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Thema:

The association of basal serum cortisol and alexithymia in the general population

Inaugural – Dissertation
zur
Erlangung des akademischen
Grades
Doktor der Wissenschaften in der Medizin
(Dr. rer. med.)

der
Universitätsmedizin
der
Universität Greifswald

2022

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in: Bad Gandersheim

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Tag der Disputation: 27.02.2023

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List of abbreviations

ACTH	adrenocorticotropic hormone
ANS	autonomic nervous system
ATC	Anatomical Therapeutic Chemical
BDI-II	Beck Depression Inventory- II
BMI	body mass index
BPD	borderline personality disorder
CAR	cortisol awakening response
CI	confidence interval
CNS	central nervous system
CRH	Corticotropin-releasing hormone
DDF	difficulty describing feelings
DIF	difficulty identifying feelings
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMG	electromyography
EOT	externally oriented thinking
HCC	hair cortisol concentrations
HPA	hypothalamic-pituitary-adrenal
LC-NA	locus coeruleus-noradrenergic
M	mean
OCD	obsessive compulsive disorder
OCs	oral contraceptives
PHQ-9	Patient Health Questionnaire
PSNS	parasympathetic nervous system
PTSD	posttraumatic stress disorder
SD	standard deviation
SHIP	Study of Health in Pomerania
SNS	sympathetic nervous system
TAS-20	20-Item Toronto Alexithymia Scale
WHR	waist-to-hip ratio
WHtR	waist-to-height-ratio

1. Introduction

1.1. The alexithymia construct

Alexithymia is widely defined as a multifaceted personality construct of relative temporal stability (Grabe et al., 2008) characterized by four interrelated facets: (1) difficulty identifying feelings by one's self or others and distinguishing between the emotional feelings and bodily sensations of emotional arousal, (2) difficulty describing feelings to others, (3) constricted imaginal processes – evidenced by a lack of fantasy, and (4) an externally-oriented cognitive style (Taylor et al., 1999).

The 20-Item-Toronto Alexithymia Scale (TAS-20) – the most frequently and widely used self-report instrument for measuring alexithymia (Bagby et al., 2020) – operationalizes the construct in three factors, each contributing significantly but differentially to the overall measurement of alexithymia: (1) Difficulty identifying feelings (DIF), (2) difficulty describing feelings (DDF) and (3) externally oriented thinking (EOT) (Bagby, Parker, et al., 1994; Bagby, Taylor, et al., 1994).

Alexithymia is normally distributed in the general population. Alexithymic characteristics can be found in approximately 10 to 13 percent of the general population (Franz et al., 2008; Salminen et al., 1999).

Generally, a quarter (Grabe et al., 2008) up to one third (Terock et al., 2015) of all patients seeking psychotherapeutic treatment are considered to be alexithymic, indicating that alexithymia is a possible personality risk factor of relatively high prevalence and clinical importance.

Theoretical and empirical model conceptions linking stress or stress-related disorders and alexithymia are manifold and well-known. Martin and Pihl (1985) proposed the stress-alexithymia hypothesis already almost 40 years ago, stating that alexithymic characteristics lead to an enhanced and prolonged physiological reaction to emotionally stressful situations while the perception and description of emotions in these situations is limited. Consequently, as the capacity to adapt or to counteract stressful situations is limited, this may increase the risk for developing stress-related disorders. Martin and Pihl's theory was expanded by the deviant decoupling hypothesis (Papciak et al., 1985), which states a dissociation of physiological responses to stress from an accurate report of feelings and emotional arousal in alexithymic individuals. The terminology of decoupling is inconsistent and empirical findings are heterogeneous.

Martin and Pihl (1986), e.g., found high alexithymic individuals to manifest high levels of sympathetic activity and a dissociation between their subjective and physiological stress responses hinting at a potential contribution of alexithymia to the development of stress-related disorders. However, the stress-alexithymia hypothesis was supported and extended by progressive studies also focusing on underlying physiological and neuroendocrine mechanisms (de Timary et al., 2008; Friedlander et al., 1997; R. Lane et al., 1998; Terock, Van der Auwera, et al., 2019).

Continuously, advances in research, theory and clinical practice of alexithymia are published in thousands of studies each year focusing on expanding fields of inquiry: the refinement of the conceptualization and assessment of the construct, its relation to basic cognitive-affective processes (e.g., emotion regulation, memory, executive functioning, and language), neuroscience, physiology (e.g., genetics, immune and endocrine activity, psychophysiology), body awareness, attachment, empathy, morality, social behavior, culture as well as psychological and somatic disorders, treatment approaches and therapeutic outcomes (Luminet et al., 2018).

Alexithymic personality characteristics might influence physical and mental health via several pathways, inter alia leading to alterations in endocrine, immune, and autonomic nervous stress reactions: There is evidence of a reduced ability of the brain to adapt to acute and chronic stress, possibly due to a certain genetic and immunologic architecture (Guilbaud et al., 2006; Kano et al., 2018; Reed & Raison, 2016) or due to interoceptive deficits or disturbances in the multi-sensory integration between interoceptive and exteroceptive channels (Pollatos & Herbert, 2018).

1.2. The human stress response

Stress can be defined as a state of threatened homeostasis which is triggered by intrinsic or extrinsic adverse forces and counteracted by various interconnected physiological and behavioral short- and long-term responses. The adaptation process activates the organism's stress system, a highly interconnected neuroendocrine, cellular, and molecular infrastructure aiming to maintain or to reestablish the optimal body equilibrium (Chrousos, 2009; Pinel et al., 2019). Hence, stress can also be defined as a state of difficulty in maintaining allostasis (Boucher & Plusquellec, 2019). Key components of a stress response are the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic or vegetative nervous system (ANS) acting largely unconsciously and

regulating bodily functions, such as heart rate, digestion, respiratory rate, pupillary response, urination, and sexual arousal. The ANS is mediated by the antagonistic and synergistic interplay of the sympathetic and the parasympathetic nervous system (SNS and PSNS).

ANS and HPA axis in turn interact with other vital centers in the central nervous system (CNS) as well as tissues and organs in the peripheral nervous system to mobilize an adaptive response to the stressor. Dysregulation of the stress system, i.e., a hyper- or hypo-activation in association with pronounced or chronic stress, can strongly disrupt the body's homeostasis, leading to diverse clinical manifestations (Chrousos, 2009; Pinel et al., 2019).

Internal or external stress exposure or its perception leads to the activation of both the SNS and the HPA axis. Corticotropin-releasing hormone (CRH) is released from the hypothalamus. CRH activates the posterior pituitary gland to secrete adrenocorticotropic hormone (ACTH) and arginine vasopressin. Additionally, CRH stimulates the locus coeruleus-noradrenergic system (LC-NA system) synthesizing catecholamines (epinephrine, norepinephrine/noradrenaline) primarily leading to the organism's acute "fight or flight" short-term stress response of the SNS. Concurrently, as a long-term stress response, ACTH affects the production of mineralocorticoids and glucocorticoids such as cortisol in the adrenal cortex. Cortisol as a pleiotropic modulator of cellular activity is an important player for the organism's immediate survival and homeostasis, enabling it to adjust to new situations and to show an adequate behavioral response. It is accompanied by short-term catabolic actions, e.g., mobilizing glucose from energy stores or raising cardiovascular activity and immunosuppressive actions.

The fluctuating production and release of CRH and ACTH underlies a circadian rhythm and is inhibited via negative feedback loops depending on the level of blood cortisol, which ensures a limitation of long-term stress responses. Additionally, the return to homeostasis after an acute stress response is controlled by the PSNS activating the release of acetylcholine. Nonetheless, chronic or repeated stress exposure can lead to an HPA-axis dysregulation, disrupting an appropriate cortisol secretion and affecting diverse end-organ functions (e.g., Pinel et al., 2019).

Chronic stress can increase or decrease the activity of the HPA axis depending on the examined sample or disease profile and the study design (Chrousos, 2009; Chrousos

& Gold, 1992): An increase of HPA-axis activity was, e.g., associated with melancholic depressive disorders (P. Gold et al., 2015), anorexia nervosa (Misra & Klibanski, 2010), obsessive compulsive disorder (OCD) (Insel et al., 1982), panic disorder (P. W. Gold et al., 1988), chronic active alcoholism (Wand & Dobs, 1991), diabetes mellitus (Roy et al., 1993), sexual abuse in children (De Bellis et al., 1994). A decrease in HPA-axis activity was associated with atypical/seasonal depression (Joseph-Vanderpool et al., 1991), chronic fatigue syndrome (Demitrack et al., 1991), fibromyalgia (Griep et al., 1993), premenstrual tension syndrome (Hou et al., 2019; Rabin et al., 1990), depressive disorder during the menopause or postpartum period (de Rezende et al., 2016), rheumatoid arthritis (Chikanza et al., 1992), and bronchial asthma (Chrousos & Gold, 1992; S. J. Lane et al., 1996).

Occasionally, results are also conflicting, e.g., childhood trauma has been associated with both hyper- and hypoactivity of the HPA axis (Danese & McEwen, 2012; De Bellis & Zisk, 2014; Heim et al., 2008). The same applies to adult posttraumatic stress disorder (PTSD) (de Kloet et al., 2006; Parker et al., 2003; Wingenfeld et al., 2010; Yehuda, 2002).

Physiological stress responses or HPA-axis activity can be triggered by emotional experiences, e.g., of grief, excitement, fear, anxiety, guilt, or embarrassment, as well as by mental processes set in motion, e.g., during public speaking, performance evaluations or clinical interviews. The extent of the stress response and its recovery is more dependent on the individual's valuation of the stressor than the quality of the stressor itself. The level of the HPA-axis response to a mental or emotional stressor is primarily determined by the following factors: the stressor's novelty and unpredictability, the threat to oneself or the ego, and a sense of loss of control (Boucher & Plusquellec, 2019; Marin et al., 2010; McEwen & Wingfield, 2003).

1.3. Stress and the immune system

Short- and long-term stress responses respectively adaptive responses are the result of an interplay of the endocrine and the immune system with the autonomic nervous system. Through the major pathways of the SNS, the PSNS and the HPA axis, the immune system is modulated by stress: Acute and chronic stress can down-regulate the cellular immune response while activating anti-inflammatory agents of the immune system, for instance cortisol.

The SNS releases catecholamines, increasing the production of circulating pro-inflammatory mediators enhancing inflammation. In the PNS, the cholinergic anti-inflammatory pathway in turn down-regulates the production of proinflammatory cytokines. Vagal, i.e., parasympathetic withdrawal in response to stress may promote inflammation. Cortisol reduces the number and activity of circulating inflammatory cells and inhibits the production of pro-inflammatory mediators suppressing the immune system.

