Accepted Manuscript

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PII: S0306-4530(19)30348-8
DOI: https://doi.org/10.1016/j.psyneuen.2019.104384
Article Number: 104384

Reference: PNEC 104384

To appear in:

Received date: 12 April 2019
Revised date: 11 July 2019
Accepted date: 17 July 2019

Please cite this article as: Jahangard L, Hedayati M, Abbasalipourkabir R, Haghighi M, Ahmadpanah M, Faryadres M, Mikoteit T, Sadeghi Bahmani D, Brand S, Omega-3-polyunsatured fatty acids (O3PUFAs), compared to placebo, reduced symptoms of occupational burnout and lowered morning cortisol secretion, *Psychoneuroendocrinology* (2019), https://doi.org/10.1016/j.psyneuen.2019.104384

Omega-3-polyunsatured fatty acids (O3PUFAs), compared to placebo, reduced symptoms of occupational burnout and **lowered** morning cortisol secretion

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HIGHLIGHTS

- ~~**The influence of omega-3-polyunsaturated fatty acids on symptoms of burnout and cortisol awakening response levels are unknown**~~
- After eight weeks, nurses with burnout improved in burnout scores in the omega-3-polyunsaturated fatty acids condition, but not in the placebo condition

- **Cortisol awakening response levels decreased over time, but more so in the Omega-3-polyunsaturated fatty acids condition, compared to the placebo condition**
- Older age and longer work experience were associated with higher burnout scores, but not with higher cortisol awakening response levels
- Burnout scores and cortisol awakening response levels were unrelated

Abstract

Background: Occupational burnout is both a serious health concern at both public and individual levels. Treatment options are psychopharmacological, psychological and physical activity-related interventions. Here, we tested whether, compared to placebo, omega-3-polyunsaturated fatty acids (O3PUFAs) have a positive impact on burnout and morning cortisol secretion.

Method: A total of 43 individuals (mean age: 38.4 years, 76.7% females) took part in the present double-blind and placebo-controlled intervention. Participants were randomly assigned either to the O3PUFA or to the placebo condition. At baseline and again eight weeks later, participants completed the Maslach Burnout Inventory and collected morning saliva samples for analysis of the cortisol awakening response (CAR).

Results: Emotional exhaustion and depersonalization decreased, and sense of personal accomplishment increased over time, but more so in the O3PUFA condition than in the placebo condition. Likewise, CAR decreased over time, but again more so in the O3PUFA condition than in the placebo condition. Conclusions: The present pattern of results suggests that, compared to placebo, administration of daily omega-3-polyunsaturated fatty acids for eight consecutive weeks positively influences both psychological and physiological markers of occupational burnout.

Key words: Burnout; saliva cortisol; omega-3-polyunsaturated fatty acids; cortisol awakening response

1. Introduction

Burnout describes the cognitive-emotional and behavioral state of emotional exhaustion, depersonalization and lack of personal accomplishment as a result of a long lasting imbalance between the demands of performing and accomplishing tasks (at work) and the personal resources to cope with these demands (Maslach & Jackson, 1981). Following Maslach and Jackson (1981), emotional exhaustion is defined as lack of emotional and physical energy as a continuous and enduring state after a few hours of work, along with symptoms of anxiety, frustration, and continual tiredness in the evenings and weekends. Depersonalization (lack of empathy; cynicism) reflects unfavorable negative and unempathic attitude towards the social environment, and more specifically towards customers, patients, students, peers and colleagues at work. Lack of personal accomplishment reflects feelings of low quality and quantity of (workplace-related) performance (Brand & Holsboer-Trachsler, 2010). Importantly, the feelings of emotional exhaustion, depersonalization and lack of personal accomplishment are gradual and emerge slowly over time; subtle changes are involved which makes them difficult to recognize.

