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Hypothalamic-pituitary-thyroid axis function in female adolescent nonsuicidal self-injury and its association with comorbid borderline personality disorder and depression

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ABSTRACT

Objectives: Behavioral disturbances in adolescence are potentially linked to aberrant functioning of the thyroid gland. Accordingly, alterations of the hypothalamic-pituitary-thyroid (HPT) axis might impact psychopathological development. Yet corresponding research in adolescents with nonsuicidal self-injury (NSSI) and comorbid mental disorders is scarce.

Methods: The present study examined HPT axis functioning in adolescents with NSSI compared to healthy controls (HC) using blood-based assays of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and the ratio of these hormones (fT3/fT4 ratio). Cortisol was additionally examined to contrast HPT axis functioning with a well-established biomarker of stress responsivity. Moreover, associations between clinical characteristics, HPT axis and HPA axis functioning were investigated. Female adolescents meeting NSSI criteria according to DSM-5 criteria ($n = 117$) were compared to adolescent HC ($n = 41$). Standardized serum-based endocrinological assays and interview- and questionnaire-based psychiatric assessments were used. Smoking status was included as covariate for all analyses.

Results: NSSI patients displayed altered HPT axis functioning as fT3/fT4 ratio values were blunted in comparison to HC. Negative correlations were further present between fT3, fT3/fT4 ratio and severity of BPD symptoms, depression scores and symptomatic distress. TSH correlated negatively with severity of BPD symptoms and symptomatic distress exclusively. Cortisol values differed neither significantly between experimental groups nor correlated significantly with clinical characteristics.

Conclusions: Longitudinal examinations, assessing links between psychopathology and endocrinological alterations, are warranted to address potential clinical implications of thyroid markers in child and adolescent psychiatry.

1. Introduction

Nonsuicidal self-injury (NSSI) is a serious and common phenomenon in adolescence. Consequently, NSSI has been introduced as a disorder warranting further research in the 5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). Proposed criteria include intentional and self-inflicted damage to the surface of one's body without suicidal intent on five or more days within a year. Epidemiological research estimated that *single events of NSSI* occur in 17% of adolescent nonclinical samples while 5% even meet criteria for *NSSI disorder* (NSSID) (Swannell et al., 2014). NSSI is often accompanied by comorbid disorders such as

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borderline personality disorder (BPD) or major depressive disorder (MDD) (Ghinea et al., 2020). Both disorders emerge commonly during adolescence and include severe emotion dysregulation. Existing evidence suggests that NSSI may serve as a coping strategy to diminish the intensity of negative emotions (Klonsky et al., 2014). Taken together, research shows that NSSI, BPD and depression are common phenomena in adolescence, yet biological markers potentially underlying these psychopathologies have been investigated insufficiently.

To investigate somatic correlates of psychiatric disorders, there has been a growing interest in endocrinological markers, such as hormones of the hypothalamic-pituitary-adrenal (HPA) axis. A closely related axis, the hypothalamic-pituitary-thyroid (HPT) axis, has received far less interest, although it can be assumed that HPT axis functioning influences psychosocial health significantly. Here, thyrotropin-releasing hormone (TRH) stimulates secretion of thyroid-stimulating hormone (TSH) in the anterior pituitary gland, which prompts triiodothyronine (T3) and thyroxine (T4) secretion in the thyroid gland. T3 and T4 are available in free form (fT3; fT4) or attached to proteins. And importantly, thyroid hormones do not only regulate the metabolism, but also impinge upon the cardiovascular system, bone maintenance, pregnancy outcomes, child development, and mental health.

Given the absence of research investigating HPT axis hormones in NSSI, the present study aimed at investigating HPT axis functioning in adolescents engaging in NSSI compared with healthy controls (HC). Based on prior research in BPD and MDD, NSSI patients were expected to show altered HPT axis hormones (i.e. elevated TSH and decreased fT3, fT4, fT3/fT4 ratio). Additionally, cortisol, the primary marker of the HPA axis, was included to reassess links between psychopathology and endocrinological functioning more generally. Lastly, we investigated whether comorbid psychopathological characteristics, i.e. severity of BPD and depression as well as symptomatic distress, would correspond to stronger blunting of HPT axis hormones or cortisol.