The HPA axis also generates negative feedback, suppressing the immune response when it is no longer necessary. As acute stress may have an effect of immune enhancement by activating these stress response systems, chronic stress conditions, i.e., a prolonged activation of the HPA axis and the SNS, can induce glucocorticoid resistance or insufficient glucocorticoid signaling, possibly leading to increased or decreased immune reactions (Elenkov & Chrousos, 1999; Reed & Raison, 2016). The cytokines produced by immune cells provide feedback to the CNS. Within the brain, proinflammatory cytokines decrease the activity of noradrenaline, dopamine, and serotonin, activating physiological and behavioral responses (Irwin & Cole, 2011). Several pro-inflammatory cytokines are associated with the etiology of depression and anxiety disorders (Dowlati et al., 2009; Maes et al., 1998). Genetic polymorphisms and epigenetic modulation may furthermore influence the complex physiological and psychological response systems to acute or chronic stress conditions (Kano et al., 2018).

1.4. Stress-related psychological and physical disorders

The human stress response has evolved to maintain homeostatic processes with regard to an elevated demand for energy substrates under conditions of any kind of stress (Peckett et al., 2011). The HPA axis is the key endocrine response system to acute and chronic bodily and mental stress with cortisol being the primary agent facilitating HPA-axis actions. Cortisol is secreted in a pulsatile pattern with a circadian rhythm. Short-term as well as long-term stress responses are related to elevated cortisol concentrations (Lee et al., 2015). If cortisol levels remain chronically upregulated, however, beneficial effects of this adaptive stress reaction become reversed (Melmed et al., 2015; Russell & Lightman, 2019).

Measurements of baseline and stress response cortisol levels indicate an association of alterations in the HPA-axis activity in patients with various psychiatric disorders including depression, post-traumatic stress disorder, borderline personality disorder (BPD) or OCD – mental conditions which are in turn highly associated with alexithymia and stress (Grabe et al., 2006; Lumley et al., 1996; Muhtz et al., 2009; Rufer et al., 2004).

Major depressive disorder as well as BPD are predominantly associated with higher basal cortisol concentrations combined with a reduced feedback sensitivity of the HPA axis (Wingenfeld & Wolf, 2015). In contrast, findings on the relation of PTSD and HPA-axis activity produced mixed results with a majority of findings also demonstrating reduced baseline cortisol concentrations and increased cortisol responses to acute psychological stress (de Kloet et al., 2006; Parker et al., 2003; Wingenfeld et al., 2010; Yehuda, 2002).

On the one hand, the HPA axis seems to adapt to chronic stress with lowered basal cortisol levels; on the other hand, a stronger cortisol response to acute stress can occur. Childhood trauma is, for example, associated with a persistent sensitization of the neuroendocrine stress responses as well as altered dynamics of the HPA axis, resulting in increased responsiveness to acute stress. Therefore, it is in turn a potent risk factor – particularly in response to additional stress – for developing depression or anxiety disorders in adulthood (Heim et al., 2008; Heim & Nemeroff, 2001).

An experimental study by Flory et al. (2009) suggests distinct neuroendocrine alterations depending on the nature of experience: physical abuse was related to lower basal cortisol levels, whereas physical neglect was associated with higher basal cortisol levels.

Since dysregulation of the HPA system is linked to stress-related psychological and physical disorders, which are in turn highly associated with alexithymia, alterations of these endocrine systems may represent a mechanism for the association of alexithymia with somatic and mental disorders.

Studies investigating the association of alexithymia and the activation of the autonomic nervous system suggest a hypofunction of the HPA axis at baseline or at rest, and a hyperfunction of the HPA axis under stress conditions (Kano et al., 2018).

There is evidence of an altered sympathicotonic psychovegetative arousal in alexithymia operationalized by heart rate (Papciak et al., 1985; Stone & Nielson, 2001;

Wehmer et al., 1995), electrodermal activity (Friedlander et al., 1997; Gündel et al., 2002; Infrasca, 1997; Rabavilas, 1987; Stone & Nielson, 2001) or electromyography (EMG) values (Martin & Pihl, 1986). It should be taken into consideration that the above-mentioned studies examined samples which are probably not representative for the general alexithymic population.

Furthermore, especially with regard to the decoupling hypothesis (Papciak et al., 1985), the quality of the used stimuli or stressors is of great importance: The individual's subjective involvement or interpersonal relevance plays a decisive role regarding psychophysiological responses especially in highly alexithymic people (Ahrens & Deffner, 1986).

Previous studies provided some evidence for altered HPA-axis activity in alexithymic subjects. However, these results are mainly based on small and selective samples and yielded inconsistent results: (Bruni et al., 2006; Finset et al., 2006; Henry et al., 1992; McCaslin et al., 2006; McIntosh et al., 2014; Melin et al., 2017; Pedrosa et al., 2008). In an experimental investigation by Härtwig et al. (2013), the mean cortisol awakening response (CAR) was significantly lower in the alexithymic group. Moreover, the authors found that HPA-axis activity was negatively correlated with age of alexithymic individuals, indicating that lifelong accumulation in alexithymic subjects may result in lasting HPA-axis alterations. Additionally, de Timary et al. (2008), e.g., report higher baseline cortisol levels in male alexithymic individuals when anticipating a social stress test, but not during stress exposure. However, Spitzer et al. (2005) found a generally decreased basal activity of the HPA axis as determined by high norepinephrine/cortisol ratios among men.

Given the inconsistencies in previous findings in alexithymic and psychiatric samples, this work aimed at investigating the relation of alexithymia and its subfactors with basal cortisol levels. No such study is known to have been conducted among a large, representative general-population sample yet.

Based on previous findings demonstrating reduced basal cortisol levels in response to chronic stress, negative associations with alexithymia were expected.

Due to earlier results regarding associations of alexithymia and endocrine alterations, as well as of depression and alexithymia, the specific influencing effect of this common diagnosis was particularly investigated in this study.

Significant associations of alexithymia and cortisol levels could contribute to explain the relationship between alexithymia on the one hand and somatic as well as mental health conditions on the other hand. Adjusting for depression could help to disentangle the putative effects of alexithymia and mental disorders on basal cortisol levels.

1.5. Association of alexithymia with other disorders

Alexithymia accumulates in patients suffering from a variety of, inter alia, stress-related somatic, psychosomatic and psychiatric clinical syndromes and disorders like subclinical atherosclerosis (Grabe et al., 2010), diabetes (Chatzi et al., 2009; Martino, Caputo, Vicario, et al., 2020), hypertension (Grabe et al., 2010; Todarello et al., 1995), inflammatory bowel disease (Martino, Caputo, Schwarz, et al., 2020), metabolic syndrome (Conti et al., 2020; Karukivi et al., 2016), chronic pain disorders (Esin et al., 2017; Lumley et al., 1997), somaticizing disorders (Bach & Bach, 1995), eating disorders (Conti et al., 2020; Nowakowski et al., 2013; Westwood et al., 2017), anxiety disorders (Terock et al., 2015, 2016), depression (Honkalampi et al., 2001; Saarijärvi et al., 2001) or BPD (Loas et al., 2012; New et al., 2012).

Furthermore, strong associations between alexithymia and childhood trauma (Terock et al., 2018; Terock, Hannemann, et al., 2019) as well as PTSD (Frewen et al., 2008; Yehuda et al., 1997) and dissociation (Terock et al., 2016) have repeatedly been found.

General medical outpatients mainly suffering from unexplained somatic symptoms in combination with a mental disorder have more alexithymic traits (difficulties in identifying feelings) only when they additionally have the conviction that emotional problems did not contribute to their physical symptoms (Kooiman et al., 2000). This result hypothesizes a multifactorial interplay between somatic symptoms, psychiatric disorders and alexithymic personality traits.

Alexithymia is more often associated with male gender and advanced age (R. Lane et al., 1998; Mattila et al., 2006; Pasini et al., 1992; Salminen et al., 1999). TAS-26 scores were generally higher in groups of advanced age (Pasini et al., 1992), and Salminen (1999) found a weak but positive correlation between older age and TAS-20 scores. A positive correlation between an increase in age and the prevalence of alexithymia has been demonstrated (Mattila et al., 2006), albeit only weakly in one study (R. Lane et al., 1998).

There was a significant difference in the occurrence of alexithymia in men and women, even when confounders had been adjusted for (Mattila et al., 2006). In a study using the TAS-26, there was no difference between sexes regarding TAS-26 total scores, but women scored higher in one of the subfactors (ability to identify and distinguish between feelings and bodily sensations) (Pasini et al., 1992). Newer studies showed that men scored higher than women in general (R. Lane et al., 1998) or at least in two of the three factors of the TAS-20 scale (DEF, EOT) (Salminen et al., 1999). In addition, other factors that have been shown to be associated with alexithymia include low educational level, low socioeconomic status (R. Lane et al., 1998; Mattila et al., 2006; Pasini et al., 1992; Salminen et al., 1999), physical inactivity and unhealthy nutrition in men (Helmers & Mente, 1999) and a greater body mass index (BMI) (Neumann et al., 2004; Pink et al., 2018), as well as addiction, especially to alcohol and other drugs (Helmers & Mente, 1999; Kauhanen et al., 1992; Morie et al., 2016), but in contrast likely not cigarette smoking or nicotine dependence (Lumley et al., 1994), although data on this are scarce (Kajanoja et al., 2019). This suggests that maladaptive social and behavioral factors could partly explain the association of alexithymia and physical as well as mental disorders.

There was a difference between sexes in basal serum cortisol concentrations, with higher concentrations found in men than in women even after adjusting for sex hormone concentrations (Klinger-König et al., 2021). This difference between sexes could also be shown in hair cortisol concentrations (HCC) (Stalder et al., 2017). In contrast, higher cortisol levels were found in women than in men in healthy adults of older age (Laughlin & Barrett-Connor, 2000). This was also shown over a larger age-range when accounting for morning and evening cortisol levels (Larsson et al., 2009). Despite this, there was some evidence that sex was not associated with baseline cortisol (Liu et al., 2017).

A pronounced elevation of circulating cortisol levels was found in women using oral contraceptives (OCs) (Carr et al., 1979; Hertel et al., 2017), as well as higher levels of free and salivary cortisol and cortisone (Meulenberg et al., 1987).

A positive relation between HCC and increased age was found in correlation-based analyses (Stalder et al., 2017). This extended on previous findings of a mild hypercortisolism in the elderly, presumably due to a reduced feedback sensitivity of the HPA

axis as a result of lifetime stress exposure (Van Cauter et al., 1996). There was a significant association of higher cortisol levels with older age in both genders, especially regarding evening cortisol levels (Larsson et al., 2009).