While there is broad consensus that people with burnout are in distress and need medical treatment and psychological help, the debate remains ongoing as to whether burnout should be considered a specific and well-defined psychiatric disorder or instead an epiphenomenon of a major depressive disorder (ICD-10: F33.xx), an adjustment disorder (ICD-10: F43.xx) (Bianchi et al., 2013; Bianchi et al., 2017a, b, c; Bianchi et al., 2016; Laurent et al., 2017), or a chronic fatigue syndrome (ICD-10: G93.3). Not surprising, there are no established diagnostic criteria (Weber & Jaekel-Reinhard, 2000), and in the Classification of Diseases (ICD 10), "burnout" is listed under Z.73.0 as "Burnout – state of total exhaustion". Thus, from a psychiatric point of view, individuals with burnout display traits very similar to those with chronic fatigue syndrome or major depressive disorder. As regards the association between burnout and biomarkers Danhof-Pont et al. (2011), in their systematic review of 31

studies, noted 38 different biomarkers had been assessed focusing variously on the hypothalamus-pituitary-adrenal axis, the autonomic nervous system, the immune system, metabolic processes, antioxidant defense, hormones, and sleep. Accordingly, given the heterogeneity of outcome variables, together with methodological differences in defining and operationalizing symptoms of burnout, it is not surprising that no clear pattern of association between biomarkers and burnout has yet been established. Furthermore, Traunmüller et al. (2019) investigated middle-aged adults at either low or high risk of burnout and concluded that burnout might not necessarily involve physiological disturbances.

A principal outcome variable in the research on major depressive disorders and its treatment is the dynamic of the hypothalamus-pituitary-adrenocortical (HPA) axis activity (HPA AA). Briefly, research has indicated that individuals with major depressive disorders show increased HPA AA, as operationalized in terms of elevated cortisol concentrations (Hatzinger, 2000; Hatzinger et al., 2002; Holsboer & Ising, 2010; Miller et al., 2007). However, as regards the association between burnout and HPA AA/cortisol secretion, results are conflicting. While Chida and Steptoe (2009) concluded from their systematic review and meta-analysis that higher cortisol awakening response (CAR) levels were positively associated with (acute) job and general life stress, the opposite was observed for fatigue, burnout and exhaustion; the lower the cortisol levels, the higher the scores for fatigue, burnout, and exhaustion. Mommersteeg et al. (2006) compared the CAR levels of 22 individuals with clinical burnout and those of 21 healthy controls and observed significantly lower CARs in the former group. However, Danhof-Pont et al. (2011) reported in their systematic review that there were no significant differences between the CARs of participants respectively with and without burnout. In contrast, Menke et al. (2014) showed among a small sample of males with burnout that at baseline plasma cortisol levels were higher than those of healthy controls, and that eight weeks after a thorough intervention involving a program of exercise, plasma cortisol

levels had reduced to the level of healthy controls. Likewise, Traunmuller et al. (2019) observed higher CARs in middle-aged individuals with burnout than in comparable individuals without burnout.

To summarize, it appears that no consistent pattern has so far been observed between HPA AA/cortisol secretion and symptoms of burnout. Accordingly, to shed more light on this issue, the first aim of the present study was to investigate the CARs of individuals with burnout both at baseline and after an intervention involving medication with omega-3-polyunsaturated fatty acids (O3PUFAs), and compared to a placebo condition.

To our knowledge, no systematic and evidence-based algorithms have as yet been established or the treatment of burnout. West et al. (2016), in their systematic review of the treatment of burnout among physicians, noted that among the various interventions applied were the following: structural interventions in the work environment, such as reducing the length of attending rotations, modifications to clinical work processes, and shortened resident shifts; individual-focused interventions such as small group curricula, stress management and self-care training, communication skills training, and mindfulness-based approaches (see West et al., 2016 for a thorough overview).

Face validity suggests that regular exercising also has the potential to reduce symptoms of burnout. However, although Gerber et al. (2013) showed that a 12-week program of exercise improved symptoms of burnout, Ochentel et al. (2018), in their systematic review and meta-analysis, concluded that the evidence did not support the argument that exercise therapy could be a successful way of alleviating burnout symptoms.

As regards medication, again there appear to be no currently available evidence-based treatment algorithms. Given the large overlap between symptoms of burnout and those of major depressive disorders, the most likely result is that residents and psychiatrists follow the established guidelines for treating symptoms of depression (Bauer et al., 2013), or else

prescribe phytopharmacological products such as hypericum perforatum (St. John's Wort (Apaydin et al., 2016)). Surprisingly and to the best of our knowledge, the use of omega-3-polyunsaturated fatty acids (O3PUFAs) has not yet been investigated as a treatment for burnout.

