliva samples is time-consuming and may be a reason for grieving participants not to take part in a study. One possibility to address this issue and to enable data on aggregated cortisol levels to be collected over an extended time period of weeks to months is the use of hair samples to quantify, for example, cortisol secretion. Ecological momentary assessment could be used to reduce the participants' burden of being torn out of their every-day life. Regardless of discussing in what way neuroendocrine measures serve as an indicator for treatment success, the Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health explicitly recommends the inclusion of objective measures into interventional studies.[117] All in all, more research is necessary, investigating potential factors that may influence the efficacy of bereavement interventions with different populations, varying age groups and social background So far, only one early study has investigated the effects of a psychosocial intervention before the separation experience with the aim of *preventing* grief reactions and associated neuroendocrine alterations after loss. As far as we know, the anticipation of losing someone close may already lead to neuroendocrine changes,[84] which highlights the need for early strategies preventing neuroendocrine dysfunction and buffering the negative effects of social loss. It is known from studies on healthy couples' interventions that positive psychosocial interventions together with the partner or a family member activates the reward system and exerts stress-buffering effects.[118,119] This leads to the assumption that the described stress and under-stimulation reaction to social loss can be influenced by appropriate interventions and specific death and bereavement management programmes.[6,46] Psychosocial interventions before the loss of the partner might strengthen the bond, reduce stress levels, affect the endogenous OT release and buffer grief-related stress-reactions, preventing long-term negative health effects such as the development of CG or other psychiatric problems. According to the dual process model of coping,[120] oscillations between thoughts about the lost attachment figure on the one hand and evaluating a future without the lost loved one on the other hand are considered important factors of an adaptive grief coping process. In this context, interventions that help to strengthen the bond, and which make unresolved issues a subject of discussion, might foster a healthy coping process and therefore affect neuroendocrine as well as psychological health changes after the loss. Although there is no study investigating the effects of pre-death interventions on neuroendocrine reactions such as OT signalling, initial studies show that psychosocial interventions before loss are able to improve the well-being of the participants.[121,122] However, this hypothesis needs further investigation and additional research is necessary to understand whether mechanisms such as OT signalling contribute to the efficacy of such treatments. Furthermore, it is important to consider inter-individual differences when deciding on whether to implement an intervention or not.

In summary, neuroendocrine correlates of anticipatory grief and grief after social loss could help us identify individual needs and serve as tools to evaluate not only impairment, but also treatment success. In the long run, this knowledge might allow the development of specific interventions that improve stress-related responses in the survivors and thereby their health.

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CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

DH, ME, CAR and BD defined the literature search criteria. DH conducted the literature search and summarised the findings. DH, ME and CAR rated the internal validity of the studies by the National Heart, Lung, and Blood Institute Study Assessment Tool. DH, CAR, ME and MW wrote the paper. BD reviewed the manuscript and gave critical advice.

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Appendix III: Paper III

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Still With Me? Assessing the Persisting Relationship to a Deceased Loved-One - Validation of the "Continuing Bonds Scale" in a German Population

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Abstract

Continuing the bond (CB) to a deceased loved one plays a clinically significant role in grief. We validated the Continuing Bonds Scale (CBS) examining externalized CB (illusions and hallucinations) versus internalized CB (use of the deceased as a secure base) in relation to risk factors of complicated grief and bereavement-related adjustment. Data from 364 bereaved German participants on CBS, Inventory of Complicated Grief (ICG), and Posttraumatic Personal Growth Inventory (PPGI) entered an exploratory factor analysis. This yielded a two-factor-solution representing externalized and internalized CB (*KMO* = .89, $\chi 2$ = 2100.5, *df* = 120). Both factors demonstrated high internal consistency (Cronbach's α = .87). ICG and PPGI highly correlated with externalized and internalized CB. Cause of death and feelings of responsibility were associated with externalized CB. In the future, the use of the CBS could help predict problems in grief processing and consequently implement early interventions.

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Keywords
Continuing Bonds Scale, prolonged grief disorder, attachment, posttraumatic personal growth, bereavement complicated grief

Introduction

Theoretical Background

Losing someone you love through their death is one of the most stressful life-events, which is accompanied by intense psychological and physiological reactions in the bereaved. Those reactions involve crying, yearning, insecurity, aggression, depressive and (psycho-) somatic symptoms (Biondi & Picardi, 1996; Zisook & Shear, 2009), but also neuroendocrine (Hopf et al., 2020), immunological (Knowles et al., 2019), and cardiovascular changes (Fagundes et al., 2018). Suffering from the loss of a loved one may even increase mortality amongst survivors (Manzoli et al., 2007; Moon et al., 2011), highlighting the massive effects of this experience. The individual's response to the loss can be placed on a continuum that goes from "normal" grief to prolonged, complicated grief (CG). Since grief is an extremely complex process and reactions to a loss are expressed in very different ways, the definition of "normal" grief remains highly individual. However, on the one hand, typical psychological reactions involve feelings of insecurity, anxiety, aggression and depressive and (psycho-) somatic symptoms (Biondi & Picardi, 1996; Kristensen et al., 2012; Stroebe et al., 2001). On the other hand, CG is characterized by longing for and preoccupation with the deceased, accompanied by emotional distress that persists beyond 6 months after the loss (Steinig & Kersting, 2015). CG symptomatology is found in up to 10–20% of the bereaved individuals (Shear & Shair, 2005; Steinig & Kersting, 2015) and has been shown to be associated with depression, hypertension and cardiac problems, work and social impairment, psychotropic drug use, and reduced quality of life (Boelen & Prigerson, 2007; Bonanno et al., 2007; Neria et al., 2007; Simon et al., 2007). In addition, bereaved individuals are at increased risk of suicide and suicidal behavior (Agerbo, 2005; Latham & Prigerson, 2004; Prigerson & Slimack, 1999; Stroebe et al., 2005, 2007).

The term CG does not represent an official diagnosis but, instead, comprises a larger category, with diagnostic disordered grief encompassing a smaller group. This disordered grief is called Prolonged Grief Disorder (PGD) or Persistent Complex Bereavement Disorder, which just recently have been added to the ICD-XI (WHO, 2018) and the Diagnostic Manual for Psychiatric Disorders (DSM-5).

Although the loss of a loved one seems a final event that requires the physical detachment of the bereaved from the attachment figure, it does not mean that the emotional or psychological relationship with that person immediately ends (Root & Exline, 2014). According to the Continuing Bonds Theory (Root & Exline, 2014), which was inspired by the attachment theory (Bowlby, 1980), people sense that the