While the association of cortisol levels and anthropometric measures has been shown in various studies, results are incongruous. In women, salivary morning cortisol levels were negatively associated with abdominal obesity as measured in waist-to-hip ratio (WHR) (Larsson et al., 2009). On the contrary, studies using HCC showed a positive association of cortisol levels and stress-related anthropometrics (BMI, WHR, weight, waist circumference) as well as long-term obesity (Jackson et al., 2017; Stalder et al., 2017).

Taking into consideration the still unclear causalities and interactions in the current state of research, alexithymia can most likely be considered an aspect in a multifactorial etiopathogenesis of numerous physical and mental disorders, at least partially. Whereas prior research focused on exploring associations of alexithymia with somatic illness, substance abuse and PTSD (Emery, 1989; Nemiah et al., 1976), recent investigations focus rather on the examination of potential underlying mechanisms such as emotional and cognitive processing deficits, the etiology and co-morbidity of alexithymia. Additionally, an important focus is set on bio-markers considering brain imaging or physiological measures (Bagby et al., 2020; Friedlander et al., 1997; Luminet et al., 2018; Taylor & Bagby, 2004).

1.6. Hypotheses

Due to earlier results regarding the associations of alexithymia and endocrine alterations and further associations of depression and alexithymia, the following hypotheses were made:

There is (1) a negative association of alexithymia (TAS-20 score) with basal serum cortisol levels and (2) this association differs in dependence of sex and age. (3) Waist-to-height-ratio (WHtR) as a risk indicator could moderate the association between alexithymia and basal cortisol, which are both shown to influence health status. (4) The assumed association of alexithymia and basal cortisol could be mediated by the level of depression (Beck Depression Inventory- II, BDI-II) as well as health behavior and physical health status (i.e., smoking status, alcohol consumption, physical activity, WHtR).

2. Materials and Methods

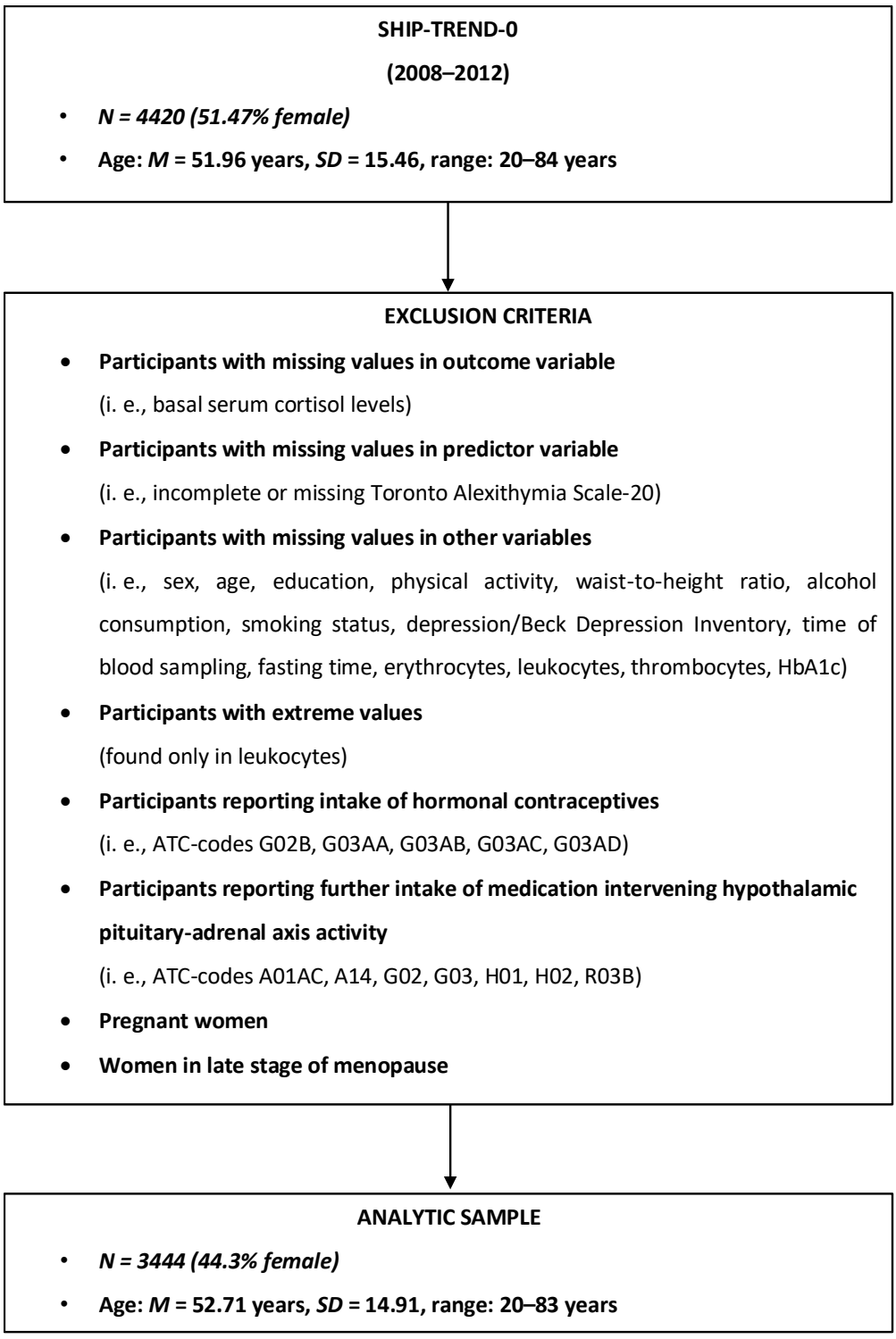
2.1. Analytic sample

The Study of Health in Pomerania (SHIP) is a longitudinal population-based epidemiological study of Caucasian participants in northeastern Germany aiming to assess prevalence and incidence of a broad range of common risk factors, subclinical disorders, clinical diseases, and interactions among them. The data collection and instruments include four parts: oral health examination, medical examination, health-related interview, and a health- and risk-factor-related questionnaire (John et al., 2001). The two-stage stratified and clustered SHIP-0 baseline study randomly drawn from local registries was conducted between 1997 and 2001. In parallel to the second follow-up of the initial SHIP cohort (SHIP-2), a second, independent sample was recruited from the same local area between 2008 and 2012 (SHIP-TREND-0, *N* = 4420) (Völzke, 2012). Details on the SHIP project including purpose, sampling and design can be found by John et al. (2001) or Völzke et al. (2011). The study conformed to the principles of the Declaration of Helsinki and was approved by the ethics committee of the University Greifswald. All participants gave written informed consent.

After the selection procedure outlined in Figure 1, data of 3444 men and women of SHIP-TREND-0 aged 20–83 years were analyzed. Descriptive statistics of the analytic sample can be found in Table 1.

Outliers were detected via boxplots, Cook's distance, and standardized residuals deviating not more than five percent over 2, not more than one percent over 2.5 and zero percent over 3 standard deviations from mean (Field et al., 2012). There was only one participant with extreme values which had to be removed from the data set. Furthermore, participants with missing values or participants reporting the use of any medication intervening in cortisol levels (e.g., hormonal contraceptives or replacements, anabolic steroids, inhalative glucocorticoids and other systemic hormonal preparations) were excluded from this analysis. Detailed information on endocrine effective profiles can be found in Williams Textbook of Endocrinology (Melmed et al., 2015). As pregnancy also significantly elevates cortisol concentrations (Hertel et al., 2017; Jung et al., 2011; Meulenberg et al., 1987), corresponding participants were additionally excluded from the analyses. To approximate the late stage of menopausal transition, women who reported to have had their last period within the past 12

months were excluded, as increased urinary cortisol levels were shown in the late stage of menopause (Woods et al., 2006).



Note: M represents mean, SD represents standard variation.

Figure 1: Selection of the study population

Characteristics	TAS-20 sum score ≤ 60 Non-alexithymic	TAS-20 sum score > 60 Alexithymic	Total	p
Sex				0.371
Female	1481 (44.4%)	45 (40.2%)	1526 (44.3%)	
Male	1851 (55.6%)	67 (59.8%)	1918 (55.7%)	
Age (years)	52.755 (14.946)	51.295 (13.828)	52.707 (14.912)	0.252
Education				< 0.001
< 10 years of schooling	757 (22.7%)	44 (39.3%)	801 (23.3%)	
10 years of schooling	1724 (51.7%)	59 (52.7%)	1783 (51.8%)	
> 10 years of schooling	851 (25.5%)	9 (8.0%)	860 (25.0%)	
Physical activity				0.021
≥ 1hour of sports/week	1650 (49.5%)	43 (38.4%)	1693 (49.2%)	
< 1hour of sports/week	1682 (50.5%)	69 (61.6%)	1751 (50.8%)	
Waist-to-height ratio	0.542 (0.083)	0.563 (0.088)	0.543 (0.083)	0.009
Alcohol consumption				0.998
Low risk (< 20 g ethanol/d for women, < 30 g ethanol/d for men)	3064 (92.0%)	103 (92.0%)	3167 (92.0%)	
At-risk (≥ 20 g ethanol/d for women, ≥ 30 g ethanol/d for men)	268 (8.0%)	9 (8.0%)	277 (8.0%)	
Smoking status				0.014
Never smoker	1195 (35.9%)	26 (23.7%)	1221 (35.5%)	
Current smoker	887 (26.6%)	40 (35.7%)	927 (26.9%)	
Former smoker	1250 (37.5%)	46 (41.1%)	1296 (37.6%)	
Depression				< 0.001
No depression (BDI-II score ≤ 12)	2793 (83.8%)	36 (32.1%)	2829 (82.1%)	
Mild to severe depression (BDI-II score > 12)	539 (16.2%)	76 (67.9%)	615 (17.9%)	
Total	3332	112	3444	

Note: Data are absolute numbers (percent) for nominal and ordinal scales or mean (standard deviation) for metric scales. Group differences were tested with Kruskal-Wallis and Chi-Squared tests.

Table 1: Descriptive statistics of the analytic sample by TAS-20-score

2.2. Blood Measurements

The blood samples were taken from the cubital vein and directly analyzed or stored at -80 °C in the Integrated Research Biobank of the University Medicine Greifswald (Winter et al., 2020).

Blood sampling was conducted between 7:22 a.m. and 12:52 a.m. following a standardized protocol. The majority of blood samples was taken before 9:02 a.m. Partici-

pants were asked not to eat or drink before blood sampling. Fasting time was determined as the difference between the time of blood sampling and the last caloric intake. The mean fasting time was *M* = 8:55 h (*SD* = 5:18 h). Analytics were performed by skilled staff according to the manufacturer's instructions.