2. Methods

2.1. General procedures and participants

Data for the present analyses were collected drawing on a consecutive help-seeking cohort of adolescents (12–17 years) presenting at the outpatient clinic for adolescent risk-taking and self-harm behavior (*AtR!Sk*; Ambulanz für Risikoverhalten und Selbstschädigung) at the Clinic for Child and Adolescent Psychiatry, University Hospital Heidelberg. Patients underwent a first-stage, structured psychiatric diagnostic assessment (ethical approval: ID S-449/2013) followed by the invitation to participate in a second appointment involving various neurobiological assessments (*AtR!Sk-Bio*; ethical approval: ID S-514/2015). NSSI patients were included when reporting acts of nonsuicidal self-injury on at least five days in the past 12 months, as defined by the DSM-5 criterion A (American Psychiatric Association, 2013). Intention of self-injury as "nonsuicidal" was explicitly required to avoid conceptual overlap between NSSI and suicide attempts. Patients showing acute psychotic symptoms or insufficient speech comprehension were excluded. HC were only included when history of NSSI, endorsement of psychiatric disorder and corresponding treatments could be excluded prior to participation in the study. Patients and their legal guardians signed written informed consent to participate in both assessments. Both studies were carried out in accordance with the declaration of Helsinki.

The manuscript reports on cross-sectional data from *AtR!Sk-Bio*, which was implemented in 2016, in combination with *AtR!Sk* clinical data. Recruitment for *AtR!Sk-Bio* took place within 6 weeks after the diagnostic assessment in *AtR!Sk*. HC were recruited via public advertisement and underwent an adapted form of the diagnostic assessment prior to being invited to *AtR!Sk-Bio*. For *AtR!Sk-Bio*, height (cm) and weight (kg) were measured after a structured assessment on fasting status, handedness, smoking status, present-day coffee consumption, menstrual status, contraception use, physical illnesses, and medication use. Subsequently, fasting blood samples were taken by qualified medical staff. HPT axis hormones and cortisol were examined using standardized serum-based blood draws. Preanalytical variation was minimized by performing venipuncture in a standardized manner around 0900 h. After blood collection, samples were immediately frozen in aliquots at −80 °C until analyzed. Participants received an allowance of 40€ for participation.

2.2. Measures

2.2.1. Psychological instruments

The diagnostic procedures have been described in detail by Kaess and colleagues (Kaess et al., 2017). Frequency and severity of NSSI and suicidality were examined separately using the *Self-Injurious Thoughts and Behaviours Interview* (SITBI-G) (Fischer et al., 2014). BPD diagnoses were based on the *Structured Clinical Interview for DSM-IV Personality Disorders* (SKID-II) (First et al., 1997). Current and lifetime Axis I disorders were assessed with the Mini *International Neuropsychiatric Interview for Children and Adolescents* (MINI-KID) (Sheehan et al., 2010). Depressive symptoms were assessed based on self-reports using the *Depression Inventory for Children and Adolescents* (DIKJ) (Stiensmeier-Pelster et al., 2000). Symptomatic distress was examined based on the *Global Severity Index (GSI)* of the *Symptom-Checklist-90-Revised* (SCL-90-R) (Derogatis and Savitz, 1999). Adverse childhood experiences (ACEs) were examined using the *Childhood Experience of Care and Abuse Questionnaire* (CECA.Q) (Smith et al., 2002). The self-report questionnaire was used to examine lack of parental care (i.e. neglect and antipathy), parental physical abuse, and sexual abuse from any adult before age 17. German versions were used for all questionnaires and interviews.

2.2.2. Endocrinological assays

Baseline thyroid function was evaluated based on TSH, fT3, fT4 and fT3/fT4 ratio. The reference range was 0.4–4.0 mU/l for TSH, 2.0–4.2 ng/l for fT3, and 8–18 ng/l for fT4. The intra-assay coefficient of variation (c.v.) was 2.41–2.48% for TSH, 2.35–3.08% for fT3, and 2.23–3.33% for fT4. The inter-assay c.v. was 2.05–5.31% for TSH and 2.33–4.00% for fT4. Baseline HPA axis functioning was examined using cortisol. The reference range was 56–200 ng/ml. The intra-assay c.v. was 2.9–4.2%. The inter-assay c.v. was 4.4–6.0%. Fasting blood samples were thawed and analyzed by immunoassays (ADVIA Centaur® Assay). No prior thawing of the frozen plasma samples was performed. Blood analyses were conducted according to accredited routines at the central laboratory of the University Hospital Heidelberg.