relationship to the deceased is continuing over their death, transforming, but not terminating. This so-called Continuous Bond (CB) can also be described as "the presence of an ongoing inner relationship with the deceased person by the bereaved individual" (Stroebe & Schut, 2005). This post-death relationship manifests itself through thoughts of the deceased, reminiscence about the deceased (Marwit & Klass, 1995), telling stories about the deceased (Nickman et al., 1998), dreaming of the deceased (Black et al., 2020), looking at photographs (Foster et al., 2011), keeping possessions of the deceased (Nickman et al., 1998), but also through the influence of the deceased character, lifestyle, beliefs on the own every-day life, sometimes culminating in an interactive communication like the engagement in a direct communication with the deceased (Foster et al., 2011; Nickman et al., 1998). Within research on causes and effects of CB, there has been an ongoing discussion about whether CB is a purely natural and adaptive process, or whether it also has maladaptive components which hinder the surviving individuals from integrating the loss into their life (Field, 2006b; Fraley & Shaver, 1999; Klass & Steffen, 2017; Stroebe et al., 2010). Although back in the 20s century researchers were convinced that CB is rather maladaptive and hinders healthy grieving, more recently, it has been proposed it may be important and adaptive to psychological well-being and grief resolution (Field, 2006a). CB is considered a grief-specific coping strategy, being a source of solace for the survivors. However, the extent to which CB is (mal-) adaptive seems to depend on specific dimensions such as the degree of proximity or the locus of the CB (Field, 2006a; 2006b; Field & Filanosky, 2009; Field et al., 2005). Psychological proximity is the degree to which people reminisce the deceased person (in memory). Those reminiscences may involve externalized components such as hallucinating about or having illusions of the deceased. For example, illusions entail the misperception of a stranger as the deceased because he or she has similar characteristics to the deceased or sounds that are mistaken for the deceased's voice. Hallucinations may similarly involve the misconstruction of an internally driven source of information as emanating from an external source, when lying in bed at night (Field, 2006a). Internalized components, on the other hand, entail an ongoing connection with the deceased, thoughts of the deceased as a role model and the use of their mental representation as an internalized secure base and safe haven on the other hand. Externalized (ext.) CB is hypothesized to be indicative of unresolved loss, as it reveals the surviving individual's inability to realize that the deceased person is dead. Ext. CB could hinder the integration of the loss into one's life, the resolution of grief and, in a long-term, lead to chronic symptom burden and a greater risk of developing chronic diseases, or even higher mortality (Field & Filanosky, 2009). On the other hand, internalized (int.) CB expressions may serve to facilitate the integration of the loss in one's own life and thus fostering the resolution of grief. More precisely, int. CB nurtures the positive development of the surviving individual by helping to overcome the loss reaction and strengthening their life experiences in a long-term.

Due to its high importance for individual grief processing and the psychological and physiological health of the surviving loved ones, it is important to measure the CB construct adequately and to study CB and its associated factors. In line with hypotheses

of the adaptiveness of the subscales of CB, for example, ext. CB has been shown to be highly associated with complicated grief symptoms, demonstrating its link to unresolved loss (Field & Filanosky, 2009).

On the contrary, int. CB has been hypothesized to be associated with post-traumatic personal growth, meaning personality-strengthening reactions to this stressful life-event (Lipp & O'Brien, 2020; Scholtes & Browne, 2014; Tedeschi et al., 2017).

Personal growth takes place as the individual successfully addresses the challenges associated with the loss (e.g., managing every-day life issues that have been previously managed by the deceased, or re-orienting of personal goals and perspectives) and emerges with a revised sense of self in the world (Tedeschi & Calhoun, 2004).

Furthermore, participants who find meaning or peace in their loss, tend to have higher int. CB and lower ext. CB scores than those who do not find meaning or peace (Neimeyer et al., 2006). It has also been hypothesized that ext. CB scores are influenced by the suddenness of death and feelings of responsibility for the death (Field & Filanosky, 2009). For example, sudden deaths as well as feelings of responsibility for the death have been shown to be associated with higher ext. CB scores, showing that they may serve as risk factors for maladaptive grieving. On the other hand, relationship closeness to the deceased has been found to be positively correlated with both ext. and int. CB (Field & Filanosky, 2009).

Attachment style may also play a role in CB. Sudden deaths are associated with higher ext. CB scores, as well as feelings of responsibility for the death. Just recently, it has been hypothesized that people with insecure (high anxious or avoidant) attachment have more difficulties to adapt to the loss and thus show higher ext. CB scores. This hypothesis has only partly been confirmed (Field & Filanosky, 2009; Ho et al., 2013) and needs further investigation.

There is only one existing questionnaire measuring internalized and externalized CB – the Continuing Bonds scale (CBS). The CBS was first developed by Field and his colleagues and validated in different forms and widely used in English-speaking samples (Field & Filanosky, 2009; Field et al., 1999, 2003; Scholtes & Browne, 2014; Stroebe et al., 2012) as well as in one Italian sample (De Luca et al., 2016). There are several versions with different subscales, item numbers and response formats. Only the latest version of the CBS introduces the two subscales - ext. CB and int. CB - (Field & Filanosky, 2009). So far, there is neither a German version of the CBS nor another validated German questionnaire which measures CB components.

Present Study

The aim of this study was to examine the psychometric properties (factorial structure, item characteristics, reliability, and validity) of the translated German version of the CB scale. To evaluate the scale's construct validity, we assessed its relationship with risk factors for developing long-term problems in the adaptation to the loss (type of death, relationship to the deceased, feeling responsible for the death, feeling at peace with the loss, attachment style), relationship closeness, posttraumatic growth and complicated

grief symptoms. We hypothesized, that a violent death, feeling responsible for the death, and not feeling at peace with the loss are all associated with higher externalized CB scores. This association should go in the opposite direction or not be found for the int. CB subscale. Furthermore, we assumed that the closeness of the relationship to the deceased is positively linked with internalized and externalized CB. Higher insecure-anxious attachment style should be positively associated with externalized CB, and negatively or not associated with internalized CB. In line with the theoretical considerations and the previously found results (Field & Filanosky, 2009; Tedeschi et al., 2017), we finally assumed that the int. CB subscale is more strongly linked to posttraumatic growth, whereas the ext. CB subscale has stronger associations with complicated grief symptoms.

Materials and Methods

Participants and Procedure

This study was approved by the Ethics Commission of the Medical Faculty of Heidelberg, Germany. The Participants were recruited between May 6th 2020 and October 19th 2020 from online grief portals, grief funeral homes, bereavement groups, and hospices. Inclusion criteria were the age of at least 18 years, speaking German fluently, and having lost a close attachment relationship (parent, spouse or partner, child, or close friend) through death. The online survey was conducted via the platform *soscisurvey.de* and participation was voluntary and completely anonymous.

A total of $N = 557$ individuals participated in our online assessment. We excluded everyone who did not consent to participate ($n = 6$), everyone under the age of 18 ($n = 1$), participants who had lost a pet ($n = 2$), and those who dropped out after the first page ($n = 45$), so that $N = 503$ participants remained. From those participants $n = 364$ answered the Continuing Bonds scale. Thus, our final sample consisted of $n = 35$ men (9.5%), $n = 327$ women (89.8%) and $n = 2$ people of other sex (.5%) at the age of 18 to 78 ($M = 48.16$, $SD = 13.32$). Most of the participants had lost a child (35.4%) or a parent (24.5%), lost someone due to acute disease (27.5%), with a mean time since death of 2–5 years. Demographic characteristics are displayed in Table 1.

Measures

Demographics and Characteristics of the Deceased. At the beginning of the survey, the following demographic characteristics were assessed: Age, gender, and educational level. Characteristics of the deceased person were: Relation to the bereaved and cause of death (acute disease versus chronic disease versus natural (unexpected) versus natural (expected) versus accident versus suicide versus murder versus other cause), which was later dichotomized (violent versus non-violent). Finally, feelings of responsibility for the death (one dichotomous item with the options *yes/no*), being in

Table 1. Demographic Characteristics of the Sample (N = 364).