As cortisol secretion is pulsatile and strongly associated with food intake (Krieger et al., 1971; Melmed et al., 2015; Weitzman et al., 1971), fasting time was non-linear modulated by polynomials.

Erythrocyte count, leukocyte count and thrombocyte count were measured on the XT2000, XE5000 or SE9000 analyzers from Sysmex (Sysmex Deutschland GmbH, Norderstedt, Germany) or on the Advia 2120i (Siemens Healthcare Diagnostics, Eschborn, Germany). Glycated hemoglobin (HbA1c) concentrations were investigated by high-performance liquid chromatography (Bio-Rad Diamat, Munich, Germany). The blood serum samples were consequently processed; for details, see Eick et al. (2021). To determine the cortisol concentrations, a competitive immunoassay technique was used (ADVIA Centaur XP System, Siemens Healthcare Diagnostics, Eschborn, Germany). The manufacturer provided the cross-reactivity for 33 endogenous steroids, including corticosterone and 20-α- and 20-β-dihydrocortisol. Only two cross-reactivity values were reported to be larger than 10%: cortisone (31.1%) and 11-deoxycortisol (100 µg/dL; 23.3%).

Characteristics	TAS-20 sum score ≤ 60 Non-alexithymic	TAS-20 sum score > 60 Alexithymic	Total	p
Basal cortisol (nmol/l)	325.560 (118.168)	319.358 (127.587)	325.358 (118.471)	0.389
Time of Blood Sampling (hours)	553.318 (63.358)	556.491 (68.096)	553.422 (63.509)	0.828
Fasting time (hours)	8.898 (5.299)	9.251 (5.320)	8.910 (5.299)	0.307
Erythrocytes (Tpt/l)	4.685 (0.408)	4.668 (0.431)	4.685 (0.409)	0.650
Leukocytes (Gpt/l)	6.026 (1.719)	6.436 (2.104)	6.039 (1.734)	0.052
Thrombocytes (Gpt/l)	224.779 (53.602)	227.598 (59.031)	224.871 (53.780)	0.851
HbA1c (%)	5.401 (0.839)	5.532 (1.049)	5.405 (0.847)	0.284

Note: Data are absolute numbers (percent) for nominal and ordinal scales or mean (standard deviation) and range for metric scales. Group differences were tested with Kruskal-Wallis and Chi-Squared tests.

Table 2: Descriptive statistics of the blood sampling and basal cortisol concentration by TAS-20-score and depressive symptoms

2.3. Assessment of alexithymia and depression

The personality construct of alexithymia was assessed using the German version of the 20-Item-Toronto Alexithymia Scale (TAS-20). All items are rated on a 5-point-Likert-scale ranging from “1” (strongly disagree) to “5” (strongly agree) (Bach et al., 1996; Bagby et al., 2020; Bagby, Parker, et al., 1994; Bagby, Taylor, et al., 1994).

The German version provides a good internal consistency and test-retest-reliability. The 3-factor-structure of the alexithymia construct has been confirmed (Bach et al., 1996).

For descriptive purposes and sensitivity analyses, participants were categorized into alexithymic and non-alexithymic using the clinical cut-off of TAS-20 summary score > 60 (Bagby, Taylor, et al., 1994; Taylor et al., 1997).

In SHIP-TREND-0, current depressive symptoms were assessed using the depression module of the Patient Health Questionnaire (PHQ-9) – a 9-item self-report questionnaire providing a reliable and valid measure of depression severity (Kroenke et al., 2001). The items represent the diagnostic criteria of a major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994).

In other SHIP cohorts depressive symptoms were assessed by the German version of the BDI-II, which is a more established and comparable 21-item self-report questionnaire of high reliability and validity (Beck et al., 1996; Beck & Steer, 1987; Hautzinger et al., 2006). PHQ-9- scores therefore were transformed into BDI-II-scores applying item response theory methods. Responses to the BDI-II items were estimated and converted back into PHQ-9-items with a correlation of r = 0.98 (Wahl et al., 2014). The methodical background is described in detail by Bjorner et al. (2004), Orlando et al. (2000) and Wahl et al. (2014). BDI-II-scores between 0 and 12 mean no depression, from 13 to 19 mild depression, from 20 to 28 moderate depression and from 29 to 63 severe depression.

2.4. Assessments of further covariates

Sociodemographic factors and disease history were assessed by computer-assisted face-to-face interviews. Education was classified in three categories: < 10, 10 or > 10

years of schooling according to the German school system. Physical activity was dichotomized in physical inactive and active based on self-reported activity, i.e., no sports versus at least one hour of sports per week.

Alcohol consumption was assessed as the mean alcohol intake during the past 30 days and defined as the mean ethanol consumption in grams per day. Further, alcohol consumption at risk was categorized with a cut-off value of 30 grams or more ethanol per day for men and 20 grams or more per day for women (Baumeister et al., 2005; Völzke et al., 2015). This dichotomization was only used in the descriptive analyses.

Smoking status was classified as current smoking, former smoking, and lifelong abstinence (never smoker) according to Baumeister et al. (2007).

Participants underwent standardized medical examinations, including the measurements of height and weight. Height was measured to the nearest 1 cm. Waist circumference was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane, with the participant standing on both feet. WHtR was used as covariate in all analyses as it is advantageous over the BMI as a body fat-related anthropometric measure: It avoids the need for age-, sex- and ethnic-specific boundary values and is not biased by muscle mass. It represents the most valid measurement of abdominal obesity (Browning et al., 2010; Schneider et al., 2010). All participants were asked to bring their package containers, drug prescription sheets or to report the medication intake over the past 7 days. Medication was coded according to the Anatomical Therapeutic Chemical Classification System (ATC) (Nahler, 2009). Figure 1 lists all ATC-Codes which lead to an exclusion of the participants.

2.5. Statistical analysis

Analyses were run via R version 4.1.0 (R Core Team, 2021) using the following packages: psych version 2.1.3 (Revelle, 2020), CAR (Fox & Weisberg, 2019), mediation version 4.4.2 (Tingley et al., 2014) and apaTables version 2.0.8 (Stanley, 2021) for a total sample of N = 3444.

Descriptive statistical analyses were performed by Kruskal-Wallis and Chi-Squared tests for non-alexithymic and alexithymic individuals according to the clinical cutoff score of TAS-20 summary score > 60. The level of significance was adjusted for multiple testing by Holm—Bonferroni method with a total of 28 tests. This method was

used to control the family-wise error rate by offering a uniformly more powerful test than the Bonferroni correction (Holm, 1979). Metric variables were described by mean (*M*) and standard deviation (*SD*), while categorial variables were described by proportions.

To explore the main hypothesis, the effect of the TAS-20 summary score on basal serum cortisol by fitting multiple linear regression utilizing the cortisol concentrations as the response variable and the degree of alexithymia as the predictor of interest was investigated, while equally adjusting for multiple testing and for the following core set of variables that have been the subject of previous analyses (e.g. Eick et al., 2021; Terock et al., 2017): age, sex, education, WHtR, physical activity, alcohol consumption, smoking status, fasting time, time of blood sampling, white blood cell count, red blood cell count and platelet count as well as HBa1c. Moreover, given the high association between depression, and alexithymia as well as HPA-axis alterations, sensitivity analyses taking the putative effects of depression into account were performed.

Furthermore, a dichotomized model using the clinical cutoff score of TAS-20 summary score > 60 was calculated. In the general population sample of $N = 3444$, clinical alexithymic subjects based on this cutoff were few ($N = 112$, i.e., 3.25%) and men were overrepresented. As the large difference in the sample size goes along with large differences in estimation biases of the partial correlation matrix, an interpretation of the results is impeded. Therefore, the calculation was repeated in supplementary analyses using a median split of the TAS-20-total score of ≤ 41 and > 41. By generating nearly balanced groups with respect to the major covariates sex and age, differences in random and systematic estimation errors between both groups can then be neglected. Separated regression analyses for each of the three TAS-20-subscales were also run to identify potential differences of this multifaceted construct.

Based on the main model, separate models were then calculated for men and women as well as for three age groups inspired by Faltermaier et al. (2013): early adulthood (20–40 years), middle adult age (41–60 years) and late adulthood (> 60 years).

A similar multiple linear regression model adding the interaction term of WHtR and TAS-20 total score was fitted to investigate a hypothesized moderation effect.

The relationship between alexithymia and cortisol may be more complex than initially assumed, i.e., that alexithymia (independent variable) first influences a third intervening variable (depression or health behavior/health status as potential mediators) which in turn influences basal cortisol concentration (dependent variable). To test the significance of the indirect effect, mediation analyses were calculated via bootstrapping, i.e., a statistical approach based on the building of a sample distribution by resampling the data.

Simulation studies show that bootstrapping has high statistical power and good control of errors of the first type (Hayes, 2009; D. P. MacKinnon et al., 2004). The method is independent from distribution properties (Preacher et al., 2007) and therefore delivers reliable results for non-normally distributed variables (Berkovits et al., 2000; Kelley, 2005; Mooney et al., 1993)

A significant total effect was formerly considered to be part of the requirement to test mediation (Baron & Kenny, 1986). Conversely, according to manifold recent statistical research, it is not necessary and can even lead to incorrect statements (D. MacKinnon, 2008; Rucker et al., 2011; Zhao et al., 2010). Zhao et al. (2010) and Rucker et al. (2011) for example plead for an exclusive interpretation of the indirect effect regardless of other prerequisites. On top of that, anomalies relating to statistical power occur in testing mediation. In a model without direct effect, the power for the test of the total effect can be significantly smaller than the power for the test of the indirect effect. The same can be the case when there is a direct effect of a causal variable on the outcome controlling for the mediator (Kenny & Judd, 2014).

Therefore, mediation analyses via bootstrapping were run as well to test whether the hypothesized effects of alexithymia on basal cortisol levels were statistically mediated by health behavior and depression after correcting for multiple testing by Holm—Bonferroni method as before.

3. Results

Tables 1 and 2 outline the sample at hand and highlight the group differences regarding the degree of depressive and alexithymic characteristics (according to BDI-II and

TAS-20, respectively) for every conventional confounding covariate, revealing significant group differences in the variables education and depression (p_{adj} = < 0.01 in both cases).

Contrary to the main assumption (hypothesis 1), there was no association of alexithymic personality characteristics and basal serum cortisol levels.

While the regression model using basal cortisol as the criterion was highly significant and able to explain 14.3 percent of the variance (R^2 = .143) with a CI of [0.12, 0.16], alexithymia was not found to have a significant effect on basal cortisol levels (b = 0.23, with a 95 percent confidence interval (CI) of [-0.24, 0.69]; sr^2 = 0.00, CI: [-0.00, 0.00]). Even after adjusting for the three factors of alexithymia according to TAS-20, no association with basal cortisol could be found.

