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Abstract

Objective: Despite the increased risk for cardiovascular morbidity associated with vital exhaustion (VE), the underlying pathophysiological mechanisms remain unclear. Allostatic load may constitute the missing link between VE and cardiovascular diseases. The aim of the present study was to investigate whether men with different degrees of VE would differ in terms of allostatic load, chronic stress, and social support.

Methods: The Men Stress 40+ study sample consisted of *N*=121 apparently healthy men aged 40 to 75 years. The following allostatic load markers were aggregated to create a cumulative index of biological stress: salivary cortisol, salivary dehydroepiandrosterone sulfate (DHEA-S), waist-to-hip-ratio, systolic and diastolic blood pressure. Long-term cortisol and DHEA were additionally measured in hair. Chronic stress and social support were assessed via validated questionnaires. Groups of mildly, substantially, and severely exhausted men were compared using one-way ANOVAs with appropriate post-hoc tests.

Results: Men who reported mild or severe levels of vital exhaustion had the highest scores on the cumulative index of biological stress. Hair cortisol was unrelated to vital exhaustion; hair DHEA was highest in men with substantial levels of exhaustion. Men with mild exhaustion reported the lowest levels of chronic stress, while men with severe exhaustion reported the lowest levels of social support.

Conclusions: Signs of allostatic load are detectable in vitally exhausted men at a stage where no major cardiovascular consequences have yet ensued.

Key words: allostatic load; cortisol; social support; stress; vital exhaustion

Introduction

Vital exhaustion (VE) is characterized by a triad of excessive fatigue and energy loss, increased irritability, and feelings of demoralization [1]. An ever-increasing body of literature suggests VE to be an independent risk factor for the development and progression of cardiovascular diseases (CVD), with two recent meta-analyses yielding relative risks for cardiovascular events between 1.50 and 2.03, depending on the population studied [2, 3].

Despite the increased risk for cardiovascular morbidity associated with VE, the pathophysiological mechanisms underlying this relationship remain under-researched. One of the most commonly shared assumptions is that alterations in major stress-responsive bodily systems contribute to this increased vulnerability [4]. This notion resonates well with the concept of allostatic load, which in a nutshell claims that chronic stress can manifest in endocrine, metabolic, immune, and cardiovascular maladjustment, and ultimately lead to disease [5, 6]. Indeed, cumulative measures of allostatic load have repeatedly been shown to be strong predictors of general morbidity and mortality; and to outperform individual biomarkers in this respect [7, 8]. Based on this research and provided individuals with VE are indeed affected by such physiological maladjustments, allostatic load may thus constitute the missing link between vital exhaustion and CVD.

However, only one study has as of yet comprehensively investigated allostatic load in individuals presenting with VE [9]. The authors found VE in female school teachers to be positively associated with scores on this cumulative measure of allostatic load, thus indicating a dose-response relationship. Interestingly and further in line with the concept of allostatic load, teachers exhibiting higher levels of allostatic load also had higher levels of effort-reward-imbalance related to their job. The latter finding aligns well with observations that chronic stress [10] and work-related stress in particular seem to be associated with both VE [11] and allostatic load, as shown by our workgroup [12]. Importantly, according to the stress

diathesis model, individuals run the risk of developing stress-related conditions only if they lack in psychosocial resources to cope with stress [13]. It is for this reason that the role of stress-buffering psychosocial resources has been highlighted by recent research [14, 15]. For instance, the perceived availability of social support has been found to protect against the pathogenic effects of stress [16], but no study looking into VE has incorporated such measures to date.

The primary aim of this study was to examine whether there is a dose-response-relationship between VE and signs of allostatic load in apparently healthy men, which are known to carry higher risks for CVD when compared to women [17, 18]. The selection of a population without any major CVD was particularly important since we aimed at measuring the extent of physiological maladjustment as a risk factor for rather than a consequence of already developed diseases. Second, and in an extension of this research question, we planned to investigate for the first time whether groups of mildly, substantially, and severely exhausted men would differ in long-term concentrations of cortisol and DHEA as measured in hair, the latter of which is known to antagonize the effects of cortisol [19, 20]. In doing so, we aimed at minimizing the influence of state variables, such as day of the week, on single time point measures as obtained in blood or saliva [21]. The third aim was to examine group differences regarding chronic stress and social support.

Methods

Participants and protocol

Data was collected within the Men Stress 40+ study, which lasted from January to September 2016. The final sample size was *N*=121. All participants were recruited among members of the general population and were currently residing in Switzerland or Germany. The study was advertised online and in newspapers as well as via leaflets that were distributed in the city of Zurich.