	Categories	*n* (%)
Gender	Female	327 (89.8)
	Male	35 (9.5)
	Diverse	2 (0.5)
Education	Elementary school	12 (3.3)
	High school	134 (36.8)
	College	194 (53.3)
	Still at school/training	13 (3.6)
Deceased's relation to the bereaved	Child	125 (34.3)
	Spouse/partner	67 (18.4)
	Sibling	45 (12.4)
	Parent	89 (24.5)
	Unborn child	4 (1.1)
	Close friend	11 (3)
	Something else	23 (6.3)
Time since death	0–3 months	21 (5.8)
	3–6 months	21 (5.8)
	6–9 months	13 (3.6)
	9–12 months	12 (3.6)
	1–2 years	44 (12.1)
	2–5 years	71 (19.5)
	5–10 years	83 (22.8)
	10–20 years	76 (20.9)
	>20 years	19 (5.2)
Cause of death	Acute disease	100 (27.5)
	Accident	78 (21.4)
	Chronic disease	59 (16.2)
	Natural (unexpected)	52 (14.3)
	Suicide	26 (7.1)
	Natural (expected)	15 (4.1)
	Pregnancy loss	13 (3.6)
	Murder	5 (1.4)
	Other cause	13 (3.6)
Cause of death (dichotomous)	Non-violent	239 (65.7)
	Violent	109 (29.9)
Feeling responsible for the death	No	262 (72)
	Yes	67 (18.4)

Note. percentages refer to the total sample (N = 364); percentages of missings range between 0.8% and 4.4%.

peace with the loss (one dichotomous item with the options *yes/no*), and relationship closeness were measured.

Experience in Close Relationships

The German short version of the Experience in Close Relationships Questionnaire (ECR-RD-8) (Ehrenthal et al., 2021) was used to assess attachment style, more precisely attachment-related anxiety versus attachment-related avoidance. Participants had to assess their feelings regarding close relationships in general, using a 7-point Likert scale (1 – *strongly disagree* to 7 – *strongly agree*). The questionnaire shows good internal consistency in this sample (anxiety scale: α = .78; avoidance scale: α = .87). Subscales (attachment related anxiety vs. attachment-related avoidance) were calculated by computing the average of the relevant items.

Continuing Bonds Scale

The CB scale (Field & Filanosky, 2009), which is a self-report measure, was used to assess the ongoing relationship to the deceased. The original questionnaire consists of 16 items (with two subscales) which can be answered on a 4-point Likert scale regarding the past month. The externalized CB subscale with 6 items measures hallucinations and illusions of the deceased, indicative of unresolved loss (e.g., item 15 "I imagined that the deceased might suddenly appear as though still alive.") (Field & Filanosky, 2009). The internalized CB subscale entails 10 items, which include thoughts of the deceased as a role model and safe haven (e.g., item 1 "I thought about the positive influence of the deceased on who I am today."). The factor analysis conducted by Field and Filanosky confirmed the two factors structure (externalized vs. internalized CB) with an internal consistency of α =.73 and α = .92 respectively (Field & Filanosky, 2009).

In this study, we decided to utilize a 5-point Likert scale (0 – *not at all* to 4 – *constantly*) instead of the original 4-point Scale (0–3), to provide the opportunity to choose a neutral category. It has been previously shown that an additional middle category enhances the reliability and validity of self-report scales (O'Muircheartaigh et al., 1999) and that people tend to systematically (and not randomly) choose one adjacent category over the other if there is no middle option (Krosnick et al., 2009).

In this version with 5 response categories, internalized CB scores range between 0 and 50; whereas externalized CB scores range between 0 and 30. To obtain the German version, two German native-speaker translated the items into German. Then, they were back-translated into English. The translated German version were reviewed by comparing the original CBS with the back-translated CBS by discussing and adjusting the items until reaching consent regarding the exact wording. The final version of the German CBS can be found in Appendix A.

Inventory of Complicated Grief

In order to measure complicated grief symptoms, we used the German version of the Inventory of Complicated Grief (ICG-D) (Lumbeck et al., 2012). The ICG was

originally developed to identify grief-related symptoms that could help discriminate between uncomplicated and complicated grievers (people reporting high levels of maladaptive aspects of grief) (Prigerson et al., 1995). Exemplary items are "I feel bitter over the person's death", or "I feel stunned or dazed about what happened". The ICG consists of 19 items and the participants report the frequency with which they currently experienced each of the emotional, cognitive, and behavioral states on a 5-point Likert scale (0 *never* – 1 *rarely* – 2 *sometimes* – 3 *often* – 4 *always*). ICG-D sum scores range between 0 and 76. The one-factor-structure as well as reliability and validity of the ICG-D have been examined with good results (Lumbeck et al., 2012). Within the present sample, the ICG-D shows excellent internal consistency (Cronbach's α= .90).

Posttraumatic Personal Growth Inventory

We assessed posttraumatic growth via the Posttraumatic Growth Inventory (PTGI) (Tedeschi & Calhoun, 1996). The PTGI consists of 21 items and 5 subscales ("New possibilities", "Personal strengths", "appreciation of life" and "Religious changes"). Participants were asked to indicate the strength of changes that had been caused by the most stressful life event via a 6-point Likert Scale (*not at all – hardly – a little – quite – strong – very strong*). Therefore, PTPG total sum score ranges between 0 and 126. The questionnaire used in this survey was the translated and validated German version (Maercker & Langner, 2001) and has high overall internal consistency within this sample (Cronbachs α = .93), with subscale-specific consistencies between α = .78 and α = .92. Exemplary items are "I'm able to do better things with my life.", "New opportunities are available which wouldn't have been otherwise."

Statistical Analysis

To evaluate the feasibility of the data for Exploratory Factor Analysis (EFA), we calculated Bartlett's test of sphericity to value that the variables are correlated, and the Kaiser-Meyer-Olkin (KMO) test to measure sampling adequacy. Furthermore, to test for problematic multicollinearity between the variables, we calculated the determinant of the correlation matrix, which should be higher than .00001 (Field et al., 2012). We used the Screeplot with scree test and parallel analysis to assess the optimal number of factors, as recommended by Field (Field et al., 2012). Then we conducted a principal axis analysis (PAA) with oblique rotation (oblimin) on the set of 16 items, as recommended by Field and Filanosky (Field & Filanosky, 2009), and only items that loaded >.40 were retained (Thompson, 2004).

Furthermore, confirmatory factor analysis (CFA) was performed to assess the model fit (Tanaka et al., 1991). The item correlation matrix indicated that there is linearity in the variable pairs. Mardia test was calculated to test for multivariate normality (Mardia, 1974). Mardia test and QQ plots indicated non-normality of the data (mardia skewness: $\chi^2 = 1835.724, p < .001$; mardia kurtosis: $\chi^2 = 12.584, p < .001$). Therefore, we used the robust maximum likelihood method to estimate and interpret the robust standard errors.

For the assessment of the model fit, the following fit indices were considered: Comparative Fit Index (CFI) (Bentler, 1990), Tucker Lewis Index (TLI) (Tucker & Lewis, 1973) and Root Mean Square Error of Approximation (RMSEA). Guidelines suggested that CFI and TLI equal to .90 or above (Bentler, 1990; Bollen, 1989), and RMSEA equal to .05 or below (Brown & Cudeck, 1993; Hu & Bentler, 1998) were indicative of a good fit. An internal consistency reliability analysis was performed for each factor using Cronbach's alpha coefficients.