2.3. Statistical analyses

Adolescents reporting ≥5 acts of NSSI within the past year were included for the NSSI group, adolescents without history of NSSI were included for the HC group. Sociodemographic and clinical differences between groups were compared using *t*-tests for dimensional variables and χ^2-tests for categorical variables. Groups differed significantly with regard to smoking status ($p = .005$), which was therefore included as covariate to all subsequent analyses. Groups differed also with regard to school type ($p = .027$), however, there were no significant relationships with endocrinological parameters. As all variables other than smoking neither correlated with experimental groups nor biological markers, they were not included as covariates in the statistical analyses. Group differences on endocrinological parameters were analyzed using regression analyses. Associations between hormonal and clinical characteristics were analyzed using Pearson's correlations. Subsequently, semipartial correlations were run to determine the relationship between endocrinological markers and psychopathology whilst controlling for smoking status. Statistical analyses were performed using STATA (*Stata Statistical Software: Release 15*, 2017, StataCorp LP, College Station, TX, USA) with α set to 0.05.

3. Results

3.1. Sociodemographic and clinical characteristics

The study sample comprised $n = 117$ NSSI patients and $n = 41$ HC (see Supplement 1 for in- and exclusion criteria and sociodemographic characteristics). NSSI patients smoked more frequently in the past month ($p = .005$) and attended lower school types than HC ($p = .027$). Groups did not differ on age, body weight, body height, body mass index (BMI), average physical activity per week, estradiol levels, menstrual status, hormonal contraceptive use, medical condition within the past 3 months, alcohol consumption, or illicit drug use (all $p \geq .117$). Comorbid diagnoses, clinical characteristics, as well as frequency of ACEs are shown in Supplement 2. Approximately one third of the NSSI group ($n = 34$; 29%) met at least five BPD criteria in the clinical interview; diagnostic criteria for depression were met by $n = 72$ (62%). Besides, NSSI patients reported a significant higher frequency of ACEs in general ($p < .001$) and also scored higher on several subscales of the CECA.Q, i.e. parental antipathy ($p < .001$), parental neglect ($p < .001$), and sexual abuse from any adult before age 17 ($p < .001$). Traumascores, which were calculated based on frequency and severity of ACEs, were positively correlated with number of BPD criteria ($p = .013$), depression scores ($p = .024$) and suicide attempts in the past 12 months ($p = .017$). Traumascores were neither correlated with GSIs ($p = .081$) nor with frequency of nonsuicidal self-injury in the past 12 months ($p = .382$).

3.2. Hormonal levels

As shown in Table 1, groups differed significantly with regard to fT3/fT4 ratio. Ratio values were lower in NSSI patients ($M = 0.30$, $SD = 0.05$) than in HC ($M = 0.32$, $SD = 0.05$). For fT3, the regression model was significant ($p = .004$), yet groups did not differ significantly ($t_{(156)} = -1.78$, $p = .77$).

3.3. Associations between clinical characteristics and hormone levels

As shown in Table 2, BPD severity correlated negatively with TSH ($p = .027$), fT3 ($p = .009$), fT3/fT4 ratio ($p = .009$), and smoking status ($p < .001$). As shown in Table 3, semipartial correlations for BPD severity were significant for TSH ($p = .013$) and fT3/fT4 ratio ($p = .009$). Depression severity correlated negatively with fT3 ($p = .008$), fT3/fT4 ratio ($p = .003$), and smoking status ($p = .034$). Semipartial correlations for depression severity were significant for fT3 ($p = .019$) and smoking status ($p = .020$), as well as fT3/fT4 ratio ($p = .003$). Symptomatic distress correlated negatively with TSH ($p = .014$), fT3 ($p = .017$) and fT3/fT4 ratio ($p = .003$). Semipartial correlations for symptom distress were significant for TSH ($p = .022$), fT3 ($p = .026$) and smoking status ($p = .010$), as well as fT3/fT4 ratio ($p = .002$).