All individuals interested in taking part in the study first underwent an online screening. Eligible participants had to be men aged 40 to 75 who were fluent German speakers. Furthermore, they had to report significant levels of vital exhaustion, defined as scoring 4 or higher on the Maastricht Vital Exhaustion Questionnaire [22]. Exclusionary criteria were: acute or chronic physical or mental illness (self-report), intake of psychotropic medication or illegal substance use in the past two months, current hormone replacement therapy, treatment for any mental disorder in the past six months, and consuming more than two alcoholic beverages per day. All other medication was allowed but recorded.

After the screening, participants received detailed study information and answered several questionnaires (see below). Next, they were invited to a laboratory appointment at the University of Zurich, which started at 7.45 am. Before their appointment, participants were asked to abstain from caffeinate or alcoholic beverages for 48 hours, not to engage in heavy exercise for 24 hours, and to refrain from smoking, brushing their teeth, chewing gum, and eating for three hours. During the appointment, saliva and hair samples were collected first (see below for a more detailed description), followed by anthropometric and cardiovascular measures. Participants were offered a detailed feedback about their individual study results as compensation. The study protocol was approved by the Ethics Committee of the Canton of Zurich and written informed consent was obtained from all participants.

Cumulative index of biological stress

To create a cumulative index of biological stress, a number of markers were selected, which together represented both the neuroendocrine and metabolic cluster of allostatic load, as originally described in the MacArthur studies of successful aging [23]. These were: salivary cortisol, salivary dehydroepiandrosterone sulfate (DHEA-S), the waist-to-hip ratio (WHR), systolic blood pressure and diastolic blood pressure. We refrained from taking any blood samples as venepuncture procedures can artificially induce endocrine responses [24], but instead decided to collect hair samples, which were analyzed separately (see below).

The individual biomarkers were assessed as follows: during the laboratory appointment, participants were instructed to salivate into a polypropylene tube (SaliCaps, IBL, Hamburg, Germany) at 8 am by means of passive drool. All saliva samples were immediately stored at -20°C until biochemical analysis (see below). The WHR was assessed according to World Health Organization guidelines [25]. Participants were asked to stand upright and breathe normally. A stretch-resistant measuring tape was used, which provided a constant tension of 100g. Waist circumference (in cm) was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference (in cm) was measured at the widest point of the buttocks. Systolic and diastolic blood pressure were measured twice via arm cuffs after a resting phase of about 10 min. The first measurement was taken in a supine position and the second measurement was taken in a sitting position. Only the second measurement was used for the present analyses in order to reduce any white coat effects.

For each biomarker and subject and in accordance with the procedures outlined in the MacArthur studies [23], it was subsequently determined whether values fell into the high-risk quartile of the whole sample. For WHR, systolic and diastolic blood pressure, the highest quartile was coded as “1”. Salivary DHEA-S was coded as “1” whenever concentrations were

in the lowest quartile of the sample. Since it is still unclear whether vital exhaustion is associated with elevated or attenuated cortisol levels, both individuals pertaining to the lowest and the highest 12.5% obtained as score of "1" – again, in accordance with previous recommendations [see 9]. All other values were rated as "0". Individual scores were then aggregated to create a cumulative index of biological stress, with possible scores ranging from 0 to 5.

Hair measures

Three hair strands of 2 cm length were taken from the posterior vertex of all consenting participants with enough hair to measure cortisol and DHEA concentrations over the past two months [26]. The root end was marked and all samples stored in aluminum foil at room temperature and away from daylight before they were shipped to the biochemical laboratory (see below).

Psychological measures

Vital exhaustion was measured using the short form of the German Maastricht Vital Exhaustion Questionnaire [MVEQ; 27, 28]. It consists of nine items that are rated as either "no", "don't know", or "yes", with corresponding scores of 0 to 2. An example item is "Do you often feel tired?". Possible scores ranged from 0 to 18. Three groups were built reflecting different degrees of VE. The classification scheme was: 4-10=mild VE, 11-14=substantial VE, and 15-18=severe VE [29]. Additionally, we asked participants to indicate the duration of their exhaustion in weeks.

Perceived chronic stress was assessed via the Screening Scale of the short version of the Trier Inventory for the Assessment of Chronic Stress [TICS-2-K; 30]. Participants reported how frequently they experienced stress in the past three months using 6 items. An example item is: "times during which I had to fulfil too many responsibilities", with an

answering format ranging from "never" (score of 0) to "very often" (score of 4) and resulting in a total score between 0 and 24.

A subscale of the Berlin Social Support Scales [BSSS; 31] was administered to determine the amount of *perceived social support*. Participants answered eight items, which were then averaged to build a total score. An exemplary item is "There is always someone there for me when I need to be comforted". The answering format ranged from "strongly disagree" (score of 1) to "strongly agree" (score of 4).