In contrast, BDI-II had a significant effect on basal cortisol levels (b = -1.55, CI: [-2.32, -0.78]; sr^2 = 0.00, CI: [-0.00, 0.01]).

Conventional confounding covariates such as sex, education, physical activity, WHtR, alcohol consumption, smoking status, erythrocytes, leukocytes and HbA1c significantly influenced the basal cortisol concentration, with the time of blood sampling reaching the highest explanation of variance (sr^2 = 0.005 CI: [0.04, 0.07]). Age, fasting time, and thrombocytes did not significantly influence basal cortisol concentration.

Subsequently, the TAS-20-variable was dichotomized using a cutoff score of TAS-20 > 60 and did not reach an alteration in explanation of variance. By using a median split of the TAS-20 total score, results differed only marginally from the previous analyses and did not change the obtained finding.

Furthermore, no significant effect of alexithymia on basal cortisol in sex- and age-stratified regression analyses was found (hypothesis 2).

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
Intercept	487.23**	[414.13, 560.33]			
Toronto Alexithymia Scale-20 total score	0.23	[-0.24, 0.69]	.00	[-.00, .00]	
Beck Depression Inventory- II total score	-1.55**	[-2.32, -0.78]	.00	[.00, .01]	
Sex (female)	-37.06**	[-46.59, -27.53]	.01	[.01, .02]	
Age (years)	0.12	[-0.21, 0.46]	.00	[-.00, .00]	
Education (< 10 years of schooling)	16.48**	[6.44, 26.53]	.00	[-.00, .01]	
Education (> 10 years of schooling)	-16.75**	[-25.97, -7.53]	.00	[-.00, .01]	
Physical activity (active)	8.75*	[1.13, 16.37]	.00	[-.00, .00]	
Waist-to-height ratio	-168.70**	[-223.16, -114.24]	.01	[.00, .02]	
Alcohol consumption (ethanol in g/d)	0.83**	[0.54, 1.12]	.01	[.00, .01]	
Former smoker	27.89**	[17.51, 38.27]	.01	[.00, .01]	
Never smoker	36.00**	[25.34, 46.66]	.01	[.00, .02]	
Time of blood sampling (min)	-0.45**	[-0.51, -0.39]	.05	[.04, .07]	
Fasting time (min)	-82.24	[-304.70, 140.23]	.00	[-.00, .00]	
Fasting time squared (min^2)	23.47	[-204.39, 251.32]	.00	[-.00, .00]	
Erythrocytes (Tpt/l)	17.14**	[6.56, 27.72]	.00	[-.00, .01]	
Leukocytes (Gpt/l)	7.21**	[4.70, 9.72]	.01	[.00, .01]	
Thrombocytes (Gpt/l)	-0.01	[-0.09, 0.07]	.00	[-.00, .00]	
HbA1c (%)	6.35*	[1.46, 11.25]	.00	[-.00, .00]	
					R^2 = .143** 95% CI [.12,.16]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. A significant *b*-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

* indicates p < .05. ** indicates p < .01.

Table 3: Results of the multiple linear regression model using basal cortisol concentration (nmol/l) as the criterion

As shown in Table 4, the interaction term of WHtR and TAS-20 total score was implemented in the main model to investigate the assumed moderation effect (hypothesis 3). Model fit did not change ($R^2 = 0.143$) and there was no significant effect on cortisol concentration. In this case, WHtR did not have a significant impact on serum basal cortisol either.

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
Intercept	453.37**	[321.67, 585.06]			
Toronto Alexithymia Scale-20 total score	1.02	[-1.58, 3.61]	.00	[-.00, .00]	
Beck Depression Inventory-II total score	-1.54**	[-2.32, -0.77]	.00	[-.00, .01]	
Sex (female)	-36.92**	[-46.46, -27.38]	.01	[.01, .02]	
Age (years)	0.12	[-0.22, 0.45]	.00	[-.00, .00]	
Education (< 10 years of schooling)	16.55**	[6.50, 26.59]	.00	[-.00, .01]	
Education (> 10 years of schooling)	-16.72**	[-25.94, -7.50]	.00	[-.00, .01]	
Physical activity (active)	8.77*	[1.14, 16.39]	.00	[-.00, .00]	
Waist-to-height ratio	-107.28	[-313.30, 98.75]	.00	[-.00, .00]	
Alcohol consumption (ethanol in g/d)	0.83**	[0.54, 1.12]	.01	[.00, .01]	
Former smoker	27.95**	[17.57, 38.34]	.01	[.00, .01]	
Never smoker	36.07**	[25.40, 46.73]	.01	[.00, .02]	
Time of blood sampling (min)	-0.45**	[-0.51, -0.39]	.05	[.04, .07]	
Fasting time (min)	-82.09	[-304.57, 140.40]	.00	[-.00, .00]	
Fasting time squared (min^2)	24.85	[-203.07, 252.77]	.00	[-.00, .00]	
Erythrocytes (Tpt/l)	17.18**	[6.60, 27.76]	.00	[-.00, .01]	
Leukocytes (Gpt/l)	7.22**	[4.71, 9.73]	.01	[.00, .01]	
Thrombocytes (Gpt/l)	-0.01	[-0.09, 0.07]	.00	[-.00, .00]	
HbA1c (%)	6.46**	[1.55, 11.36]	.00	[-.00, .00]	
WHtR: TAS-20 total score	-1.45	[-6.13, 3.23]	.00	[-.00, .00]	R^2 = .143** 95% CI[.12,.16]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. A significant *b*-weight indicates the semi-partial correlation is also significant. Shown in bold are the predictors of interest. Toronto Alexithymia Scale-20 total score was already not significant before adjusting via Holm–Bonferroni method.
* indicates p < .05. ** indicates p < .01.

Table 4: Results of the multiple linear regression model with additional interaction term using basal cortisol concentration (nmol/l) as the criterion

To examine possible mediation effects of the level of depression according to BDI-II on the one hand and health behavior and health status on the other hand on the

association between alexithymia and basal cortisol (hypothesis 4), two mediation analyses were calculated independently of the regression results via boot strapping.

Mediation analysis with depression as a possible mediator revealed a coefficient of determination larger than 1, not meeting a necessary condition for a causal mediation effect (see Table 5).

Direct effects	Estimate	SE	p			Fit
Alexithymia on basal cortisol (total)	-0.18	0.21	0.379			
Alexithymia on basal cortisol (direct)	0.24	0.24	0.311			
Alexithymia on depression	0.28	0.01	< 0.001			
Depression on basal cortisol	-1.5	0.4	< 0.001			
Indirect effect	Estimate	boot SE	SD	95 % CI		
				LL	UL	
Alexithymia on basal cortisol via depression	-0.42	-0.42	0.11	-0.63	-0.21	
						R^2 = 1.13
						p = 1

Note: SE represents standard error. *boot SE* represents bootstrapped standard error. LL and UL indicate the lower and upper limits of a confidence interval, respectively.

Table 5: Mediation analyses: effect of alexithymia on cortisol mediated by depression

The same mediation analysis was done with health behavior and health status (i.e., smoking status, alcohol consumption, physical activity, WHtR) (see Table 6), also revealing a coefficient of determination larger than 1, likewise not meeting a necessary condition for a causal mediation effect.

Direct effects	Estimate	SE	p			Fit
Alexithymia on basal cortisol (total)	-0.38	0.21	0.073			
Alexithymia on basal cortisol (direct)	-0.21	0.21	0.307			
Physical activity on basal cortisol	9.27	3.89	0.017			
Alcohol consumption on basal cortisol	0.83	0.15	< 0.001			
Smoking status on basal cortisol	-17.46	2.68	< 0.001			
WHtR on basal cortisol	-165.40	27.63	< 0.001			
Alexithymia on physical activity	0.00	0.00	< 0.001			
Alexithymia on alcohol consumption	0.02	0.02	0.507			
Alexithymia on smoking status	0.00	0.00	0.0288			
Alexithymia on WHtR	0.00	0.00	< 0.001			
Indirect effect	Estimate	boot SE	SD	95 % CI		
				LL	*UL*	
Alexithymia on basal cortisol via all mediators	-0.17	-0.03	0.02	-0.07	0	
Alexithymia on basal cortisol via physical activity	-0.03		0.01	-0.06	0	
Alexithymia on basal cortisol via alcohol consumption	-0.02		0.01	-0.06	0	
Alexithymia on basal cortisol via smoking status	-0.05		0.02	-0.1	-0.01	
Alexithymia on basal cortisol via WHtR	-0.1		0.03	-0.17	-0.05	
						R^2 = 1.13
						p = 1

Note: SE represents standard error. *boot SE* represents bootstrapped standard error. LL and UL indicate the lower and upper limits of a confidence interval, respectively.

Table 6: Mediation analyses: effect of alexithymia on cortisol mediated by health behavior and health status

4. Discussion

The present study aimed at investigating the relation between alexithymia and HPA-axis activity, i.e., cortisol levels, among a large, representative general-population sample contributing to explain the relationship between alexithymia, endocrine alterations, and health impairment. Contrary to the given hypothesis, no significant association of alexithymia with enhanced or decreased basal cortisol plasma levels was found, neither in dependence of sex nor age. In conformity with the state of research, the time of blood sampling, sex, education, body status, most blood parameters, alcohol consumption and smoking status significantly influenced the basal cortisol concentration, whereas age, physical activity and fasting time inexplicably did not. In this study, only fasting time was non-linear modulated by polynomials. Future research might expand on these results by also regarding time of blood sampling and age as non-linear variables. Additionally, the concentration of sexual hormones might prove as a variable of interest. WHtR represents a consequence of health behavior which is associated with cortisol levels, but no moderating effect on alexithymia and cortisol was found. Analyses examining a possible mediating effect of the level of depression,

health behavior and health on the association between alexithymia and basal cortisol were not efficacious.

Martin and Pihl (1986) had already found high alexithymic individuals to manifest high levels of sympathetic activity, hinting at a potential contribution of alexithymia to the development of stress-related disorders. The associated stress-alexithymia hypothesis was supported and extended by progressive studies also focusing on underlying physiological and neuroendocrine mechanisms (de Timary et al., 2008; Friedlander et al., 1997; R. Lane et al., 1998; Terock, Van der Auwera, et al., 2019).

Previous studies with research designs different from the one used here provided evidence for altered HPA-axis activity in alexithymic subjects.

Härtwig et al. (2013) found the mean CAR significantly lower in alexithymic subjects and a negative correlation of HPA-axis activity with age in alexithymic individuals.

Spitzer et al. (2005) found a generally decreased basal activity of the HPA axis as determined by high norepinephrine/cortisol ratios among men whereas de Timary et al. (2008) report higher basal cortisol levels in male alexithymic individuals when anticipating a social stress test, albeit this was not the case during stress exposure.