Table 1
Group differences on thyroid markers and cortisol.

Biomarker	NSSI	HC	Comparison			
	Mean ± SD	Mean ± SD	*F*	*p*	Adj. R^2	*ES*
TSH (mU/l)	2.16 ± 1.05	2.31 ± 1.18	0.59	0.557	< −0.01	0.06
fT3 (ng/l)	3.38 ± 0.35	3.53 ± 0.42	5.81	0.004	0.06	0.57
fT4 (ng/l)	11.52 ± 1.50	11.07 ± 1.21	2.69	0.071	0.02	0.39
fT3/fT4 ratio	0.30 ± 0.05	0.32 ± 0.05	5.46	0.005	0.06	0.56
Cortisol (ng/ml)	161.55 ± 66.22	175.73 ± 71.45	2.19	0.116	0.02	0.01

Note. Sample sizes for all TSH, fT3, fT4, and fT3/fT4 ratio were $n = 117$ for NSSI patients and $n = 41$ for HC. Degrees of freedom (*df*) were (2, 141) for these endocrinological markers. Sample sizes for cortisol were $n = 110$ for NSSI patients and $n = 39$ for HC. Degrees of freedom (*df*) were (2,132) for cortisol. Nicotine use in the past month (yes/no) was included as covariate. Due to reasons of space, statistics for these covariates are not shown but available on request. TSH = thyroid-stimulating hormone; fT3 = free triiodothyronine; fT4 = free thyroxine; fT3/fT4 ratio = ratio between free triiodothyronine and free thyroxine.

Table 2
Partial correlations between endocrinological markers and clinical characteristics for the full study sample.

Biomarker	No. BPD criteria (SCID-II)		Depression score (DIKJ)		Global Severity Index (SCL-90-R)	
	$n = 158$		$n = 144$		$n = 145$	
	r	*p*	*r*	*p*	*r*	*p*
TSH (mU/l)	−0.176	0.027*	−0.097	0.250	−0.203	0.014*
fT3 (ng/l)	−0.206	0.009**	−0.221	0.008**	−0.198	0.017*
fT4 (ng/l)	0.072	0.367	0.123	0.143	0.139	0.096
fT3/fT4 ratio	−0.206	0.009**	−0.249	0.003**	−0.246	0.003**
Cortisol (ng/ml)	−0.020	0.809	−0.115	0.183	−0.087	0.313
Smoking (yes/no)	0.401	< 0.001***	0.186	0.034*	0.114	0.192

Note. SCID-II = Structured Clinical Interview for DSM-IV Personality Disorders; DIKJ = Depression Inventory for Children and Adolescents. SCL-90-R = Symptom-Checklist-90-Revised. Cortisol samples were available for $n = 149$ participants for correlation analyses with BPD criteria, for $n = 135$ participants for correlation analyses with depression scores, and for $n = 136$ participants for correlation analyses with global severity indices. Details related to smoking status were available for $n = 144$ participants for correlation analyses with BPD criteria, for $n = 131$ participants for correlation analyses with depression scores, and for $n = 132$ participants for correlation analyses with global severity indices. *$p < .05$, **$p < .01$, ***$p < .001$.

4. Discussion

The current study examined HPT axis hormones in adolescents with NSSI compared to healthy controls. Above all, findings suggest that altered fT3/fT4 might be a biological correlate of NSSI in adolescence, which in turn might indicate disrupted conversion from T4 to T3 in NSSI patients. Abnormal conversion from T4 to T3 may lead to fatigue, depression, and difficulty concentrating, which suggests that these symptoms should be taken seriously during physical examinations of NSSI patients. In this context, one may further question whether a higher frequency of NSSI coincides with stronger endocrinological alterations. Yet, our results suggest no such association and exploratory analyses assessing links between frequency of NSSI and thyroid markers failed to reach statistical significance. However, as we investigated a clinical help-seeking sample presenting with severe and repetitive NSSI, findings might not generalize to population- or college-based samples frequently studied in the field. Put differently, as a higher frequency of NSSI is associated with greater psychopathological distress, our findings might not generalize to occasional NSSI, which has not readily been captured in the present sample. However, and given the heterogeneity of NSSI frequency in the present sample, it seems rather unlikely that the inclusion of patients with low to mild NSSI frequency would have challenged these findings. Additionally, most endocrine markers were in the normal physiological range in the current study. Yet, HPT axis markers have relatively fixed *individual* setpoints, which tend to be stable over lifetime (Medici et al., 2015). As our analyses showed that NSSI patients reported more frequent and severe adverse childhood experiences and as these were further associated with BPD severity and suicide attempts in the past year, it might be particularly important to examine long-term relationships between psychopathology and HPT axis alterations to investigate whether such early experiences lead to changes in individual HPT axis setpoints. And, as setpoints can be affected by factors such as inflammation and lack of sleep, a normalization of HPT axis functioning resulting from psychosocial stabilization, for instance due to psychotherapy, needs to be investigated in future studies. Taken together, the