Biochemical analyses

Salivary cortisol and DHEA-S were analyzed at the biochemical laboratory of the Institute of Psychology (University of Zurich) using luminescence immunoassays (IBL, Hamburg, Germany). Inter- and intra-assay variance was below 10%. Hair cortisol and DHEA were processed at the biochemical laboratory of the Technical University of Dresden as described in Kirschbaum, Tietze, Skoluda and Dettenborn [32] and analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Statistical analyses

Statistical analyses were performed using SPSS (version 23). Due to the fact that salivary DHEA-S, hair cortisol, and hair DHEA were not normally distributed as indicated by the Kolmogorov-Smirnov test, these parameters were log-transformed for statistical analyses. Unless otherwise specified, results are given as mean ± standard deviation. For all analyses including salivary markers, we excluded 30 participants because they reported gum bleeding (n=11), injuries in the mouth cavity (n=5), or having had a cold in the last two weeks (n=14). The sample size for these analyses was thus n=91. For appropriate analysis of DHEA and

cortisol concentrations in hair, the hair strands had to be at least 2cm long. Hair samples of n=96 participants fulfilled this criterion.

Groups of mildly, substantially, and severely exhausted individuals were first compared in terms of socio-demographic variables, lifestyle variables, and duration of VE, using the Kruskal-Wallis and Fisher's exact test, respectively. Groups of mildly, substantially, and severely exhausted individuals were subsequently compared regarding individual allostatic load markers, the cumulative index of biological stress, hair parameters (cortisol and DHEA), and psychological measures (perceived chronic stress and social support), using one-way ANOVAs with appropriate post-hoc tests. Second, associations between the psychobiological measures and VE were examined using regression analyses, exploring both linear as well as nonlinear associations. Third, the cumulative index of biological stress, perceived chronic stress, and social support were included in a multiple regression model. Age and BMI were controlled for in all analyses. Whenever salivary measures were used in the analysis, awakening time was included as an additional covariate. With regard to hair cortisol, the season that was mainly reflected in the hair sample was added as a covariate [33]. The statistical significance level was set at α=.05.

Results

Sample characteristics

Participants were classified into three different groups based on the extent of their VE: mild (n=48), substantial (n=54), and severe (n=19). As evident from Table 1, the three groups did not differ regarding socio-demographic variables, lifestyle variables, or duration of VE.

Table 1. Participant characteristics (*N*=121); data are presented as median and interquartile range or absolute and relative frequencies; men with mild (*n*=48), substantial (*n*=54), and severe exhaustion (*n*=19) were compared using the Kruskal-Wallis and Fisher's exact test, respectively.

	Descriptive	X^2 statistic	*p* value
Age (years)	51 (13)	0.487	0.784
Body Mass Index	25.17 (4.74)	3.797	0.150
Educational attainment		2.800	0.853
Vocational training	35 (28.9%)		
High school degree	20 (16.5%)		
College/university degree	55 (45.5%)		
Other	11 (9.1%)		
Employment status		6.454	0.893
Unemployed	2 (1.7%)		
Up to 60% employed	2 (1.6%)		
61-80% employed	9 (7.4%)		
81-100% employed	95 (78.5%)		
Retired	13 (10.7%)		
Annual income (Swiss Francs)	117'000 (54'500)	0.436	0.804
Relationship status		9.140	0.274
Not in a relationship	8 (6.6%)		
In a relationship	24 (19.8%)		
Married	89 (73.5%)		

Smoking		3.716	0.158
No	107 (88.4%)		
Yes	14 (11.6%)		
Physical Activity (hours/week)*			
Mild	3 (3)	0.887	0.642
Moderate	3 (3)	2.519	0.284
Intense	1 (3)	2.737	0.255
Duration of vital exhaustion (weeks)	30.00 (88)	3.567	0.168

Note. *Assessment of physical activity: mild: "how many hours per week do you engage in low-intensity activities, such as walking or stretching exercises?"; moderate: "how many hours per week do you engage in medium-intensity activities that still enable you to carry on a conversation, such as housekeeping or fast walking?"; intense: "how many hours per week do you engage in high-intensity activities that make you sweat, such as tennis or running?"

Cumulative index of biological stress

The three groups did not differ in terms of individual allostatic load markers: cortisol (p=.63), DHEA-S (p=.53), WHR (p=.35), systolic blood pressure (p=.14), and diastolic blood pressure (p=.47). Table 2 presents their distribution and the cut-off values used to obtain a cumulative index of biological stress. The scores ranged from 0 to 4 with a mean of 1.51±1.10 (maximum score of 5).