In preparation of the validity analyses, we calculated spearman rank correlations, *t*-tests and one-way analyses of variance (ANOVA) to detect if the demographic variables had any associations with the variables of interest (CB subscales, ICG-D scores, PTPG-scores and ECR-RD8 scores).

For validity analysis, we performed one-way analyses of covariance (ANCOVA) for the association between type of death, relationship to the deceased, feeling responsible for the death, as well as being at peace with the death (independent variables) and the CB subscales (dependent variables), including potential demographic characteristics (age, gender, time since death occurred) as covariates. For associations between CB subscales and attachment style, posttraumatic personal growth and complicated grief, we conducted partial correlations with potential demographic characteristics being ruled out.

Both EFA and CFA were performed with *R* version 3.0.3 (The *R* Foundation for Statistical Computing, Vienna, Austria). Item characteristics as well as all other analyses were performed using IBM® SPSS® Statistics for Windows version 27. The two-tailed significance level was set to $p < .05$.

Results

Exploratory Factor Analysis

The Kaiser–Meyer–Olkin measure verified the sampling adequacy for the analysis KMO = .89 ('great' according to Kaiser (1974)). All KMO values for individual items were >.83, which is well above the acceptable limit of .5. Bartlett's test of sphericity (χ^2 (120) = 2100.502, $p < .001$), indicated that correlations between items were sufficiently large for PAA. The scree plot showed inflexions that justify a 2-factor solution, which was also supported by the Parallel test (see Figure 1). Given the test and the scree plot as well as the theoretical and empirical considerations of the original publication, we decided to retain two components in the final analysis. Table 2 shows the factor loadings after rotation, as well as other item characteristics.

A two-factor solution accounted for 42% of the total variance: Int. CB (eigenvalue = 4.15; variance explained = 26%) and ext. CB (eigenvalue = 2.53; variance explained = 16%). The discriminative power of all items is medium to high and lies between .427–.699. The Cronbach's α values are satisfying (overall CB: α = .87, internalized CB subscale: α = .88; externalized CB subscale: α = .78).

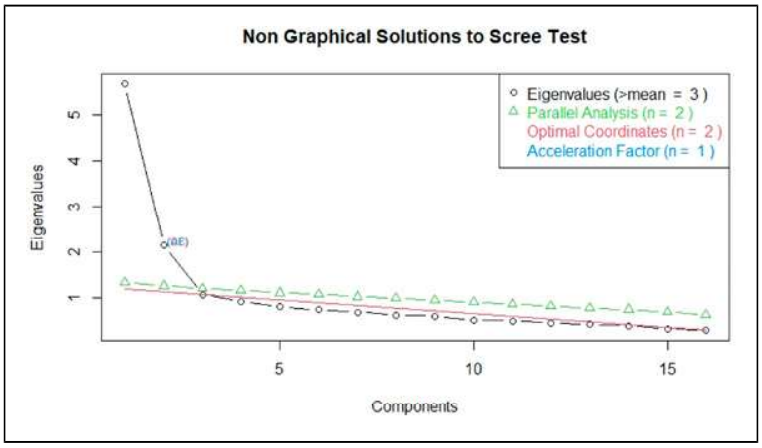

Figure 1. Results from the Scree Test prior to the Exploratory Factor Analysis.

Confirmatory Factor Analysis

Confirmatory Factor analysis was conducted, with the CB items no. 1 to no. 10 representing factor1 and items no. 11 to no. 16 representing factor 2. Results indicated a fair fit of the two-factor model to the data (*TLI* = .84, *CFI* = .86, *RMSEA* = .08, *SRMR* = .07). Th path coefficients results of the CFA are displayed in Figure 2.

Validity of the CB Scale

On average, participants had an int. CB score of *M* = 22.23 (*Range*: 0–69), and an ext. CB score of *M* = 6.72 (*Range*: 0–27). Furthermore, self-reported complicated grief symptoms were on average *M* = 32.12 (*Range*: 0–69), and PTPG total scores *M* = 53.61 (*Range*: 0–100). Descriptive statistics and intercorrelations between the variables of interest are shown in Tables 3 and 4, respectively.

Before conducting the validity analyses, we assessed whether control variables (age, gender, and time since death) correlated with our variables of interest (CB scores, ICG-D scores, and PTPG scores). Age significantly correlated with both the int. CB scale ($r = -.11$, $p < .05$) and the ext. CB scale ($r = .13$, $p < .05$). Gender did not correlate with either of the variables, except for the ICG-D scores: Complicated Grief Symptoms were significantly lower in men than in women ($t(40.22) = -2.48$, $p = .02$, *Cohens d* = .486). Time since death had no associations with int. CB (*Spearman rho* = - .09; $p = .12$), but significant associations with ext. CB (*Spearman rho* = .13; $p = .02$), ICG-D scores (*Spearman rho* = - .13; $p = .01$), and PTPG scores (*Spearman rho* = .26; $p < .001$). We included all the significant variables as control variables into our models.

Cause of Death. To assess the association between cause of death (violent vs. non-violent) and ext. versus int. CB, we conducted two one-way ANOVAs with int. and ext. CB as dependent variables and type of death as independent variables. Age and time since death were included as covariates (time since death only for ext. CB). As

Table 2. Results From the Factor Analysis of the German Continuing Bonds Questionnaire (CBS).

Item No.	Factor Loadings		Communalities	M (*SD*)	Item Difficulties	Item Discrimination	Cronbach's α if tem is dropped
	Int. CB[a]	Ext. CB[b]					
1	**.589**	−.161	.296	2.935 (*1.244*)	.587	.472	.872
2	**.687**	−.108	.424	2.025 (*1.383*)	.405	.583	.864
3	**.682**	−.087	.425	1.452 (*1.341*)	.29	.586	.864
4	**.578**	.182	.452	2.36 (*1.478*)	.472	.616	.862
5	**.767**	−.024	.574	1.854 (*1.423*)	.371	.699	.855
6	**.629**	.116	.469	1.854 (*1.349*)	.371	.627	.861
7	**.687**	.003	.475	1.938 (*1.362*)	.388	.640	.860
8	**.569**	.083	.370	2.938 (*1.229*)	.588	.575	.865
9	**.548**	.137	.379	2.781 (*1.295*)	.556	.579	.865
10	**.499**	.317	.478	2.09 (*1.508*)	.418	.595	.864
11	.082	**.634**	.451	.882 (*1.31*)	.176	.547	.739
12	.120	**.523**	.339	1.219 (*1.413*)	.244	.523	.744
13	−.028	**.479**	.219	.963 (*1.362*)	.193	.426	.767
14	.097	**.660**	.497	1.076 (*1.464*)	.215	.590	.726
15	.099	**.504**	.304	1.938 (*1.591*)	.388	.477	.759
16	−.131	**.759**	.513	.669 (*1.257*)	.134	.6	.728
Eigenvalues	4.15	2.53					
% Of variance explained	26	16					
Cronbach's α	.88	.78					

Note. Rotated factor solutions are displayed; loadings above .40 are written in bold letters.
[a]int. CB = Continuing Bonds Scale, internalized subscale;
[b]ext. CB = Continuing Bonds Scale, externalized subscale.