Alexithymia accumulates in subjects suffering from depression (Honkalampi et al., 2001; Honkalampi, Hintikka, Saarinen, et al., 2000; Honkalampi, Hintikka, Tanskanen, et al., 2000; Saarijärvi et al., 2001). Honkalampi et al. (2000) found that depression is strongly associated with alexithymia in the general population. In studies with depressive outpatients, alexithymic patients were more often moderately or severely depressed and a decrease in alexithymia was associated with a simultaneous decrease in depression (Honkalampi et al., 2001; Honkalampi, Hintikka, Saarinen, et al., 2000). Saarijärvi et al. (2001) specified these findings in a closer examination of TAS-20 subfactors: a recovery from depressive outpatients was associated with a decrease in the factors difficulties in identifying and describing feelings, whereas there was no alteration in the factor externally oriented thinking.

The influence of depression on the association of alexithymia and basal cortisol was particularly considered in this study. Although a significant negative association of depression and basal serum cortisol was found, the level of depression according to BDI-II was determined to neither have an impact on alexithymia and its subfactors itself nor a mediating impact on the association of alexithymia and basal cortisol.

Due to the observational, cross-sectional design of this cohort study accompanying missing interventional or longitudinal data, causal conclusions cannot be drawn. In addition, a selection or response bias cannot safely be neglected, as participants with missing or extreme values were excluded from the used data set. Furthermore, pregnant participants, those in the late stage of menopausal transition, and those reporting the intake of hormonal contraceptives or other medication intervening with HPA-axis activity were excluded from these analyses. It should be noted that because of the particular biology associated with the menstrual cycle, women represent a unique and relevant subgroup. The use of OCs and other hormonal preparations further adds to the complexity, especially since previous studies have shown a significant association between OC use and cortisol levels (Carr et al., 1979; Hertel et al., 2017; Meulenberg et al., 1987). To date, research on a possible association between the use of hormonal contraceptives and alexithymia is scarce and could warrant further investigation in the context of this study. Furthermore, the influence of menopausal transition stage on cortisol levels within the given data set may be of interest. Further research should include a deeper analysis of the actual and not only presumed association of certain drugs to cortisol in order to exclude from the sample only those individuals whose medications have a relevant effect.

Possibly untreated or undetected endocrine disorders linked to HPA-axis activity like Addison's or Cushing's disease were not assessed and could in turn not be excluded. It should be mentioned that there are further biases which creep into every survey situation and can at best be minimized: non-response bias, survivorship sampling bias, acquiescence bias, question order bias, primacy bias or conformity bias, to name a few. As with the TAS-20 and the BDI-II in particular, exclusively self-reported data was conducted, potentially more differentiated and valid information by structured interviews or observer-rated instruments is missing.

Nonetheless, this study was conducted in a large, representative general-population sample adjusting for many covariates. More decisive proves the consideration of relevant subsamples: The sample size N = 112 of high alexithymic individuals diminishes the evaluation of potential associations with cortisol plasma levels. This was countered by supplementary analyses using a median split of the TAS-20-total score and generating nearly balanced groups with respect to the major covariates sex and age.

Beyond, Franz et al. (2008) propose that the widespread cut-off of 61 (Bagby, Parker, et al., 1994; Bagby, Taylor, et al., 1994) is possibly too restrictive for selecting alexithymic individuals in experimental studies with the German version of the TAS-20. The authors propose the 66th percentile for the identification of the highly alexithymic. However, in the case at hand, results differed only marginally and changes in cutoff position did not change the obtained finding. The reference by Franz et al. (2008) should be considered in future investigations.

Furthermore, only basal serum cortisol values were available. Hence the results cannot be generalized to, e.g., acute stress reactions on specific stimuli or potential differences in day profiles. Cortisol levels usually underly a typical diurnal rhythm of a rapid decline throughout the waking day and reach the lowest value at midnight, notwithstanding fluctuating broadly intra- and inter-individually. Due to the circadian rhythm of cortisol secretion, this study provides limited informative value. Specifically, the CAR should be the focus of further investigations as seen by Härtwig et al. (2013). A daily cortisol profile can also provide further information. Cortisol secretion is highly sensitive to stress and the time of collection and intra-individual variation is wide. The individual's wake-up and get-up times or a possible prior exposure to stressors could not be taken into consideration. The blood level of cortisol falls during fasting, whereas very long fasts or strong calorie restrictions cause increased cortisol levels (Melmed et al., 2015). A standardized fasting time and an accompanying consistent time of blood sampling could not be ensured in this study. Additionally, the blood collection itself as an invasive approach is a potential affectively occupied stressor. A salivary cortisol determination should be preferred over blood cortisol analyses even for certain additional advantages, as resulting data are sufficiently comparable (Kirschbaum & Hellhammer, 1994; Lac, 2001). Additionally, salivary as well as urinary cortisol show primarily free and active cortisol. Furthermore Lee et al. (2015) question if biochemical markers like serum and salivary cortisol can depict acute, chronic, or diurnal variations properly. The authors suggest the analysis of cortisol in scalp hair as a technique for the retrospective assessment of overall long-term systemic cortisol exposure, e.g., chronic stress. The best results are to be expected from a multimethodological approach, combining the different methods of cortisol level determination.

This study does not support previous findings and extends them by indicating a differentiation of CARs, stress exposure or specific sample compositions on the one hand and basal cortisol levels of the general population on the other hand. A precise compliance of fasting and get up time, sampling time and several sampling methods should be part of the research procedure when examining psychological or psychiatric phenomena and cortisol secretion. Yet unidentified additional factors underlying the association of endocrine activity and alexithymic personality should be the subject of further research at best longitudinally conducted among a large, representative general-population sample.

5. Summary

Objective

Alexithymia is associated with various mental and physical disorders. Some rare evidence also suggested high alexithymia to affect the HPA axis based on small and selective samples. It was aimed to investigate the impact of alexithymia on basal cortisol levels in a large population-based cohort.

Methods

In a sample of *N* = 3444 individuals from the Study of Health in Pomerania (SHIP-TREND-0), the effect of alexithymia on basal serum cortisol levels was investigated in a cross-sectional design.

Multiple linear regressions utilizing cortisol levels as the response variable and alexithymia as the predictor of interest were calculated, while adjusting for conventional confounding covariates including depression. Multiple stratified, moderation and mediation analyses were performed to validate the results.

Results

Alexithymia was not significantly associated with basal cortisol levels (b = 0.23, 95 percent confidence interval (CI) of [-0.24, 0.69]; sr^2 = 0.00, CI: [-0.00, 0.00]).

Sex- and age-stratified regression analyses as well as dichotomized models of non-alexithymic and alexithymic individuals substantiated the non-significance.

Additional mediation analyses with (1) depression and (2) physical health (R^2 > 1 in both cases) and moderation analysis regarding the interaction of physical health and alexithymia (b = -1.45, 95 percent confidence interval (CI) of [-6.13, 3.32]; sr^2 = 0.00, CI: [-0.00, 0.00]) corroborated the results.

Conclusion

This study does not support previous findings as it shows no association between alexithymia and basal cortisol; however, a consideration of the circadian rhythm, stress exposure or specific sample compositions heeding the methodological design should be the subject of further research.

6. References

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7. Appendix

7.1. Additional tables

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
Intercept	490.30**	[418.22, 562.37]			
Toronto Alexithymia Scale-20, DIF	0.56	[-0.61, 1.72]	.00	[-.00, .00]	
Beck Depression Inventory- II total score	-1.62**	[-2.48, -0.76]	.00	[-.00, .01]	
Sex (female)	-37.65**	[-47.13, -28.16]	.02	[.01, .02]	
Age (years)	0.13	[-0.21, 0.47]	.00	[-.00, .00]	
Education (< 10 years of schooling)	16.75**	[6.74, 26.75]	.00	[-.00, .01]	
Education (> 10 years of schooling)	-17.09**	[-26.29, -7.89]	.00	[-.00, .01]	
Physical activity (active)	8.63*	[1.01, 16.24]	.00	[-.00, .00]	
Waist-to-height ratio	-168.35**	[-222.78, -113.91]	.01	[.00, .02]	
Alcohol consumption (ethanol in g/d)	0.83**	[0.54, 1.12]	.01	[.00, .01]	
Former smoker	27.93**	[17.54, 38.31]	.01	[.00, .01]	
Never smoker	36.23**	[25.55, 46.90]	.01	[.00, .02]	
Time of blood sampling (min)	-0.45**	[-0.51, -0.39]	.05	[.04, .07]	
Fasting time (min)	-79.91	[-302.31, 142.49]	.00	[-.00, .00]	
Fasting time squared (min^2)	25.53	[-202.34, 253.40]	.00	[-.00, .00]	
Erythrocytes (Tpt/l)	17.15**	[6.57, 27.73]	.00	[-.00, .01]	
Leukocytes (Gpt/l)	7.22**	[4.71, 9.73]	.01	[.00, .01]	
Thrombocytes (Gpt/l)	-0.01	[-0.09, 0.07]	.00	[-.00, .00]	
HbA1c (%)	6.40*	[1.51, 11.29]	.00	[-.00, .00]	
					R^2 = .143** 95% CI[.12,.16]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. A significant *b*-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

* indicates p < .05. ** indicates p < .01.

Table 7: Results of the multiple linear regression model for TAS-20 subscale difficulty identifying feelings (DIF) using basal cortisol concentration (nmol/l) as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
Intercept	490.11**	[417.85, 562.37]			
Toronto Alexithymia Scale-20, DDF	0.51	[-0.65, 1.67]	.00	[-.00, .00]	
Beck Depression Inventory- II total score	-1.49**	[-2.23, -0.76]	.00	[.00, .01]	
Sex (female)	-37.00**	[-46.56, -27.44]	.01	[.01, .02]	
Age (years)	0.12	[-0.21, 0.46]	.00	[-.00, .00]	
Education (< 10 years of schooling)	16.82**	[6.82, 26.82]	.00	[-.00, .01]	
Education (> 10 years of schooling)	-17.01**	[-26.21, -7.81]	.00	[-.00, .01]	
Physical activity (active)	8.68*	[1.06, 16.30]	.00	[-.00, .00]	
Waist-to-height ratio	-167.77**	[-222.17, -113.36]	.01	[.00, .02]	
Alcohol consumption (ethanol in g/d)	0.83**	[0.54, 1.12]	.01	[.00, .01]	
Former smoker	27.86**	[17.48, 38.25]	.01	[.00, .01]	
Never smoker	35.98**	[25.32, 46.64]	.01	[.00, .02]	
Time of blood sampling (min)	-0.45**	[-0.51, -0.39]	.05	[.04, .07]	
Fasting time (min)	-83.17	[-305.73, 139.39]	.00	[-.00, .00]	
Fasting time squared (min^2)	24.04	[-203.81, 251.90]	.00	[-.00, .00]	
Erythrocytes (Tpt/l)	17.17**	[6.59, 27.76]	.00	[-.00, .01]	
Leukocytes (Gpt/l)	7.22**	[4.71, 9.73]	.01	[.00, .01]	
Thrombocytes (Gpt/l)	-0.01	[-0.09, 0.07]	.00	[-.00, .00]	
HbA1c (%)	6.36*	[1.47, 11.25]	.00	[-.00, .00]	
					R^2 = .143** 95% CI[.12,.16]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. A significant *b*-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

* indicates p < .05. ** indicates p < .01.