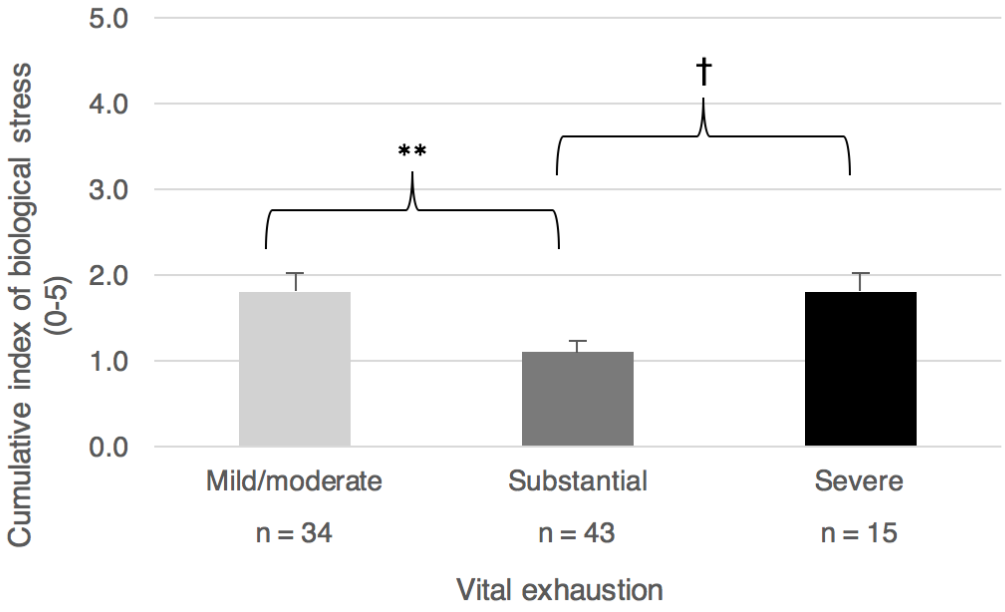
Table 2. Distribution of allostatic load parameters and cut-off values (*N*=91). Data are presented as mean ± standard deviation (normally distributed variables) or median and interquartile range (non-normally distributed variables).

	Central tendency	Range	Cut-off*
Salivary Cortisol (nmol/l)	7.63±3.88	1.49-21.83	<3.35, >11.71
Salivary DHEA-S (pg/ml)	1.74 (1.28)	0.53-5.87	<0.16
Waist-to-hip ratio	0.96±0.06	0.81-1.14	>0.97
Systolic blood pressure (mmHg)	135.78±14.09	108-178	>143
Diastolic blood pressure (mmHg)	89.33±10.22	69-119	>95

Note. *For cortisol: extreme scores on either end of the continuum were considered indicative of allostatic load (within the highest and lowest 12.5%). For DHEA-S: low values (within the lowest quartile of log-transformed values). For waist-to-hip ratio, systolic and diastolic blood pressure: high values (within the highest quartile).

A one-way ANOVA indicated significant differences in the biological stress index across the three groups of mildly, substantially, and severely exhausted individuals (F (2, 83)=5.324, p=0.007, partial eta^2=0.114). A post-hoc Bonferroni test revealed that men with substantial levels of VE had the lowest scores; they scored significantly lower when compared to men with mild VE (M=1.10±0.93 vs. M=1.88±1.23, p=0.005) and marginally lower when compared to men with severe VE (M=1.10±0.93 vs. M=1.80±0.86, p=0.081). By contrast, the mild group did not differ significantly from the severe group (p=0.99). All group comparisons regarding the index are depicted in Figure 1.

Figure 1. Mean cumulative index of biological stress (±standard error of mean) in men with mild, substantial, and severe vital exhaustion (*N*=91).