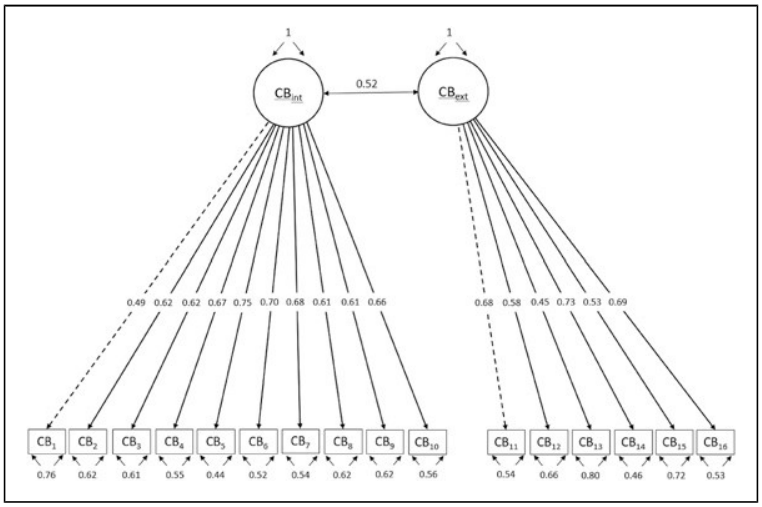

Figure 2. Standardized Factor Solutions from the Confirmatory Factor Analysis.

expected, there was no significant association of death type with int. CB ($F(1,337) = .01$; $p = .93$), but a sig. association with ext. CB ($F(1,336) = 6.29$; $p = .01$; $\eta^2 = .02$), showing that participants who lost someone due to a violent death showed significantly higher ext. CB scores than participants who lost someone due to a non-violent death.

Relationship to the Deceased. To assess the association between the relationship to the deceased and int. versus ext. CB, we conducted two ANCOVAs with the relationship as independent and the CB subscales as dependent variables. Age and time since death were included as covariates (time since death only for ext. CB). The results yielded no significant overall associations with the int. CB subscale ($F(6,348) = .86$; $p = .52$; partial $\eta^2 = .03$) and no significant overall associations with the ext. CB subscale ($F(6,347) = 1.96$; $p = .07$; partial $\eta^2 = .001$). Furthermore, linear contrasts were significant (estimated mean difference = - 3.7; $p = .003$), showing that the ext. CB scores were higher the closer the relationship to the deceased person was.

Feeling Responsible for the Death and CB. As expected, feeling responsible for the death had no significant association with int. CB ($F(1,314) = 1.72$; $p = .19$, partial $\eta^2 = .005$), but a significant overall association with ext. CB ($F(1,317) = 4.27$; $p = .04$; partial $\eta^2 = .03$). People who felt responsible for the death, showed significantly higher CB scores ($M = 7.94$; $SD = .71$) than those who did not feel responsible ($M = 6.3$; $SD = .36$).

Attachment Style and CB (Anxious Attachment Subscale). Partial correlations indicated, that externalized CB did neither correlate with attachment-related anxiety (ECR subscale) ($r_p(302) = .06$; $p = .29$), nor with attachment-related avoidance ($r_p(303) = - .02$; $p = .71$), while controlling for age and time since death. However, both subscales correlate significantly positively with complicated grief (.13 and .17).

Table 3. Means and Standard Deviations of the Main Outcomes of Interest.

	Int. CB	Ext. CB[b]
	M[a] (*SD*)	M[c] (*SD*)
Type of death		
Violent	22.13 (*9.01*)	7.71 (*5.45*)
Non-violent	22.27 (*9.5*)	5.93 (*5.59*)
Relationship to the deceased		
Child	21.46 (*9.62*)	7.72 (*6.21*)
Spouse/partner	22.68 (*9.74*)	7.77 (*6*)
Sibling	22.36 (*8.16*)	6.49 (*4.87*)
Parent	23.4 (*9.13*)	5.89 (*5.65*)
Unborn child	16.5 (*7.33*)	4.25 (*4.79*)
Close friend	21.82 (*10.29*	4.09 (*3.76*)
Something else	21.57 (*10.29*)	3.83 (*4.17*)
CB total	22.23 (*9.37*)	6.72 (*5.78*)
	M (SD)[d]	
ICG[e]-D	22.23 (*9.37*)	
PTPG[f] total	53.61 (*19.87*)	
PTPG appreciation of life	9.82 (*3.67*)	
PTPG new possibilities	12.31 (*5.73*)	
PTPG relationships with others	16.58 (*6.32*)	
PTPG personal strength	10.99 (*4.82*)	
PTPG spiritual change	3.96 (*3.38*)	

Note. This table presents means and standard deviations of int. CB, ext. CB, depending on type of death and relationship to the deceased, as well as means and standard deviations of the validity measures;
[a]int. CB = Continuing Bonds Scale, internalized subscale;
[b]ext. CB = Continuing Bonds Scale, externalized subscale;
[c]M = mean;
[d]SD = standard deviation;
[e]ICG-D = Inventory of Complicated Grief - German version;
[f]PTPG = Posttraumatic Personal Growth Inventory.

Feeling at Peace With the Loss and CB. To examine the association between feelings at peace with the loss and ext. versus int. CB, we conducted an ANOVA with Age and time since death as covariates (time since death only for ext. CB). There was no significant association between feeling at peace and ext. CB ($F(1,274) = .34$; $p = .56$, partial $\eta^2 = .001$) and no significant association between feeling at peace and int. CB ($F(1,273) = 3.03$; $p = .083$; partial $\eta^2 = .011$). People who found peace in the loss showed higher int. CB scores than people who did not find peace.

Associations Between CB and Complicated Grief. Because men and women differed in their level of complicated grief symptoms, we conducted partial correlations for men and women separately, with age (and time since death for the ext. Subscale) as control

Table 4. Means, Standard Deviations, and Correlations of the Variables of Interest With Confidence Intervals.

Variable	*M*	*SD*	1	2	3	4	5	6	7	8	9	10	11
1. ECR Anxiety	11.36	6.30											
2. ECR Avoidance	11.20	6.36	.25** [.14, .35]										
3. ICG	32.12	13.64	.13* [.02, .24]	.17** [.06, .27]									
4. CB Internalized	22.23	9.37	.17** [.06, .27]	−.00 [−.12, .11]	.37** [.27, .45]								
5. CB externalized	6.72	5.78	.05 [−.07, .16]	−.01 [−.12, .10]	.34** [.25, .43]	.43** [.34, .51]							
6. CB total	28.97	12.98	.14* [.03, .25]	−.01 [−.12, .10]	.42** [.33, .50]	.92** [.90, .93]	.76** [.71, .80]						
7. PTPG appreciation of life	9.82	3.67	−.05 [−.16, .06]	−.08 [−.19, .03]	−.14* [−.24, −.03]	.07 [−.04, .17]	.06 [−.05, .17]	.07 [−.04, .18]					
8. PTPG new possibilities	12.31	5.73	−.04 [−.15, .07]	−.10 [−.21, .01]	−.20** [−.31, −.10]	.10 [-.01, .20]	.15** [.04, .25]	.14* [.03, .24]	.72** [.67, .77]				
9. PTPG relationship with others	16.58	6.32	−.06 [−.17, .05]	−.27** [−.37, −.16]	−.06 [−.17, .05]	.19** [.08, .29]	.16** [.06, .27]	.21** [.10, .31]	.62** [.55, .68]	.66** [.60, .72]			
10. PTPG personal strength	10.99	4.82	-.06 [-.17, .06]	-.17** [-.27, −.06]	-.21** [−.31, −.10]	.12* [.01, .22]	.16** [.05, .27]	.15** [.05, .26]	.70** [.64, .75]	.79** [.74, .82]	.63** [.55, .69]		
11. PTPG spiritual change	3.96	3.38	.04 [−.07, .15]	−.07 [−.18, .04]	−.03 [−.14, .08]	.21** [.11, .31]	.24** [.13, .34]	.26** [.15, .36]	.38** [.28, .47]	.41** [.32, .50]	.45** [.36, .53]	.44** [.35, .52]	
12. PTPG total	53.61	19.87	-.05 [−.16, .07]	−.18** [−.29, −.07]	−.16** [−.26, −.05]	.16** [.06, .27]	.19** [.08, .29]	.20** [.09, .31]	.83** [.79, .86]	.90** [.87, .92]	.85** [.82, .88]	.88** [.85, .90]	.61** [.54, .68]