As regards the administration of O3PUFAs, as extensively reported elsewhere (Jahangard et al., 2018), numerous meta-analyses and systematic reviews indicate that administration of O3PUFAs has a positive impact on major depressive disorders (Appleton et al., 2016; Berger et al., 2017; Deacon et al., 2017; Jahangard et al., 2018; Messamore et al., 2017; Pompili et al., 2017; Thesing et al., 2018), on anxiety (Buydens-Branchey et al., 2008; Thesing et al., 2018; Wilson and Madrigal, 2017), and on sleep-related problems (Christian et al., 2016; Schneider et al., 2018). One line of research that has sought to explain the influence of O3PUFAs on major depressive disorders has focused on the HPA AA. Jazayeri et al. (2010) showed that, in patients with major depression disorder, O3PUFAs alone or in combination with fluoxetine (as well as fluoxetine alone) decreased serum cortisol after eight weeks of treatment. Likewise, Komori (2015) treated 18 individuals suffering late life depression with both phosphatidylserine and supplements containing O3PUFAs. This author observed that the basal levels and circadian rhythm of salivary cortisol were normalized among responders, as compared to non-responders, and concluded that the combination of phosphatidylserine and omega-3 fatty acids appeared to be effective for late life depression, and that such improvements are associated with the correction of basal levels and circadian rhythm of salivary cortisol.

As regards the intake of O3PUFAs on symptoms of burnout, a literature review on pubmed® yielded only one study; Watanabe et al. (2018) investigated the influence of O3PUFAs on the mental state of 80 junior nurses who were randomly assigned either to the O3PUFA or to a placebo condition. One year after baseline, expert raters, blind to participants'

study allocation, assigned significantly lower scores for symptoms of depression and anxiety to participants in the O3PUFA condition than to participants in the placebo condition. However, there were no significant mean differences in self-reported burnout symptoms between the two study conditions, where these were assessed with the Maslach Burnout Inventory (Maslach & Jackson, 1981). Likewise, no significant mean differences were observed for workplace absenteeism, insomnia or generalized anxiety disorder. One reason why Watanabe et al. (2018) failed to find significant mean differences between the O3PUFA and the placebo condition might be that all participants had generally very low depression scores. In other words, the participants were mentally healthy and floor effects might best account for the zero-results ("You cannot fix what is not broken"). A second aim of the present study was therefore to fill a gap in our knowledge by investigating the influence of O3PUFAs on symptoms of burnout compared to placebo.

The following two hypotheses were formulated. First, following studies on major depressive disorders (Appleton et al., 2016; Berger et al., 2017; Deacon et al., 2017; Jahangard et al., 2018; Messamore et al., 2017; Pompili et al., 2017; Thesing et al., 2018), we anticipated that, compared to placebo, O3PUFAs would reduce self-rated symptoms of burnout. Second, following Jazayeri et al. (2010) and Komori (2015), we expected that, compared to placebo, O3PUFAs would **reduce** the CAR.

2. Methods

2.1. Procedure

The study was performed at the Hamadan University of Medical Sciences Hospital (HUMS, Hamadan, Iran). Advertisements were posted on pin-boards of recreation rooms and on the main page of the intranet. Male and female nurses self-reporting signs of workplace-

related exhaustion were asked to contact the principal investigators (LJ, MH, MH, MA). Eligible participants were fully informed about the study aims and the confidential and anonymous data handling. Thereafter, participants signed a written informed consent. They completed questionnaires on sociodemographic information and on burnout and collected morning saliva samples following the standardized procedure (see below). Next, they were randomly assigned either to the O3PUFA condition or to the placebo condition (see Figure 1; CONSORT diagram). Eight weeks later, morning saliva samples were again collected, and the burnout questionnaire was again completed. The ethical committee of the Hamadan University of Medical Sciences (HUMS, Hamadan, Iran; ethical committee code = IR.UMSHA.REC.1397.1; registration code of the Hamadan University: 9704051848; registration at the Iranian Registry of Clinical Trials; www.irct.ir: IRCT20090304001743N14) approved the study, which was performed in accordance with the ethical principles laid down in the seventh and current edition (2013) of the Declaration of Helsinki.