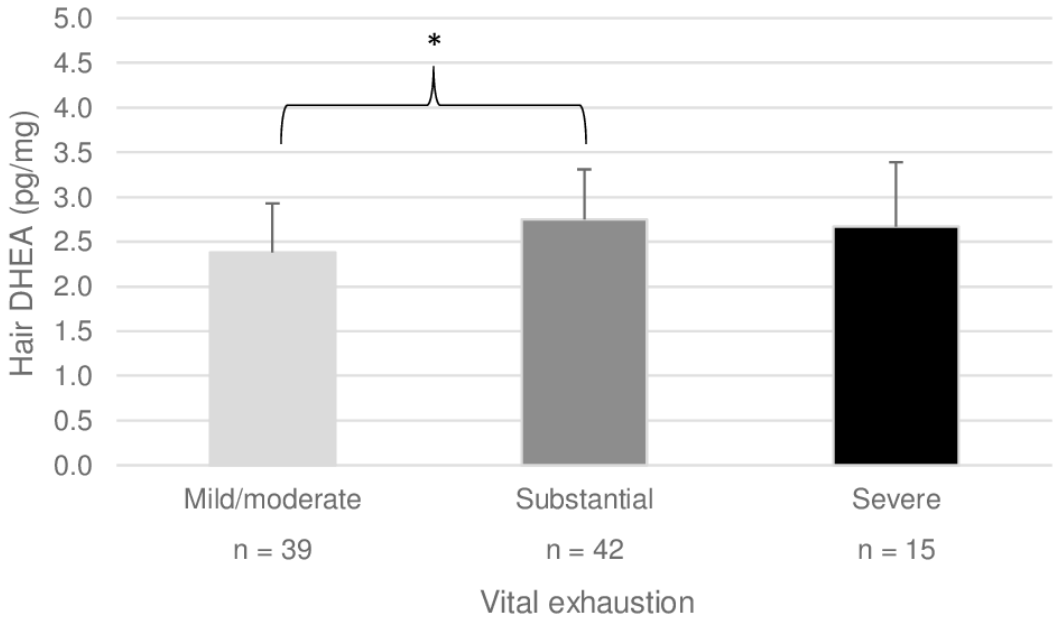
Note. Vital exhaustion was assessed by the Maastricht Vital Exhaustion Questionnaire (MVEQ). Three different groups were created based on the extent of vital exhaustion: 4-10=mild, 11-14=substantial, 15-18= severe. The individual biomarkers were: salivary cortisol, salivary DHEA-S, waist-to-hip ratio, systolic and diastolic blood pressure. Significance levels: † $p<0.10$, ** $p<.01$.

Linear regression did not reveal a significant relationship between VE and the cumulative index of biological stress (β=-0.113, p=0.28, adj. R^2=0.114). However, mirroring what was revealed in the group comparisons, a quadratic relationship between the two variables emerged in that individuals on both ends of the VE spectrum were more likely to have a high score on the biological stress index (β=1.196, p=0.022, adj. R^2=0.158).

Hair cortisol and DHEA

There were no significant differences between the three exhaustion groups regarding hair cortisol (F (2, 91)=0.119, p=0.89, partial eta^2=0.003). By contrast, the mean scores for hair DHEA differed marginally between the three groups (F (2, 91)=2.537, p=0.085, partial eta^2=0.053). Post hoc comparisons using the Games-Howell test revealed that men with substantial VE had significantly higher levels of hair DHEA compared to men with mild VE (M=2.75±0.71 vs. M=2.38±0.61, p=0.038). No significant differences between men with substantial and severe VE emerged (M=2.75±0.71 vs. M=2.67±0.98, p=0.96), nor were there any differences in DHEA between men with mild and severe VE (M=2.38±0.61 vs. M=2.67±0.98, p=0.55). Group comparisons regarding hair DHEA are illustrated in Figure 2.

Figure 2. Mean hair DHEA (±standard error of mean) in men with mild, substantial, and severe vital exhaustion (N=96).

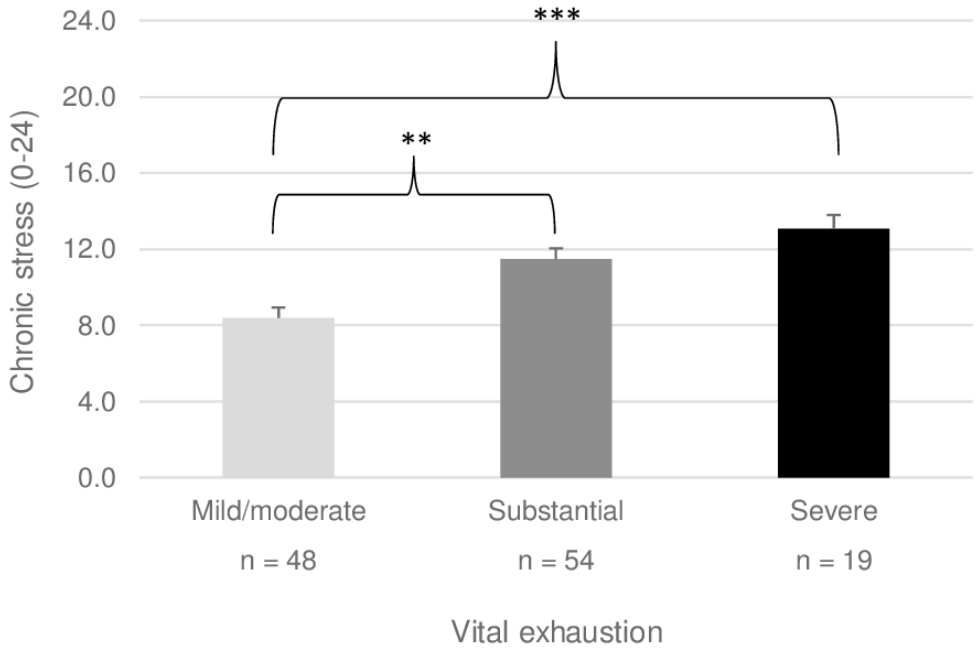


Note. Vital exhaustion was assessed by the Maastricht Vital Exhaustion Questionnaire (MVEQ). Three different groups were created based on the extent of vital exhaustion: 4-10=mild, 11-14=substantial, 15-18= severe. Significance level: * p<.05.