Note. *M* and *SD* are used to represent mean and standard deviation, respectively. Values in square brackets indicate the 95% confidence interval for each correlation. The confidence interval is a plausible range of population correlations that could have caused the sample correlation (Cumming, 2014). * indicates $p < .05$. ** indicates $p < .01$.

variables. Partial correlations between CG symptoms and ext. CB were highly significant ($r_p(317) = .35$; $p < .001$) in women, but not significant in men ($r_p(32) = .31$; $p = .08$). Partial correlations between CG symptoms and int. CB were highly significant for both women ($r_p(317) = .32$; $p < .001$) and men ($r_p(317) = .58$; $p < .001$).

Associations Between CB and Posttraumatic Personal Growth. Partial correlation analyses between internalized CB and posttraumatic personal growth subscales indicated significant small to medium correlations between CB and almost all of the PTPG subscales ("Relationships with others": r_p (311) = .19; $p = .001$; "Personal strength": r_p (313) = .13; $p = .02$; Spiritual change": $r_p = .23, p < .001$). Int. CB did not correlate significantly with the New possibilities" subscale (r_p (313) = .1; $p = .08$), and not significantly with the "Appreciation of life" subscale ($r_p(313) = .07$; $p = .24$). The overall PTPG scale correlation with int. CB was small but significant (r_p (314) = .17; $p = .002$). Partial Correlations analyses between externalized CB and posttraumatic personal growth subscales indicated small to medium correlations ("Relationships with others": r_p (313) = .16; $p = .004$; "Personal strength": $r_p(315) = .15$; $p = .01$; "Spiritual change": r_p (315)= .22, $p < .001$, "New Possibilities": r_p (315) = .114; $p = .01$). Ext. CB did not correlate significantly with the "Appreciation of life" subscale (r_p (315) = .06; $p = .28$). The overall PTPG scale correlation with ext. CB was small but significant (r_p (313) = .18; $p = .001$).

Discussion

This study examined the validity of the German version of the two-factor CB Scale. Our validation study provides empirical evidence for a two-factor solution with 16 items. Hence, the CBS-G is a reliable instrument to measure internalized ongoing bond to the deceased and externalized components indicating aspects of unresolved loss. The CBS-G is time-saving and easily applicable in research and practice.

Based on the exploratory factor analysis suggesting a two-factorial solution as in the original English version, we tested the two-factorial solution by a confirmatory analysis, which yielded just barely satisfactory model fits. A single-factor solution did not yield significantly better fit indices either. Although a three-factor solution turns out statistically better than a two-factor solution according to the model fits, a two-factor solution makes much more sense for substantive reasons. We tested the distinction between the two subscales respectively and were able to present mostly sound evidence in support of it. Overall, the ability to internalize and stay connected to the deceased may be an adequate means to deal the experience of loss but could also manifest in more unfavorable ways.

Violent death, the closeness to the deceased and feeling responsible for the death may represent risk factors for an unfavorable trajectory toward complicated grief, so we tested the associations with ext. and int. CB: As expected, those had significantly higher ext. CB scores if they had lost someone violently, the closer they were to the deceased, and if they felt responsible for the death, which was not the case for int. CB, as hypothesized. On the one hand, this suggests the importance of these factors as risk- or,

conversely, protective factors; on the other hand, it implies that unfavorable ext. CB processing is more likely while confronted with these unfavorable factors.

In contrast, higher int. CB expressions were found if bereaved individuals were able to make peace with the loss, although we were unable to uncover any significant correlations in this respect. Nevertheless, the peace-making dimension can be understood as a resource for the further mourning process, which is reflected, for instance, in the fact that the bereaved tend to have internalized a secure bond to the deceased.

Although the previous literature produced heterogeneous results, we expected to find a high correlation between ext. CB and the insecure-anxious attachment style. We assumed that the ability to internalize a secure attachment bond to the deceased should be rather impaired in the case of high levels of insecure-anxious attachment. However, contrary to prediction, we could not find any correlations between ext. CB with attachment style - neither with the anxiety nor the avoidance component. This could be due to several reasons, but we were not able to examine them within the scope of this study. Yet, our results here are consistent with those of the English validation study. One possible explanation could be that ext. CB, in terms of the difficulty of adequately integrating the experience of loss, does not express loss or separation per se, but rather the traumatic dimension of death. However, due in part to the majority of individuals in our sample who did not experience violent death, we cannot confirm this interpretation with our data. However, we were able to show a significant and positive correlation with complicated grief for both dimensions of attachment style. It is therefore reasonable to assume that attachment style plays an important role in the coping with a loss experience. Still, it remains to be clarified to what extent in under which circumstances the ability to maintain an inner bond with the deceased prevents the development towards pathology.

Interestingly, just about a third of the participants had lost a child – which is one of the most severe experiences of loss (d'Epinay et al., 2010), followed by a lost parent and finally a deceased partner in our sample. Why it was particularly individuals with the loss experience of a child who came forward in this difficult-to-recruit sample remains speculative. Although child-parent relations are particularly strong, it is still important to assess their relationship quality, as it may play a crucial role in how grief is experienced. On the one hand, low relationship quality may serve as a protective factor, while on the other hand, high relationship quality may be a risk factor for developing a maladaptive grief response.

We found that women differed significantly from the few men in our sample, in the additional burden of self-reported symptoms of complicated grief. There are already some studies that suggest gender differences in coping with loss experiences. For example, widows tend to have higher mean levels of traumatic grief, depressive and anxiety symptoms than widowers (Chen et al., 1999). When analyzing changes in prolonged grief symptoms across time, men seem to express prolonged grief as an acute, decreasing reaction, whereas women show an adjourned, mounting grief reaction (Lundorff et al., 2020). Furthermore, according to a recent meta-analysis, grieving adolescent girls tend to show higher levels of internalized grief responses and higher

levels of PTSD symptoms than grieving boys (Shulla & Toomey, 2018). In general, differences between men and women in grief processing could also be mediated by psychobiological, historical, social, and cultural variables. Complex emotions such as guilt and shame vary between gender, probably due to traditional cultural roles of masculinity or femininity (De Boeck et al., 2018) and might also influence mourning behavior.

It is important to note that the concept of grief is perceived, processed and communicated differently depending on the culture we live in. For example, this can be seen in post-colonial African-American history, where grief and grief processing are described in much more melancholic terms similar to CB. Integrating cultural differences into research on grief and adapting self-report measures of grief to respective cultural habits provides a valuable expansion of our understanding of grief (see also Killikelly et al., 2020; Stelzer et al., 2020).