2.2. Sample

Initially, 68 male and female nurses with self-reported signs of workplace-related exhaustion were approached. Of these, 50 (73.5%) fulfilled the inclusion and exclusion criteria, and a total of 43 (63.2%) agreed to participate (see Figure 1). Inclusion criteria were as follows: 1. Age between 18 and 65 years; 2. Male or female nurses employed at the local hospital and working full time for at least the last five years; 3. Suffering from burnout, as ascertained as follows: a) as in a previous study (Gerber et al., 2013; Menke et al., 2014) the score on the dimension “Emotional exhaustion” (Maslach Burnout Inventory; (Maslach & Jackson, 1981) was 27 or higher, and the score on the dimension “Depersonalization” was 10 or higher; b) an experienced psychiatrist or clinical psychologist performed a thorough psychiatric interview (Sheehan et al., 1998) to assess participants’ psychiatric status and to further clarify

participants' answers on the Maslach Burnout Inventory; 4. Able to comply with the study conditions; 5. Stable day shifts for four weeks before entering the study and throughout the whole study period. 6. Signed written informed consent. Exclusion criteria were: 1. The thorough psychiatric interview based on the Mini International Neuropsychiatric Interview for ICD-10 diagnoses (MINI (Sheehan et al., 1998) indicated that symptoms of work-related exhaustion could be better defined as major depressive disorders or adjustment disorder. 2. Presence of other psychiatric comorbidities such as substance use disorder, post-traumatic stress disorder, bipolar disorder, personality disorder, or dysthymia. 3. Acute or **repeated risk of suicidality**. 4. Regular intake of psychopharmacologic medications such as antidepressants, hypnotics, or anxiolytics. 5. Regular intake of mood- or sleep-altering medications such as analgesics by prescription, or over-the-counter pain killers. 6. Unable or unwilling to comply with the study conditions. 7. Female participants; pregnant or willing to get pregnant during the study; breast feeding. 8. Chronic diseases such as diabetes mellitus, hypertension or epilepsy, as ascertained by a thorough medical interview and from medical records.

2.3. Sample size calculation and randomization

Given the lack of previous studies with very similar study conditions, no sample size calculation was performed. As in previous studies (Jahangard et al., 2018), randomization was achieved using the software randomization.com. Based on this list, a psychologist not otherwise involved in the study assigned participants to the two study conditions (O3PUFA vs. placebo). Participants and staff members involved in the study were blind as regards participants' allocation to the study conditions.

2.4. Medication and placebo

As in a previous study (Jahangard et al., 2018) participants in the O3PUFA condition received one capsule of 1000 mg **fish oil** daily for eight consecutive weeks. **Each capsule contained 120mg of docosahexaenoic acid (DHA), 180mg of eicosapentaenoic acid (EPA) and other fatty acids, while no other vitamins were added. Other ingredients were: glycerin, methylparaben, and propylparaben.** Participants in the placebo condition received one capsule daily for eight consecutive weeks. Placebo capsules consisted of **lactose powder, glycerin, methylparaben, and propylparaben**. Capsules of O3PUFA and placebo were identical in shape, color, weight, and smell. The Zahravi Pharmaceutical Company (Tabriz, Iran) provided both the O3PUFA and placebo capsules.

2.5. Burnout questionnaire

For the assessment of burnout, participants completed the Maslach Burnout Inventory (Maslach and Jackson, 1981). **Akbari et al. (2011)** translated and validated the Farsi version and reported satisfactory psychometric properties of the Farsi MBI. The questionnaire consists of 22 items loading on the factors Emotional exhaustion, Depersonalization and (lack of) Personal accomplishment. Typical items are "I feel burned out from my work." (emotional exhaustion), "I don't really care what happens to some recipients." (depersonalization/lack of empathy), "I have accomplished many worthwhile things in this job." (personal accomplishment). Answers are given on seven-points rating scales ranging from 0 (= never) to 6 (= every day), with higher scores reflecting greater impairments on the dimensions of Emotional exhaustion and depersonalization. In contrast, higher scores for Personal accomplishment reflect a higher level of resources and greater workplace-related satisfaction. Cronbach's alphas for the present study: Emotional exhaustion, alpha = .84; Depersonalization, alpha = .86; (lack of) Personal accomplishment, alpha = .81.

2.6. HPA AA under baseline conditions (CAR: cortisol awakening response)

To assess morning cortisol saliva sampling, we followed the recommendations and procedures as described in Stalder et al. (2016). Specifically, they have shown that the morning cortisol response with strict reference to the time of awakening is a reliable index of basal HPA AA, irrespective of time of awakening, sleep duration, physical activity, or morning routines. As described elsewhere (Brand et al., 2018; Clow et al., 2010; Hatzinger et al., 2008; Hatzinger et al., 2012; Stalder et al., 2016), four saliva cortisol samples were taken in the morning at 0, 10, 20, and 30 min after awakening. Waking time ranged from 6.00 to 6.30 am. Saliva sampling was started immediately after awakening without first rinsing the mouth with water. Additionally, to avoid contamination of saliva with food or drinks or with blood caused by micro-injuries in the oral cavity, participants were asked not to take breakfast or to brush their teeth before sampling was completed.