Chronic stress

Significant differences emerged when comparing the mild, substantial, and severe VE groups in terms of chronic stress (F (2, 116)=9.495, p=0.001, partial eta^2=0.141). As shown in Figure 3, men with mild levels of VE had significantly lower levels of chronic stress compared to men reporting substantial VE (M=8.79±3.78 vs. M=11.48±4.10, p=0.002) and men reporting severe VE (M=8.79±3.78 vs. M=12.79±3.16, p=0.001) using post hoc Bonferroni comparisons. No significant differences were apparent when contrasting the substantial and the severe VE group (p=0.61).

Figure 3. Mean perceived chronic stress scores (±standard error of mean) in men with mild, substantial, and severe vital exhaustion (N=121).



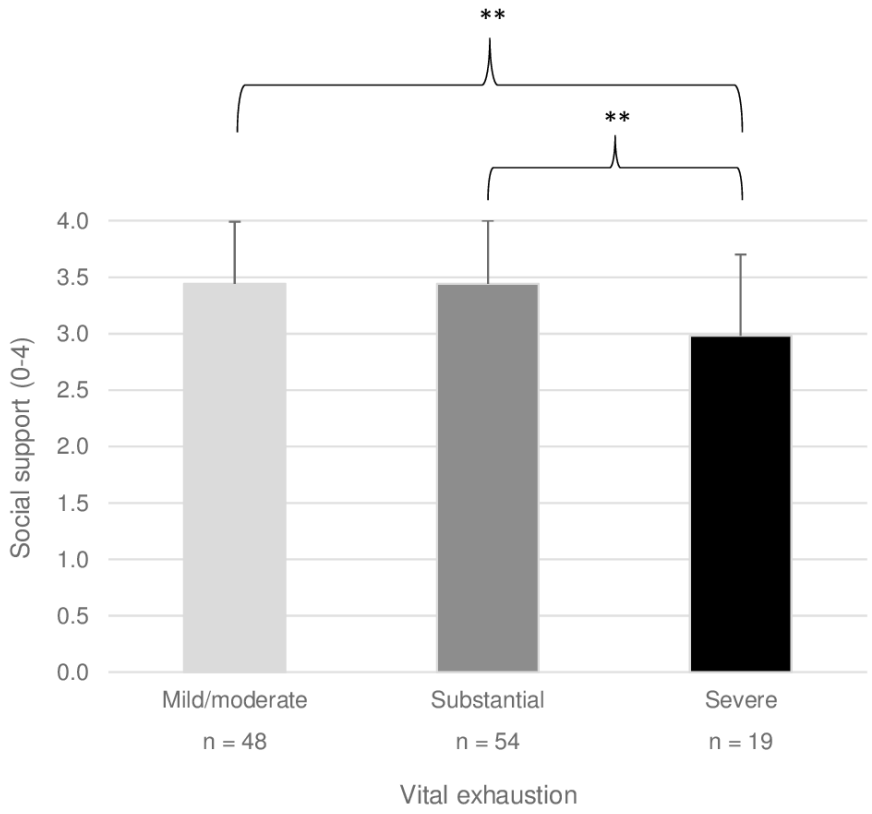
Note. Vital exhaustion was assessed by the Maastricht Vital Exhaustion Questionnaire (MVEQ). Three different groups were created based on the extent of vital exhaustion: 4-10=mild, 11-14=substantial, 15-18= severe. Chronic stress was measured by the Screening Scale of the short version of the Trier Inventory for the Assessment of Chronic Stress (TICS-2-K). Significance levels: ** p<.01, *** p<.001.

Linear regression revealed a significant relationship between chronic stress and VE (β=0.383, p=0.001, adj. R^2=0.156).

Perceived social support

When the three groups reflecting different degrees of VE were compared with respect to social support, significant differences were detected (F (2, 116)=5.323, p=0.006, partial eta^2=0.084). Post hoc comparisons using the Bonferroni test revealed that men with severe levels of VE felt significantly less socially supported compared to men with substantial levels of VE (M=2.98±0.64 vs. M=3.44±0.49, p=0.005) and men with mild levels of VE (M=2.98±0.64 vs. M=3.44±0.51, p=0.005). No significant differences appeared between the groups with mild and substantial levels of VE (p=0.99). Group comparisons regarding perceived social support are illustrated in Figure 4.