Table 3
Semipartial correlations between endocrinological markers and clinical characteristics for the full study sample.

Biomarker	No. BPD criteria (SCID-II)				Depression score (DIKJ)				Global Severity Index (SCL-90-R)			
	$n = 158$				$n = 144$				$n = 145$			
	Clinical		Smoking		Clinical		Smoking		Clinical		Smoking	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
TSH (mU/l)	−0.208	0.013*	0.134	0.105	−0.095	0.285	0.030	0.735	−0.200	0.022*	0.040	0.645
fT3 (ng/l)	−0.153	0.061	−0.154	0.059	−0.200	0.019*	−0.199	0.020*	−0.188	0.026*	−0.218	0.010*
fT4 (ng/l)	0.119	0.158	−0.084	0.317	0.149	0.090	−0.060	0.496	0.165	0.060	−0.054	0.534
fT3/fT4 ratio	−0.215	0.009**	−0.032	0.692	−0.261	0.003**	−0.085	0.314	−0.265	0.002**	−0.103	0.222
Cortisol (ng/ml)	−0.091	0.290	0.172	0.046*	−0.125	0.167	0.148	0.105	−0.080	0.378	0.134	0.140

Note. SCID-II = Structured Clinical Interview for DSM-IV Personality Disorders; DIKJ = Depression Inventory for Children and Adolescents. SCL-90-R = Symptom-Checklist-90-Revised. Details related to smoking status were available for $n = 144$ participants for correlation analyses with BPD criteria, for $n = 131$ participants for correlation analyses with depression scores, and for $n = 132$ participants for correlation analyses with global severity indices. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

current findings are in line with empirical evidence, however, antecedents leading to altered HPT functioning in adolescent NSSI patients need to be examined in greater detail.

Second, negative associations could be demonstrated for focal clinical characteristics and HPT markers. Here, BPD severity predicted blunting of TSH, fT3 and fT3/fT4 ratio, while depression severity predicted blunting of TSH and fT3/fT4 ratio. Symptomatic distress predicted blunting of TSH, fT3 and fT3/fT4 ratio. As suggested by Duval and colleagues (Duval et al., 2010), blunted thyroid levels may either originate from a downregulation of TRH receptors of the pituitary thyrotrophs secondary to a prolonged increase in hypothalamic TRH stimulation or from previously increased thyroid hormone levels and subsequent negative feedback of the HPT axis, which in turn could be associated with more pronounced psychopathology. Since we rely on single assessments, we can only speculate on the underlying cause. In any case, the associations signified in the current study may be linked with emotion dysregulation – commonly underlying NSSI – as thyroid receptors are localized on limbic structures acting on mood regulation (Bauer and Whybrow, 2001). Besides, it has previously been speculated that serotonin (5-hydroxytryptamine; 5-HT) – which likely plays a crucial role with regard to depressive symptoms and BPD (Maurex et al., 2010) – may act peripherally on the thyroid gland and could thereby decrease 5′-deiodinase activity (Sullo et al., 2011). In this context, it has been hypothesized that patients with mood disorders are particularly sensitive to changes in thyroid status, even when peripheral thyroid hormone assays in the normal range (Marangell and Callahan, 1998). This could suggest that even minor deviations of thyroid hormones may parallel markers for psychopathology. To further investigate this hypothesis, it may be worthwhile to investigate if pharmalogical treatment of 5-HT receptors comes along with an increase of thyroid hormones and clinical characteristics.