2.7. Saliva cortisol sampling technique and cortisol analysis

As described extensively elsewhere (Brand et al., 2018; Hatzinger et al., 2008; Hatzinger et al., 2013), "Salivette" devices were used for quick and hygienic saliva sampling (Sarstedt, Nümbrecht/Germany). Once the participant had chewed a small cotton swab for about one minute, the swab was placed in the small plastic tube, the Salivette container, and stored in the freezer. Saliva samples were returned to the laboratory, where they were centrifuged at 7000 rpm for 10 min and stored at -20°C until assay. Next, free salivary cortisol concentrations were analyzed using a specific monoclonal anti-cortisol antibody (Monobind Cortisol EIA Kit, USA) by Eliza Reader (Sunrise Tecan, Austria). The absorbance of each sample in the well was read at 450nm using reference wavelength of 630nm to minimize imperfections. Intra- and interassay variability of this assay were less than 4.30% and 4.20%, respectively.

2.8. Statistical analysis

For the cortisol awakening response (CAR), the area-under-the-curve (AUC) was calculated, using the trapezoidal integration. Sociodemographic information for participants in the two study conditions was compared with a X^2-test and t-tests. With series of ANCOVAs with the factors Time (baseline vs. study end), Group (O3PUFAs vs. placebo), the Time by Group interaction, and baseline values as co-variates, differences in burnout dimensions (emotional exhaustion, depersonalization, personal accomplishment) and CAR were calculated. For F-tests, **following Cohen (1988)** effect size calculations were reported as partial eta-squared (η_p^2) with the following ranges: $0.01 \leq \eta_p^2 \leq 0.059$: small effect size (S); $0.06 \leq \eta_p^2 \leq 0.139$: medium effect size (M); $\eta_p^2 \leq 0.14$: large effect size (L). The nominal level of significance was set at alpha < .05. All statistical computations were performed with SPSS® 25.0 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

3. Results

3.1. Sample characteristics and sociodemographic information

Table 1 presents the descriptive and inferential statistical indices for gender, age and working experience of participants in the O3PUFA and in the placebo condition.

No descriptive or statistically significant group differences were observed for gender, age or working experience.

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Table 1 about here

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3.2. Dimensions of burnout

Table 2 presents the descriptive and inferential statistical indices for the burnout dimensions (emotional exhaustion; depersonalization; personal accomplishment) of participants in the O3PUFA and placebo conditions.

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Table 2 about here

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Emotional exhaustion and depersonalization decreased over time, but more so in the O3PUFA condition than in the placebo condition. Lower scores for emotional exhaustion and depersonalization were observed in the O3PUFA condition than in the placebo condition.
Sense of personal accomplishment increased over time, but more so in the O3PUFA condition than in the placebo condition. Higher scores for personal accomplishment were observed in the O3PUFA condition than in the placebo condition.

3.3. Cortisol awakening response levels

Table 2 also reports the descriptive and inferential statistical indices for the CAR levels of participants in the O3PUFA and in the placebo condition.

Cortisol awakening response levels decreased over time, but more so in the O3PUFA condition. No group differences were observed.

4. Discussion

The key findings of the present study were that among a sample of nurses with clinically diagnosed burnout, omega-3-polyunsaturated fatty acids (O3PUFAs), compared to a placebo, reduced symptoms of burnout and lowered morning cortisol secretion levels as a proxy of the hypothalamus-pituitary-adrenocortical axis activity (HPA AAThe present findings add to the current literature in an important way in showing that O3PUFAs may be a suitable option for the treatment of individuals with symptoms of burnout, i.e., with work-related exhaustion.

Two hypotheses were formulated and each of these is considered in turn.