Table 8: Results of the multiple linear regression model for TAS-20 subscale difficulty describing feelings (DDF) using basal cortisol concentration (nmol/l) as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
Intercept	491.43**	[418.58, 564.28]			
Toronto Alexithymia Scale-20, EOT	0.21	[-0.67, 1.09]	.00	[-.00, .00]	
Beck Depression Inventory- II total score	-1.39**	[-2.08, -0.70]	.00	[.00, .01]	
Sex (female)	-37.28**	[-46.82, -27.74]	.01	[.01, .02]	
Age (years)	0.12	[-0.22, 0.46]	.00	[-.00, .00]	
Education (< 10 years of schooling)	16.71**	[6.64, 26.78]	.00	[-.00, .01]	
Education (> 10 years of schooling)	-16.80**	[-26.07, -7.53]	.00	[-.00, .01]	
Physical activity (active)	8.71*	[1.08, 16.34]	.00	[-.00, .00]	
Waist-to-height ratio	-168.18**	[-222.67, -113.70]	.01	[.00, .02]	
Alcohol consumption (ethanol in g/d)	0.83**	[0.54, 1.12]	.01	[.00, .01]	
Former smoker	27.82**	[17.43, 38.20]	.01	[.00, .01]	
Never smoker	35.88**	[25.21, 46.55]	.01	[.00, .02]	
Time of blood sampling (min)	-0.45**	[-0.51, -0.39]	.05	[.04, .07]	
Fasting time (min)	-80.42	[-302.87, 142.03]	.00	[-.00, .00]	
Fasting time squared (min^2)	23.03	[-204.89, 250.95]	.00	[-.00, .00]	
Erythrocytes (Tpt/l)	17.09**	[6.51, 27.67]	.00	[-.00, .01]	
Leukocytes (Gpt/l)	7.22**	[4.71, 9.73]	.01	[.00, .01]	
Thrombocytes (Gpt/l)	-0.01	[-0.09, 0.07]	.00	[-.00, .00]	
HbA1c (%)	6.36*	[1.47, 11.26]	.00	[-.00, .00]	
					R^2 = .143** 95% CI[.12,.16]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. A significant *b*-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

* indicates p < .05. ** indicates p < .01.

Table 9: Results of the multiple linear regression model for TAS-20 subscale externally oriented thinking (EOT) using basal cortisol concentration (nmol/l) as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	*sr*² 95% CI [LL, UL]	Fit
Intercept	495.14**	[423.65, 566.63]			
Toronto Alexithymia Scale-20 > 60	7.15	[-14.79, 29.09]	.00	[-.00, .00]	
Beck Depression Inventory- II total score	-1.44**	[-2.16, -0.72]	.00	[.00, .01]	
Age (years)	-37.36**	[-46.86, -27.87]	.01	[.01, .02]	
Sex (female)	0.12	[-0.21, 0.46]	.00	[-.00, .00]	
Education (< 10 years of schooling)	16.81**	[6.80, 26.82]	.00	[-.00, .01]	
Education (> 10 years of schooling)	-16.99**	[-26.20, -7.79]	.00	[-.00, .01]	
Physical activity (active)	8.63*	[1.01, 16.25]	.00	[-.00, .00]	
Waist-to-height ratio	-167.83**	[-222.25, -113.41]	.01	[.00, .02]	
Alcohol consumption (ethanol in g/d)	0.83**	[0.54, 1.12]	.01	[.00, .01]	
Former smoker	27.80**	[17.42, 38.18]	.01	[.00, .01]	
Never smoker	35.99**	[25.32, 46.65]	.01	[.00, .02]	
Time of blood sampling (min)	-0.45**	[-0.51, -0.39]	.05	[.04, .07]	
Fasting time (min)	-82.26	[-304.83, 140.30]	.00	[-.00, .00]	
Fasting time squared (min^2)	23.48	[-204.39, 251.36]	.00	[-.00, .00]	
Erythrocytes (Tpt/l)	17.13**	[6.55, 27.71]	.00	[-.00, .01]	
Leukocytes (Gpt/l)	7.22**	[4.71, 9.73]	.01	[.00, .01]	
Thrombocytes (Gpt/l)	-0.01	[-0.09, 0.07]	.00	[-.00, .00]	
HbA1c (%)	6.39*	[1.49, 11.28]	.00	[-.00, .00]	
					R^2 = .143** 95% CI[.12,.16]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. LL and UL indicate the lower and upper limits of a confidence interval, respectively. A significant b-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

** indicates p < .05. ** indicates p < .01.*

Table 10: Results of the multiple linear regression model with TAS-20 dichotomized (cutoff score ≤ 60 and > 61) using basal cortisol concentration (nmol/l) as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	*sr*² 95% CI [LL, UL]	Fit
Intercept	494.65**	[423.16, 566.13]			
Toronto Alexithymia Scale-20 > 41	1.26	[-6.62, 9.14]	.00	[-.00, .00]	
Beck Depression Inventory- II total score	-1.41**	[-2.13, -0.69]	.00	[-.00, .01]	
Age (years)	-37.45**	[-46.94, -27.95]	.01	[.01, .02]	
Sex (female)	0.12	[-0.21, 0.46]	.00	[-.00, .00]	
Education (< 10 years of schooling)	16.93**	[6.92, 26.93]	.00	[-.00, .01]	
Education (> 10 years of schooling)	-16.99**	[-26.20, -7.77]	.00	[-.00, .01]	
Physical activity (active)	8.65*	[1.03, 16.27]	.00	[-.00, .00]	
Waist-to-height ratio	-167.76**	[-222.19, -113.32]	.01	[.00, .02]	
Alcohol consumption (ethanol in g/d)	0.83**	[0.54, 1.12]	.01	[.00, .01]	
Former smoker	27.82**	[17.44, 38.20]	.01	[.00, .01]	
Never smoker	35.95**	[25.28, 46.61]	.01	[.00, .02]	
Time of blood sampling (min)	-0.45**	[-0.51, -0.39]	.05	[.04, .07]	
Fasting time (min)	-79.34	[-301.77, 143.09]	.00	[-.00, .00]	
Fasting time squared (min^2)	24.16	[-203.72, 252.04]	.00	[-.00, .00]	
Erythrocytes (Tpt/l)	17.11**	[6.53, 27.69]	.00	[-.00, .01]	
Leukocytes (Gpt/l)	7.22**	[4.71, 9.73]	.01	[.00, .01]	
Thrombocytes (Gpt/l)	-0.01	[-0.09, 0.07]	.00	[-.00, .00]	
HbA1c (%)	6.39*	[1.49, 11.28]	.00	[-.00, .00]	
					R^2 = .143** 95% CI[.12,.16]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. LL and UL indicate the lower and upper limits of a confidence interval, respectively. A significant b-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

** indicates p < .05. ** indicates p < .01.*

Table 11: Results of the multiple linear regression model with TAS-20 dichotomized by median (cutoff score ≤ 41 and > 41) using basal cortisol concentration (nmol/l) as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	*sr*² 95% CI [LL, UL]	Fit
Intercept	534.69**	[428.04, 641.34]			
Toronto Alexithymia Scale-20 total score	0.26	[-0.45, 0.98]	.00	[-.00, .00]	
Beck Depression Inventory- II total score	-2.06**	[-3.19, -0.94]	.01	[-.00, .02]	
Age (years)	0.46	[-0.09, 1.00]	.00	[-.00, .01]	
Education (< 10 years of schooling)	15.86*	[0.19, 31.54]	.00	[-.00, .01]	
Education (> 10 years of schooling)	-7.89	[-22.59, 6.81]	.00	[-.00, .00]	
Physical activity (active)	4.74	[-6.91, 16.39]	.00	[-.00, .00]	
Waist-to-height ratio	-149.48**	[-225.06, -73.90]	.01	[-.00, .02]	
Alcohol consumption (ethanol in g/d)	0.98*	[0.07, 1.89]	.00	[-.00, .01]	
Former smoker	26.92**	[10.57, 43.27]	.01	[-.00, .01]	
Never smoker	39.13**	[23.46, 54.79]	.01	[.00, .02]	
Time of blood sampling (min)	-0.54**	[-0.63, -0.45]	.08	[.05, .10]	
Fasting time (min)	-134.48	[-358.86, 89.91]	.00	[-.00, .00]	
Fasting time squared (min^2)	113.10	[-117.96, 344.16]	.00	[-.00, .00]	
Erythrocytes (Tpt/l)	5.33	[-12.40, 23.06]	.00	[-.00, .00]	
Leukocytes (Gpt/l)	7.64**	[3.57, 11.70]	.01	[-.00, .02]	
Thrombocytes (Gpt/l)	0.02	[-0.09, 0.13]	.00	[-.00, .00]	
HbA1c (%)	3.32	[-4.02, 10.66]	.00	[-.00, .00]	
					R^2 = .126** 95% CI[.09,.15]

Note: b represents unstandardized regression weights. *sr²* represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. A significant *b*-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

* indicates p < .05. ** indicates p < .01.