We found highly correlated ext. CB and CG symptoms only in women, but for women and men, comparatively strong associations between int. CB and CG symptoms. In the original validation study by Field and Filanosky, perceived closeness substantially contributed to these associations, and this may also differ between sexes (Field & Filanosky, 2009). In the future, especially longitudinal research should examine the direction and trajectory of grief, taking into account the degree of int. versus ext. CB. Additionally, to test measurement invariance in terms of gender and age will be important to verify in future studies.

Moreover, personal growth resulting from successfully overcoming the challenges associated with the loss can be understood as a resource. This therefore includes not only coping with everyday life and tasks, but also the reorientation of one's own goal horizons and in relation to self-integrity. Surprisingly, we found not only significant, albeit partly small, correlations with int. CB, but also with ext. CB. Thus, we assume that both a more favorable integration of the loss is comparatively positively related to personal growth and a failed coping with the loss related to ext. CB. Differences in CB subscales do not necessarily translate into differences in everyday coping. There was no significant and positive association with the subscales of posttraumatic personal growth, reorientation or appreciation of life in either case. From these results we could conclude, that the ability to integrate the loss better or worse may be related to further variables that were not investigated in our study. For example, it is not captured in int. and ext. CB whether the affected person perceives the respective coping strategy positively or negatively in terms of relieving. Also, it could be that those who show highly ext. CB behaviors, etc., might have benefited from the severe adjustment period, especially if the death occurred a while ago. So, a temporal component could be important here and indicate to what extent one can personally grow from the event with increasing distance from the loss.

Overall, to establish a continuing bond towards a deceased close person seems to be an effective coping strategy. The differentiation of the various forms of CB could also make sense with regard to a temporal and developmental perspective: the immediate death of a close relative is usually difficult to comprehend and is sometimes

accompanied by experiences comparable to shock reactions. An initial repression, which for example manifests itself in ext. CB. could, with a certain temporal distance to the loss, transform into int. CB. It would be predictively interesting to investigate to what extent the failure of the transition into an internal representation of the attachment figure is an expression of a lack of grief integration and leads to further unfavorable developments.

Limitations

Our study has some limitations that are important to state. Its cross-sectional design does not allow interpretation of causality. Strong feelings of grief may lead to more intense CB, or vice versa. Against this background, it was also not possible to perform meditation analyses to shed light on mediating factors.

Our sample cannot be considered representative, as the majority of the mourners were female. This probably expresses a higher interest or also a higher willingness of female bereaved persons to consciously and proactively deal with these experiences. The sample showed some more important aspects worth mentioning: Overall, the majority of the sample was less burdened in relation to ext. CB, while also the values of self-reported symptoms of complicated grief as well as post-traumatic growth were in the medium range. Therefore, we did not base our analyses on an extremely burdened sample. This range restriction makes the sample less representative and may lead to less robust/more biased results.

This could be related, among other things, to the fact that for a quarter of the sample the time of death was between five and 10 years ago, and for another quarter it was as long as 20 years ago. Just about a third lost their relative due to an acute illness, followed by accidents and finally chronic illnesses. More than a half, consequently, did not lose the relative due to a violent cause, and the majority did not feel responsible for the death.

A last additional factor that remains open, but is nevertheless of considerable importance, is the qualitative experiential side of CB: Whoever loses someone by death may also get relief by expressing himself via ext. CB – in terms of avoiding the confrontation with the loss itself. However, how ext. and int. CB are predictive for the further course of an integration of the loss experience can only be clarified in a longitudinal design under consideration of further influencing factors but focusing on the emotional dimension. The differential predictive nature of the two subscales therefore needs further investigation.

Implications/Strength

This is the first study that measures different types of ongoing attachment towards the deceased – ext. and int. CB – in a German population, using a newly translated questionnaire. The validation of the German CBS gives us the opportunity to use this self-report instrument in future research on predictors for both positive and negative

grief-related mental health outcomes. With this investigation, we were able to extract both structural and relationship-related characteristics influencing the ongoing attachment to the deceased. Furthermore, as potential differences between ext. and int. CB in predicting posttraumatic growth as well as complicated grief symptoms could not be clearly extracted within our data, future investigations should examine potential personality-related, cultural social and historical factors influencing or moderating the ongoing attachment to the deceased loved one.

Regardless, intuitively, most people process the death of a near and dear one through a perpetuation of the internalized relational experience. The different configuration – in terms of int. and ext. CB – can thereby be more or less conducive to the development of complicated grief or other health-related strains. The use of this questionnaire could provide insights into the quality of grief processing in the bereaved and help to predict unresolved loss such as complicated grief. This may help to initiate early counseling when needed and, thereby, prevent prolonged burden.

APPENDIX A

Continuing Bonds Scale German

Male Version

1. Ich habe über den positiven Einfluss des Verstorbenen auf meine heutige Person nachgedacht.
2. Ich war mir dessen bewusst, dass ich versuche mein Leben auf die Art zu leben, wie es der Verstorbene gewollt hätte.
3. Ich habe den Verstorbenen als Vorbild wahrgenommen, und möchte so sein wie er.
4. Ich habe mir vorgestellt, wie der Verstorbene mich leitet oder über mich wacht als ob sie unsichtbar aber anwesend wäre.
5. Wenn ich wichtige Entscheidungen treffen musste, habe ich überlegt, was der Verstorbene vielleicht gemacht hätte, und das als Hilfe für meine eigene Entscheidungsfindung genutzt.
6. Ich war mir dessen bewusst, dass ich versuche die Wünsche des Verstorbenen zu erfüllen.
7. Ich erlebte, wie der Verstorbene durch seinen Einfluss auf meine heutige Person weiterlebt.
8. Ich habe darüber nachgedacht, wie der Verstorbene etwas, das ich selbst gesehen oder gemacht habe, genossen hätte.
9. Ich habe mir vorgestellt, wie ich etwas Besonderes mit dem Verstorbenen teile, das mir passiert ist.
10. Ich habe mir vorgestellt, wie mich die Stimme des Verstorbenen ermuntert, durchzuhalten.
11. Ich habe tatsächlich gehört, wie die Stimme des Verstorbenen zu mir spricht.
12. Ich habe kurzzeitig gehandelt, als würde der Verstorbene noch leben – ich habe zum Beispiel seinen Namen gerufen, oder den Tisch für zwei gedeckt.

13. Ich habe andere Menschen mit dem Verstorbenen verwechselt, auch wenn nur für einen kurzen Moment
14. Ich habe die körperliche Berührung des Verstorbenen tatsächlich gespürt.
15. Ich habe mir vorgestellt, der Verstorbene könnte plötzlich erscheinen, als sei er noch am Leben.
16. Ich habe den Verstorbenen tatsächlich vor mir stehen sehen.