Figure 4. Mean perceived social support scores (±standard error of mean) in men with mild, substantial, and severe vital exhaustion (*N*=121).



Note. Vital exhaustion was assessed by the Maastricht Vital Exhaustion Questionnaire (MVEQ). Three different groups were created based on the extent of vital exhaustion: 4-10=mild, 11-14=substantial, 15-18= severe. Perceived social support was measured by the Berlin Social Support Scales (BSSS). Significance level: ** $p<.01$.

Linear regression showed a significant relationship between social support and VE (β=-0.196, p=0.032, adj. R^2=0.049).

Total model: cumulative index of biological stress, chronic stress, and social support

When including the cumulative index of biological stress, perceived chronic stress, and perceived social support into one multiple regression model, perceived chronic stress remained the only significant predictor of VE (β=0.28, p=.016; see Table 3).

Table 3. Multiple regression model including the cumulative index of biological stress, perceived chronic stress, perceived social support, and covariates as predictors of vital exhaustion (n=89)

	β	R^2	R^2 adj.
		0.25***	0.19
Age	0.04		
BMI	0.08		
Awakening time	0.15		
Cumulative index	0.37		
Cumulative index (quadratic term)	-0.48		
Chronic stress	0.28*		
Social support	-0.16		

*p<.05, ***p<.001

Discussion

The aim of the present study was to determine the extent of allostatic load as present in men with different degrees of VE, and to investigate the role of chronic stress and social support. We report three main findings: First, men at the lowest and highest end of the VE spectrum had the highest scores on a cumulative index of biological stress. Second, hair cortisol was unrelated to VE, but hair DHEA was highest in men with medium levels of exhaustion. Third, men with mild exhaustion seemed least affected by chronic stress, while men with severe exhaustion reported the lowest levels of social support.

Our first finding of a U-shaped relationship between VE and a biological stress index is in partial agreement with what was found in one earlier study on this topic. In their sample of female teachers, Bellingrath, Weigl and Kudielka [9] observed higher degrees of allostatic load in women high in exhaustion versus those low in exhaustion. Notably, these authors divided participants in two rather than three groups. In doing so, they amalgamated what in the present study constituted two separate groups of substantially and severely exhausted individuals, respectively. This could mean that we were able to reveal a more nuanced picture of how allostatic load relates to VE when adhering to the originally suggested classification. Alternatively, the discrepancies between the two studies can be explained by the fact that Bellingrath, Weigl and Kudielka [9] used a more extensive measure of allostatic load, which on top of the endocrine, anthropometric and cardiovascular markers used here also included metabolic and immune parameters. Finally, it could be assumed that VE is differentially linked to allostatic load in men versus women, but seeing that both studies were confined to one sex, this remains speculative.

Our second finding is novel in that no previous study has looked into hair parameters in individuals suffering from VE, despite the increasing popularity of such measures in research on stress and stress-related disorders [34]. Our null-finding in terms of hair cortisol is

reflective of what is so far a small and rather inconsistent body of literature [35-37]. More specifically, studies finding a hypocortisolemic pattern in VE individuals did so only at specific time points during the day or in response to acute stress, which may indicate that HPA abnormalities in VE are dynamic rather than global. Both hyper- and hypoactivity of the HPA-axis have been associated with other stress-related conditions. For instance, a hypocortisolemic pattern has been detected in fatigue syndromes [38, 39]. Interestingly, Penz and colleagues [40], using hair sampling, recently reported hypercortisolism in individuals suffering from burnout. As VE occurs when personal resources needed for the adaptation to stress are exhausted, VE may be regarded as a consequence of both long-term stress and burnout [36]. Given that HPA axis activity has been found elevated at stressor onset, but decreasing as stress persists [41], the differences between burnout and VE may thus be attributable to these syndromes reflecting different stages of the stress adaptation process. Our finding of comparably elevated hair DHEA in men with substantial levels of exhaustion (medium category) somewhat parallels what we found in terms of the biological stress index, namely that this group seems to exhibit the most adaptive biological profile. Seeing that this is one of the first studies ever using hair DHEA and in VE subjects, this finding must be regarded as preliminary and warrants independent replication.

Our third finding extends the study by Falger and Schouten [11] in that not only were subjects with mild levels of VE least affected by work-related stress, but also by less social stress and worrying, as indicated by lower scores on the multidimensional measure of chronic stress used in this study. This echoes the clinical observations of Appels and Mulder [1], who coined the term VE and described it as a general state of demoralization resulting from a sense of loss and feelings of dejection and defeat. Adding to this, we were able to show for the first time that men with severe levels of exhaustion felt the least supported by their social environment. Such findings are important in that they point out potential targets for

prevention. The relevance of social support in particular is highlighted by prospective evidence showing that social isolation predicted incident heart failure in members of the general US population via increased VE [42].