Table 12: Results of the multiple linear regression model for the sample of women using basal cortisol concentration (nmol/l) as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
Intercept	434.09**	[333.70, 534.47]			
Toronto Alexithymia Scale-20 total score	0.12	[-0.49, 0.73]	.00	[-.00, .00]	
Beck Depression Inventory- II total score	-0.84	[-1.92, 0.24]	.00	[-.00, .00]	
Age (years)	-0.03	[-0.48, 0.41]	.00	[-.00, .00]	
Education (< 10 years of schooling)	13.68*	[0.40, 26.95]	.00	[-.00, .01]	
Education (> 10 years of schooling)	-22.57**	[-34.50, -10.63]	.01	[-.00, .01]	
Physical activity (active)	10.65*	[0.40, 20.90]	.00	[-.00, .01]	
Waist-to-height ratio	-189.29**	[-269.34, -109.25]	.01	[.00, .02]	
Alcohol consumption (ethanol in g/d)	0.82**	[0.51, 1.13]	.01	[.00, .02]	
Former smoker	30.01**	[16.38, 43.65]	.01	[.00, .02]	
Never smoker	31.05**	[16.19, 45.91]	.01	[.00, .02]	
Time of blood sampling (min)	-0.38**	[-0.46, -0.29]	.04	[.02, .05]	
Fasting time (min)	16.16	[-204.47, 236.79]	.00	[-.00, .00]	
Fasting time squared (min^2)	-49.03	[-274.57, 176.51]	.00	[-.00, .00]	
Erythrocytes (Tpt/l)	23.44**	[9.93, 36.95]	.01	[-.00, .01]	
Leukocytes (Gpt/l)	7.37**	[4.13, 10.61]	.01	[.00, .02]	
Thrombocytes (Gpt/l)	-0.06	[-0.16, 0.05]	.00	[-.00, .00]	
HbA1c (%)	8.55*	[1.94, 15.16]	.00	[-.00, .01]	
					R^2 = .097** 95% CI[.07,.11]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. A significant *b*-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

* indicates p < .05. ** indicates p < .01.

Table 13: Results of the multiple linear regression model for the sample of men using basal cortisol concentration (nmol/l) as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
Intercept	501.47**	[314.15, 688.78]			
Toronto Alexithymia Scale-20 total score	0.56	[-0.46, 1.58]	.00	[-.00, .01]	
Beck Depression Inventory- II total score	-3.58**	[-5.32, -1.85]	.02	[.00, .03]	
Sex (female)	-31.81*	[-56.05, -7.57]	.01	[-.00, .02]	
Age (years)	15.94	[-10.17, 42.05]	.00	[-.00, .01]	
Education (< 10 years of schooling)	-11.43	[-30.61, 7.75]	.00	[-.00, .01]	
Education (> 10 years of schooling)	13.11	[-4.26, 30.47]	.00	[-.00, .01]	
Physical activity (active)	-326.85**	[-464.56, -189.14]	.02	[.00, .04]	
Waist-to-height ratio	1.46**	[0.81, 2.11]	.02	[.00, .04]	
Alcohol consumption (ethanol in g/d)	29.46**	[7.83, 51.09]	.01	[-.00, .02]	
Former smoker	25.79*	[4.25, 47.33]	.01	[-.00, .01]	
Never smoker	-0.39**	[-0.53, -0.25]	.03	[.01, .05]	
Time of blood sampling (min)	-356.78**	[-599.82, 113.73]	-.01	[-.00, .02]	
Fasting time (min)	-61.03	[-301.77, 179.70]	.00	[-.00, .00]	
Fasting time squared (min^2)	28.58*	[0.94, 56.23]	.00	[-.00, .01]	
Erythrocytes (Tpt/l)	7.74**	[2.33, 13.16]	.01	[-.00, .02]	
Leukocytes (Gpt/l)	-0.02	[-0.20, 0.15]	.00	[-.00, .00]	
Thrombocytes (Gpt/l)	1.30	[-13.22, 15.82]	.00	[-.00, .00]	
HbA1c (%)					R^2 = .179** 95% CI[.12,.21]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. A significant *b*-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

* indicates p < .05. ** indicates p < .01.

Table 14: Results of the multiple linear regression model for the sample of early adulthood (20-40 years) using basal cortisol concentration (nmol/l) as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
Intercept	504.70**	[392.04, 617.35]			
Toronto Alexithymia Scale-20 total score	0.11	[-0.58, 0.80]	.00	[-.00, .00]	
Beck Depression Inventory- II total score	-1.04	[-2.13, 0.05]	.00	[-.00, .01]	
Sex (female)	-38.02**	[-52.69, -23.36]	.01	[.00, .03]	
Age (years)	17.39	[-2.11, 36.89]	.00	[-.00, .01]	
Education (< 10 years of schooling)	-30.83**	[-44.87, -16.78]	.01	[.00, .02]	
Education (> 10 years of schooling)	4.29	[-7.48, 16.06]	.00	[-.00, .00]	
Physical activity (active)	-163.38**	[-242.15, -84.61]	.01	[.00, .02]	
Waist-to-height ratio	0.89**	[0.48, 1.31]	.01	[.00, .02]	
Alcohol consumption (ethanol in g/d)	33.66**	[18.74, 48.59]	.01	[.00, .02]	
Former smoker	34.87**	[19.14, 50.60]	.01	[.00, .02]	
Never smoker	-0.45**	[-0.55, -0.36]	.05	[.03, .07]	
Time of blood sampling (min)	111.46	[-111.08, 333.99]	.00	[-.00, .00]	
Fasting time (min)	-65.42	[-291.75, 160.90]	.00	[-.00, .00]	
Fasting time squared (min^2)	17.10*	[0.23, 33.96]	.00	[-.00, .01]	
Erythrocytes (Tpt/l)	6.24**	[2.38, 10.11]	.01	[-.00, .01]	
Leukocytes (Gpt/l)	-0.08	[-0.20, 0.03]	.00	[-.00, .00]	
Thrombocytes (Gpt/l)	8.03*	[0.59, 15.47]	.00	[-.00, .01]	
HbA1c (%)					R^2 = .159** 95% CI[.12,.18]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. A significant *b*-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

* indicates p < .05. ** indicates p < .01.

Table 15: Results of the multiple linear regression model for the sample of middle adult age (41-60 years) using basal cortisol concentration (nmol/l) as the criterion

Predictor	*b*	*b* 95% CI [LL, UL]	sr^2	sr^2 95% CI [LL, UL]	Fit
Intercept	488.67**	[376.84, 600.50]			
Toronto Alexithymia Scale-20 total score	0.06	[-0.73, 0.84]	.00	[-.00, .00]	
Beck Depression Inventory- II total score	-0.26	[-1.71, 1.20]	.00	[-.00, .00]	
Sex (female)	-40.37**	[-55.41, -25.33]	.02	[.01, .04]	
Age (years)	8.41	[-5.63, 22.45]	.00	[-.00, .00]	
Education (< 10 years of schooling)	-5.17	[-21.59, 11.25]	.00	[-.00, .00]	
Education (> 10 years of schooling)	7.94	[-4.15, 20.02]	.00	[-.00, .01]	
Physical activity (active)	-75.92	[-161.87, 10.03]	.00	[-.00, .01]	
Waist-to-height ratio	0.14	[-0.39, 0.66]	.00	[-.00, .00]	
Alcohol consumption (ethanol in g/d)	24.42*	[2.29, 46.55]	.00	[-.00, .01]	
Former smoker	43.04**	[20.29, 65.78]	.01	[-.00, .02]	
Never smoker	-0.50**	[-0.59, -0.41]	.09	[.06, .12]	
Time of blood sampling (min)	56.75	[-149.10, 262.60]	.00	[-.00, .00]	
Fasting time (min)	36.25	[-166.71, 239.21]	.00	[-.00, .00]	
Fasting time squared (min^2)	9.86	[-5.02, 24.75]	.00	[-.00, .01]	
Erythrocytes (Tpt/l)	7.92**	[3.80, 12.04]	.01	[-.00, .02]	
Leukocytes (Gpt/l)	0.14*	[0.01, 0.26]	.00	[-.00, .01]	
Thrombocytes (Gpt/l)	4.83	[-2.02, 11.68]	.00	[-.00, .01]	
HbA1c (%)					R^2 = .151** 95% CI[.10,.18]

Note: b represents unstandardized regression weights. sr^2 represents the semi-partial correlation squared. *LL* and *UL* indicate the lower and upper limits of a confidence interval, respectively. A significant *b*-weight indicates the semi-partial correlation is also significant. Toronto Alexithymia Scale-20 total score, shown in bold as the predictor of interest, was already not significant before adjusting via Holm–Bonferroni method.

* indicates p < .05. ** indicates p < .01.

Table 16: Results of the multiple linear regression model for the sample of late adulthood (> 60 years) using basal cortisol concentration (nmol/l) as the criterion

Eidesstattliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe.

Die Dissertation ist bisher keiner anderen Fakultät, keiner anderen wissenschaftlichen Einrichtung vorgelegt worden.

Ich erkläre, dass ich bisher kein Promotionsverfahren erfolglos beendet habe und dass eine Aberkennung eines bereits erworbenen Doktorgrades nicht vorliegt.

Datum Unterschrift

Danksagung

Ich bin zuallererst sehr dankbar, dass nach einem langen Weg eine Situation eingetreten ist, für die ich meine unendliche Dankbarkeit in einem offiziellen Dokument niederschreiben darf.
Noch dankbarer bin ich dafür, dass es so viele liebe und unterstützende Menschen in meinem Leben gab und gibt, denen ich überhaupt danken kann und die einzeln aufgezählt viel mehr als eine Seite füllen könnten.

Zunächst danke ich Mama und Papa, ohne euch hätte es mich und meine Ausbildungslaufbahn mit allen Höhen und Tiefen nie gegeben. Ich habe euch sehr lieb!
Ich danke dir, Paul, für deine unaufgeregte, höchst geduldige und äußerst flexible Hilfe. Ich danke dir, Pascal, mein humorvolles Universalgenie, für einfach ALLES.
Ich danke dir, Leonard, für deine Liebe und alles, was sie mit sich brachte und hoffentlich noch bringen wird! Ich danke dir, Luca, für deine Statistiknachhilfe for Dummies, deine Unkompliziertheit und deinen Optimismus. Ich danke dir, Jan, für die Idee, dass ich überhaupt promovieren könnte, deine Ermutigung, deine Hartnäckigkeit und deinen Pragmatismus.
Ich danke meiner gesamten Familie und meinen Freunden, sei es für ein liebes Wort, eine liebe Geste, echtes Interesse oder eine willkommene Ablenkung. Für jegliche Affektregulation und Ermunterung. Insbesondere danke ich Oma Christine, Tante Nana, Yvonne, Christiane, Katrin, Friederike, Julia, Marion, Cordula, Christina, Eike, Marie, Heike, Magdalena, Miriam, Mia, Uta, Ulrike, Manja, Martina und so vielen mehr.
Ich danke meinen Dozenten an der Freien Universität Berlin, an der Medical School Berlin und dem Institut für Psychotherapie Potsdam. Ich danke meinen Kollegen in Bergen auf Rügen. Ich danke Dr. Jutta Theisen-Schreiber und Dr. med. Julian Laufer.

Ganz besonderer Dank geht an Johanna Klinger-König, an Prof. Dr. Hans Jörgen Grabe, an Prof. Dr. Hans-Joachim Hannich, posthum an Prof. Dr. Harald Jürgen Freyberger und an Prof. Dr. Michael Lucht, welche mich auf ganz unterschiedliche Weise beraten, korrigiert und unterstützt haben.