Our first hypothesis was that, compared to a placebo, O3PUFAs would reduce symptoms of burnout, and this was confirmed. Accordingly, the present pattern of results is in agreement with findings for the effect of such treatment on individuals with major depressive disorders (Appleton et al., 2016; Berger et al., 2017; Deacon et al., 2017; Jahangard et al., 2018; Messamore et al., 2017; Pompili et al., 2017; Thesing et al., 2018). In contrast, the present results are at odds with the single, 52-week intervention study investigating the influence of O3PUFAs on dimensions of psychological health among nurses (Watanabe et al., 2018): In that study, O3PUFAs has no more positive impact than a placebo on self-reported burnout. It follows that the present study expands upon previous work in showing an impact of O3PUFASs on individuals' self-reported burnout.

Our second hypothesis was that, compared to placebo, O3PUFAs would downregulate CAR levels, and again this was confirmed. We note that, for want of directly comparable previous research, the second hypothesis was based on research into the influence of O3PUFAs on CAR among individuals with depression (Jazayeri et al., 2010; Komori, 2015). Thus the

present study appears to be the very first study to show the positive influence of O3PUFAs on an aberrantly upregulated HPA AA among individuals with burnout.

On this basis of this study we cannot be definitive about the neurophysiological processes underlying omega-3-polyunsaturated fatty acids effects. However, other studies indicate the probable role of the following two classes of physiological mechanism.

First, as documented in more detail elsewhere (Jahangard et al., 2018), O3PUFAs play a vital role in maintaining cell membrane integrity and fluidity (Deacon et al., 2017), and accordingly higher O3PUFA levels are associated with more efficient cell membranes. Moreover, as described elsewhere (Bowen & Clandinin, 2002), an increased membrane fluidity positively impacts on the structure and functioning of proteins embedded in the membrane, such that it further enhances the activity of enzymes bound in the membrane. Additionally, following others (Das, 2006; Deacon et al., 2017), improvements in membrane integrity and fluidity are associated with a broad variety of other processes such as a higher number and increased affinity of receptors, the functioning of iron channels, and the production of neurotransmitters. Importantly, such processes are believed to improve both neuroplasticity and cell survival via their influence on neurotrophins such as brain derived neurotrophic factor (BDNF;(Conklin et al., 2010)). The operation of these neurobiological mechanisms appear to be consistent with the notion that O3PUFAs have a positive impact on neurological functioning, which at a behavioral level appears to benefit cognition, emotion, and behavior.

The second type of physiological mechanism concerns the anti-inflammatory properties of O3PUFAs. Others (Calder, 2006; Murck et al., 2004) have reported a higher immuno-activation in individuals with major depressive disorders. Likewise, Nakata (2012) and Wirtz and von Känel (2017) noted in their reviews that psychosocial job stress and chronic psychological stress were associated with higher inflammatory markers. Furthermore, there is good evidence that O3PUFAs has immunosuppressive properties; that is to say, it

downregulates inflammatory processes (Mocking et al., 2016; Mocking et al., 2013; Mocking et al., 2015; Mocking et al., 2018; Mocking et al., 2017; Murck et al., 2004). On this basis it might be argued that in the present study properties of O3PUFAs had the effect of downregulating inflammatory markers, which in turn helped alleviate symptoms of burnout.

Despite the novelty of the results, several limitations warn against overgeneralization of the results. First, the sample size was rather small, though we relied on effect size calculations which by definition are not sensitive to sample sizes. Second, inclusion and exclusion criteria were such that a highly selected group of participants was investigated. We cannot therefore rule out a selection bias and thus less generalizability of the results to older and younger populations, or to individuals in other professions and working under greater conditions of uncertainty. Third, it is also conceivable that further latent and unassessed dimensions such as sleep quality, critical life events, previous episodes of major depressive disorders or regular physical activity might have biased two or more dimensions in the same or opposite directions. Fourth, while we assessed the HPA AA under basal conditions, it might have been informative to have investigated the HPA AA under challenge conditions, that is, under a pharmacological (DEX-CRH test: (Hatzinger et al., 2002) or a non-pharmacological challenge (Trier Social Stress Test: TSST-test (Allen et al., 2014; Brand et al., 2018; Buske-Kirschbaum et al., 1997; Gerber et al., 2017; Stadelmann et al., 2018; Stalder et al., 2016; Wingenfeld et al., 2017), so as to further determine the elasticity or degree of adaptability of the HPA AA to external and internal stimuli. Fifth, we relied entirely on self-reports to assess participants' affect and burnout, while experts' ratings might have enhanced the robustness of the findings, or at least their generalizability. Sixth, daily intake of capsules (O3PUFAs; placebo) was entirely self-administered; it follows that we could not rule out variations in compliance. However, given the double-blind character of the study design and the pattern of results, it is highly unlikely that compliance with respect to intake of the capsules differed

systematically between conditions. Seventh, a sample size calculation would have allowed us to estimate whether the present study was underpowered and therefore if other important findings could have been missed. Last, the placebo contained lactose; we did not specifically ask participants about lactose intolerance and it is therefore possible that the health status of lactose intolerant participants in the placebo was impaired.