Items 1–10: internalized Continuing Bonds (CB int)
Items11–16: externalized Continuing Bonds (CB ext)

Scale goes from from 0 (“trifft überhaupt nicht zu”) to 4 (“trifft voll und ganz zu”) with respect to the last month

Female Version

1. Ich habe über den positiven Einfluss der Verstorbenen auf meine heutige Person nachgedacht.
2. Ich war mir dessen bewusst, dass ich versuche mein Leben auf die Art zu leben, wie es der Verstorbene gewollt hätte.
3. Ich habe den Verstorbenen als Vorbild wahrgenommen, und möchte so sein wie sie.
4. Ich habe mir vorgestellt, wie die Verstorbene mich leitet oder über mich wacht als ob sie unsichtbar aber anwesend wäre.
5. Wenn ich wichtige Entscheidungen treffen musste, habe ich überlegt, was die Verstorbene vielleicht gemacht hätte, und das als Hilfe für meine eigene Entscheidungsfindung genutzt.
6. Ich war mir dessen bewusst, dass ich versuche die Wünsche der Verstorbenen zu erfüllen.
7. Ich erlebte, wie die Verstorbene durch ihren Einfluss auf meine heutige Person weiterlebt.
8. Ich habe darüber nachgedacht, wie die Verstorbene etwas, das ich selbst gesehen oder gemacht habe, genossen hätte
9. Ich habe mir vorgestellt, wie ich etwas Besonderes mit der Verstorbenen teile, das mir passiert ist
10. Ich habe mir vorgestellt, wie mich die Stimme der Verstorbenen ermuntert, durchzuhalten.
11. Ich habe tatsächlich gehört, wie die Stimme der Verstorbenen zu mir spricht
12. Ich habe kurzzeitig gehandelt, als würde die Verstorbene noch leben – ich habe zum Beispiel seinen Namen gerufen, oder den Tisch für zwei gedeckt.
13. Ich habe andere Menschen mit der Verstorbenen verwechselt, auch wenn nur für einen kurzen Moment.
14. Ich habe die körperliche Berührung der Verstorbenen tatsächlich gespürt.
15. Ich habe mir vorgestellt, die Verstorbene könnte plötzlich erscheinen, als sei er noch am Leben.
16. Ich habe die Verstorbene tatsächlich vor mir stehen sehen.

Items 1–10: Internalized Continuing Bonds (CB int).
Items 11–16: Externalized Continuing Bonds (CB ext).
Scale goes from from 0 (“trifft überhaupt nicht zu”) to 4 (“trifft voll und ganz zu”) with respect to the last month.

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Curriculum vitae

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EDUCATION

Since 2019 **Ph.D. Program in Psychology**
Faculty of Behavioral and Cultural Studies, Heidelberg University, Germany
Mentor: Beate Ditzen, Ph.D.

2018 **M.Sc. in Clinical Psychology, Neuroscience and Rehabilitation Science**
University of Freiburg, Germany
Final Grade: 1.3

2016 **B.Sc. in Psychology**
University of Mannheim, Germany
Final Grade: 1.5

2012 **General University Entrance Qualification (Abitur)**
Karl-Friedrich-Gymnasium, Mannheim, Germany
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EMPLOYMENT AND INTERNSHIP HISTORY

Since 2019 **Research Associate**
Institute of Medical Psychology, University Hospital Heidelberg, Germany

2017-2018 **Research Assistant**
Clinic for Palliative Medicine, University Hospital Freiburg, Germany

2017 **Research and Clinical Internship**
Department of Biological and Differential Psychology, University of Freiburg, Germany

2016 **Research Internship**
Institute of Medical Psychology, University Hospital Heidelberg, Germany

2015 **Clinical Internship**
Child and Adolescent Psychiatry, Zentralinstitut für Seelische Gesundheit (ZI), Mannheim, Germany

2014 **Research Internship**
Institute Cognitive and Clinical Neuroscience, Zentralinstitut für Seelische Gesundheit (ZI), Mannheim, Germany

RESEARCH GRANTS AND SCHOLARSHIPS

2022 **Research Grant by Medical Faculty of Heidelberg University**
Funding of a research associate within the project: „Long-term effects of a dignity-based therapy for couples on the development of complicated grief“

2022 **Travel Grant by Dr. Walter and Luise Freundlich Foundation**
Conference Travel Grant to give a talk within the 52nd Congress of Deutsche Gesellschaft für Psychologie (DGPs), Hildesheim, Germany

2020	**Corona Research Grant by Deutsche Gesellschaft für Psychologie (DGPs)** Funding of a research assistant within the project „social isolation and psychobiological burden during Covid-19 pandemic“
2019-2020	**Ph.D. Scholarship by FAZIT-Stiftung** Two-year scholarship to pursue the doctoral degree
2019	**Research Grant by Medical Faculty of Heidelberg University** Funding of hormone analyses within the project: „Neuroendocrine mechanisms of grief: design and evaluation of a couple intervention at the end of life“
2019	**Travel Grant by FAZIT-Stiftung** Conference Travel Grant to give a talk within the „Social Neuroscience of Grief International Network Conference”, Tucson (AZ), USA

TEACHING

2022	Seminar for medical students, „Psychotherapy “, module „Medical Psychology and Sociology“
2021	Seminar for medical students, „Psychotherapy “, module „Medical Psychology and Sociology“
2021	Seminar for medical students, „Theories on Stress and Learning “, module „Medical Psychology and Sociology“

JOURNAL ARTICLES

Schneider, E., **Hopf, D.**, Eckstein, M., Scheele, D., Aguilar-Raab, C., Herpertz, S. C., Grinevich, V., & Ditzen, B. (submitted). Stress during the COVID-19 Pandemic moderates Pain Perception and Momentary Oxytocin Levels. *J Clin Med*

Schneider, E., **Hopf, D.**, Aguilar-Raab, C., Scheele, D., Neubauer, A.B., Sailer, U., Hurlemann, R., Eckstein, M., & Ditzen, B. (under review). Affectionate touch and diurnal oxytocin levels: An ecological momentary assessment study. *eLife*

Hopf, D., Schneider, E., Aguilar-Raab, C., Scheele, D., Morr, M., Klein, T., Ditzen, B., & Eckstein, M. (2022). Loneliness and diurnal cortisol levels during COVID-19 lockdown: the roles of living situation, relationship status and relationship quality. *Sci Rep 12*, 15076. https://doi.org/10.1038/s41598-022-19224-2

Hopf, D, Eckstein, M, Ditzen, B, & Aguilar-Raab C. (2022). Still With Me? Assessing the Persisting Relationship to a Deceased Loved-One - Validation of the “Continuing Bonds Scale” in a German Population. *OMEGA - Journal of Death and Dying*. https://doi.org/10.1177/00302228221076622

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Mannheim, 1 March 2023

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FAKULTÄT FÜR VERHALTENS- UND EMPIRISCHE KULTURWISSENSCHAFTEN

Promotionsausschuss der Fakultät für Verhaltens- und Empirische Kulturwissenschaften der Ruprecht-Karls-Universität Heidelberg / Doctoral Committee of the Faculty of Behavioural and Cultural Studies of Heidelberg University

Erklärung gemäß § 8 (1) c) der Promotionsordnung der Universität Heidelberg für die Fakultät für Verhaltens- und Empirische Kulturwissenschaften / Declaration in accordance to § 8 (1) c) of the doctoral degree regulation of Heidelberg University, Faculty of Behavioural and Cultural Studies

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Ich erkläre, dass ich die vorgelegte Dissertation in dieser oder einer anderen Form nicht anderweitig als Prüfungsarbeit verwendet oder einer anderen Fakultät als Dissertation vorgelegt habe. / I declare that I did not use the submitted dissertation in this or any other form as an examination paper until now and that I did not submit it in another faculty.

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Unterschrift / Signature	Dem Dekanat der Fakultät für Verhaltens- und Empirische Kulturwissenschaften liegt eine unterschriebene Version dieser Erklärung vom 08.03.2023 vor.