The finding that most endocrinological markers were not directly associated with NSSI behavior but rather with general psychopathology (such as symptomatic distress) further suggests that HPT axis dysfunction may present a non-specific mechanism promoting the development and maintenance of NSSI via general psychopathological distress. Recently, we proposed a temporal framework (Kaess et al., 2021), within which neurobiological factors associated with NSSI should be distinguished as (1) *distal biological traits* (e.g. biological predisposition or vulnerability for NSSI), (2) *proximal biological traits* (e.g. biological processes underlying NSSI that are of moderate stability) and (3) *biological states* directly preceding or following NSSI. As such, and based on the present findings, HPT axis dysfunction can be considered a distal biological trait, which is not necessarily linked to NSSI but to functional abnormalities related to the predisposition of the behavior. This hypothesis is further supported by the fact that HPT levels may not change in the short term or transient depending on the current frequency of NSSI. Further longitudinal research is needed, addressing the longitudinal course of HPT axis function in association with psychopathology in those developing or terminating the behavior. And, while findings were consistent with earlier research (Kirkegaard and Faber, 1998; Sinai et al., 2015), we were the first to show that such associations are present at an early developmental stage. However, future studies should examine separate clinical groups to examine the specificity of thyroid hormones, psychopathology, and emotion dysregulation. Here, future studies may also investigate if a higher frequency of NSSI coincides with more pronounced psychopathology to eventually investigate core mechanisms related to altered HPT axis functioning.

Besides, several limitations of the current study need to be acknowledged. First, generalizability with regard to male participants is limited. However, females develop thyroid diseases more frequently (Bauer et al., 2014) and receive NSSI and BPD diagnoses more often (Widiger and Weissman, 1991), which may point to a high ecological validity of our sample. Second, analyses were based on singular endocrinological assessments using blood draws, which necessitates repeated assessments in future studies to confirm the current findings. This seems especially important with regard to cortisol assessments, as prior research has shown that cortisol changes dynamically depending on current stress responsivity, which is why repeated and dynamic measurements may reflect subjective stress levels more adequately (Drews et al., 2019). Third, and notwithstanding that NSSID has been added to the DSM-5 as an independent disorder requiring further research (American Psychiatric Association, 2013), the validity of the diagnosis has only been examined empirically as of recently (Zetterqvist, 2015) and a recent study by our group indicated that NSSID as a stand-alone diagnosis is rare in help-seeking adolescents (Ghinea et al., 2020). As a matter of fact, NSSID is frequently accompanied by several comorbid disorders and marked functional impairments. In order to investigate the validity of NSSI as a stand-alone diagnostic entity, biological studies have the potential to enrich clinical descriptions and can make an important additive contribution to existing studies on the nosology of NSSI as an independent disorder. Our results seem in line with an increasing body of evidence showing that NSSI may rather serve as a transdiagnostic symptom than a distinct disorder given that many of its biological correlates may be driven by underlying psychopathology. Replication studies using thyroid markers as well as related endocrinological markers in larger samples may have sufficient power to facilitate both classification and differentiation of this clinical picture. A strength of the current study lies in its comprehensive link between biological and psychiatric data within a unique patient population. Moreover, the young age of the sample corresponds with little chronification and marginal interference of psychotropic drugs, which complements research on adult patient groups.

In summary, this study highlights potentially altered thyroid functioning in female adolescents with NSSI as well as associations between thyroid functioning and specific clinical characteristics in NSSI. Nonetheless, research based on long-term and dynamic endocrinological assessments is needed to confirm its etiological and diagnostic value. Once the clinical utility of thyroid markers can be demonstrated, parallel effects of altered hormones and psychiatric symptoms present a promising

avenue for further research. Eventually, such research may facilitate efficient treatment options for adolescents engaging in NSSI.

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Ethical statement

The work described has been carried out in accordance with 'The Code of Ethics of the World Medical Association' (Declaration of Helsinki). The manuscript has been written in line with the 'Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals' and authors aimed for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. Informed consent was obtained for experimentation with human subjects. Privacy rights of human subjects were observed at all times.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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