5. Conclusion

In a small sample of selected individuals suffering burnout (that is to say, work-related exhaustion), compared to a placebo, O3PUFAs had a positive impact on both burnout scores and saliva morning cortisol secretion.

Conflict of interest

All authors declare no conflict of interests. The entire study was performed without external funding.

Acknowledgments

The present data are part of Dr. Mahmood Hedayati's doctoral thesis. We thank Nick Emler (University of Surrey, Surrey UK) for proofreading the manuscript.

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Figure 1 about here; CONSORT diagram.

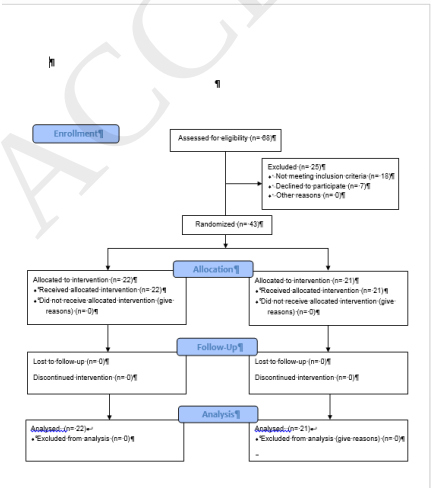

Table 1 Sociodemographic and illness-related information, separately for participants in the omega-3-polyunsaturated fatty acids **(n = 22)** and in the placebo condition **(n = 21)**.

	Groups		Statistics
	Omega-3-polyunsaturated fatty acids	Placebo	
N	22	21	
Gender (female/male)	16/6	17/4	$X^2(N = 43, df = 1) = 0.41$, $p = .52$
	M (SD)	M (SD)	
Age (years)	39.18 (6.31)	37.62 (5.37)	$t(41) = 0.87$, $p = .39$, $d = 0.27$
Working experience (years)	14.19 (4.26)	12.29 (4.62)	$t(41) = 1.39$, $p = .17$, $d = 0.43$

Table 2 Descriptive and inferential statistical indices of burnout values (emotional exhaustion; depersonalization, personal accomplishment) and saliva morning cortisol values, separately for participants with omega-3-polyunsaturated fatty acids (O3PUFAs; **n = 22**) or with placebo **(n = 21)**.

	Groups					Statistics		
	Omega-3-polyunsaturated fatty acids			Placebo				
N	22	22		21	21			
	Baseline	Study end		Baseline	Study end	Time	Group	Time x Group interaction
	M (SD)	M (SD)		M (SD)	M (SD)	F η_p^2	F η_p^2	F η_p^2
Burnout[1]								
Emotional exhaustion	39.86 (6.05)	32.50 (4.70)		37.14 (5.56)	37.09 (5.87)	5.06* .112 (M)	34.33*** .462 (L)	34.33*** .462 (L)
Depersonalization	20.82 (3.94)	14.55 (3.47)		18.95 (4.92)	18.86 (4.78)	2.63 .062 (M)	36.38*** .476 (L)	36.38*** .476 (L)
Personal accomplishment[2]	28.22 (5.50)	36.91 (7.54)		30.43 (4.22)	31.71 (3.95)	7.44** .157 (L)	19.78*** .330 (L)	19.78*** .330 (L)
Saliva cortisol[1]								

CAR	59.80 (21.94)	40.51 (17.29)		62.31 (15.73)	52.23 (15.13)		94.20*** .697 (L)	1.87 .044 (S)	9.29** .185 (L)

Notes: CAR = cortisol awakening response; [1] = always controlling for baseline values; [2] = Higher scores reflect more favorable scores of personal accomplishment. Degrees of freedom: For Burnout values: Always (1, 40). For cortisol awakening response: Always (1, 41). * = $p < .05$; ** = $p < .01$; *** = $p < .001$; (S) = small effect size; (M) = medium effect size; (L) = large effect size. Statistics always controlling for baseline values.