When taken together, our findings reveal complex biopsychosocial patterns across the three studied groups: mildly exhausted men were characterized by comparably low stress, high social support, and high allostatic load; substantially exhausted men were comparably high in both stress and support, and low in allostatic load; and finally, severely exhausted men were comparably high in stress, low in support, and high in allostatic load. Importantly, these findings were independent of the duration of exhaustion, meaning that severity does not reflect different stages of the syndrome. The finding that mildly exhausted men presented with similar physiological maladjustments as severely exhausted men despite reporting relatively low levels of stress and high levels of support is contrary to our a priori hypothesis. However, this dissociation between biological and psychological measures of stress bears resemblance to what is frequently observed in experimental studies designed to evoke an acute stress response in healthy subjects [43]. The most likely explanation for this phenomenon is that individuals differ in their ability to detect and report both signs of stress and distress. In the present context, it is conceivable that traits like alexithymia or interoceptive sensitivity [44] may account for this biopsychological discordance in mildly exhausted men, but given the dearth of research in this area, this remains an open question. Another plausible explanation are positive illusions, defined as systematic tendencies either to adopt and maintain excessively optimistic beliefs or to make overly optimistic anticipations about the self [45]. Due to these positive illusions, mildly exhausted men might have under-reported chronic stress and over-reported social support, but again, this is speculation only. By contrast, the finding that severely exhausted individuals had more signs of allostatic load than substantially exhausted individuals and that the two groups differed in the amount of

perceived social support is in line with the notion of a stress-buffering effect of social support [46, 47]. Notably, causality cannot be inferred given the cross-sectional design of the present study.

Our study presents with a number of strengths. First, it adds to the sparse literature on allostatic load and VE in being the first study conducted in men and the first to simultaneously include measures of stress and psychosocial resources. In a similar vein, it is the first study to use hair sampling, which offers a number of advantages when compared to conventional specimen to determine biomarkers (e.g., by being economical, non-invasive, and free of state-like confounders). Second, we used a sample that was devoid of any major illnesses and medication that could have influenced the biological parameters. Third, we are able to rule out that our finding of more marked physiological maladjustments in severely exhausted individuals is merely attributable to low levels of physical fitness [48]. This is crucial in research into fatigue syndromes, which are often known to cause physiological deconditioning due to general social withdrawal and avoidance of physical exertion [49]. A number of limitations equally deserve mentioning. First, even though we recruited from the general Swiss population, our final sample was composed of men with a high socioeconomic status. This needs to be kept in mind when comparing our results to those obtained in other countries. Second, the lack of a non-exhausted control group prevents us from determining exactly how "abnormal" the here reported biopsychosocial patterns are. Third, we used a rather economical measure of allostatic load, comprising only five parameters, which together reflected the neuroendocrine and metabolic cluster of allostatic load. This being said, the allostatic load concept has been operationalized in numerous ways in the past, both in terms of selected biomarkers and in terms of length [47, 48], and prior research found allostatic load indices of different length equally powerful in distinguishing groups of women with low vs. high VE [9]. Most interestingly, in the latter study, adding immune parameters to the

summary score did not significantly alter results. Thus, despite the existence of other important mediators of allostasis, such as the immune system [50, 51], it seems that the use of a more economical index of allostatic load may be justified in VE. Nevertheless, longitudinal research investigating the predictive power of different operationalizations of allostatic load in terms of incident CVD is clearly warranted.

In conclusion, the present study shows that signs of allostatic load are detectable in vitally exhausted men at a stage where no major cardiovascular or metabolic consequences have yet ensued. Contrary to our expectations, we found the relationship between exhaustion and our cumulative measure of biological stress to be non-linear, with both men at the lower and higher end of exhaustion exhibiting the most maladaptive profiles. Further research is needed to unravel the mechanisms underlying this observation. In this context, it will be of particular interest to investigate which specific types of stressors and coping strategies have an effect on VE, and how these may change over the course of the lifespan. Moreover, given the high propensity of the same individuals towards developing CVD and metabolic diseases, future studies into VE should continue to incorporate measures of psychosocial resources. Only by identifying factors that protect against the impact of chronic stress can research pave the way towards the prevention of the VE syndrome. This seems all the more important when considering that psychological interventions in populations with fully developed CVD have only been moderately successful so far [52, 53].

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Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Highlights

- This study found a u-shaped relationship between vital exhaustion (VE) and biological stress
- Apparently healthy men with mild and severe VE had the highest biological stress scores
- Mildly exhausted men were least affected by chronic stress
- Men with severe VE reported the lowest levels of social support