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Hair glucocorticoids in adults with intellectual disabilities and depressive symptoms pre- and post-bright light therapy: First explorations

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Abstract

Background: Depressive symptoms and stress are common in adults with intellectual disabilities. Our aim was to explore long-term biological stress levels, assessed by hair cortisol (HairF) and cortisone (HairE) concentrations, in adults with intellectual disabilities and depressive symptoms and to investigate the effects of bright light therapy (BLT) on hair glucocorticoids.

Method: Scalp hair samples (n = 14) were retrospectively examined at baseline and post-BLT (10.000 and 300 lux). Liquid chromatography–tandem mass spectrometry was used to measure hair glucocorticoids.

Results: A significant correlation was found between baseline HairF and depression scores (r = .605, p = .028). Post-intervention HairE levels were significantly increased ([95% CI: 11.2–17.4 pg/mg], p = .003), in particular after dim light (300 lux) ([95% CI: 10.0–18.3 pg/mg], p = .020).

Conclusions: This study showed that retrospectively examining biological levels of stress in adults with intellectual disabilities seems a potentially promising and objective method to gain insight in the stress level of adults with intellectual disabilities.

KEYWORDS
bright light therapy, cortisol, cortisone, depression, intellectual disabilities, long-term stress

1 | INTRODUCTION

A large part of the population of adults with intellectual disabilities, IQ < 70 and significant problems with adaptive functioning, is diagnosed with major depressive disorder (MDD) or has depressive symptoms (Cooper et al., 2007b; Hermans et al., 2013). It is known that many adults with intellectual disabilities also experience negative life events (Hermans & Evenhuis, 2012; Hove et al., 2016). Depressive symptoms are associated with life events and stress (Cooper et al., 2007a; Hermans & Evenhuis, 2012; LeMoult et al., 2015; Mundt et al., 2000; Vinkers et al., 2014). Stress activates the hypothalamus–pituitary–adrenal (HPA) axis and thereby prompts the release of the glucocorticoid cortisol from the adrenal glands (Gow et al., 2010). Acute (episodic) mental or physical stress can be detected by measuring cortisol in serum or saliva (Boucher & Plusquellec, 2019). However, serum cortisol concentration is a marker that poorly reflects long-term cortisol exposure and its effects at the cellular level. This is probably due to the circadian rhythm of cortisol, its pulsatile secretion and the daily variation due to changing circumstances like acute stress (Tsigos & Chrousos, 2002; van der Valk et al., 2018). Therefore, commonly used biological matrices only represent snapshots (serum, saliva) or short-term values (24 h urine) of cortisol levels instead of chronic systemic cortisol levels. Scalp hair assessment is a non-invasive reliable and valid method to measure long-term exposure to glucocorticoids and overcomes the intrinsic limitations of measuring highly fluctuating cortisol levels in serum, saliva or urine (Manenschijn et al., 2011; Noppe et al., 2015; Stalder & Kirschbaum, 2012). Hair cortisol has been used as a biomarker to retrospectively examine stress over periods of months to even years (a.i., [Staufenbiel et al., 2013]).

In the general population, a chronically elevated level of cortisol, as measured by scalp hair is not only associated with mental illnesses such as major depressive disorder (Vreeburg et al., 2009), but also with medical conditions such as cardiovascular disease, obesity and diabetes mellitus (Manenschijn et al., 2013; Schoorlemmer et al., 2009).

In recent years, a novel technique has been developed enabling the simultaneous measurement of the metabolically inactive hormone cortisone in scalp hair (Noppe et al., 2015; Wester & van Rossum, 2015). In addition to cortisol, cortisone has also been shown to be elevated in depression (Weber et al., 2000). In humans, the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) type 2 converts cortisol to cortisone, which can in turn be reactivated by 11β-HSD type 1. Previously it has been reported that patients with major depressive disorder showed a reduced activity of the intracellular cortisol-deactivating 11β-HSD2 (Römer et al., 2009). The activity of the latter enzyme can be estimated by the levels and ratio of cortisol (F) and cortisone (E).

The usefulness of hair glucocorticoids has been evaluated in previous studies showing strong associations between cortisol (HairF) and cortisone (HairE) (Staufenbiel et al., 2015), and associations with mental and physical disturbances (Manenschijn et al., 2013; Staufenbiel et al., 2013). A discrepancy was found between earlier studies where both negative as well as positive associations are described between HairF and depression and anxiety (Dettenborn et al., 2012; Gerritsen et al., 2019; Janssens et al., 2017; Pochigaeva et al., 2017; Staufenbiel et al., 2013; Steudte et al., 2011). The specific role of cortisone, and the related activity of 11β-HSD in skin and hair follicles (Baudrand & Vaidya, 2015), must be further investigated.

In the field of non-pharmacological treatment options to decrease depressive symptoms in the general population, bright light therapy (BLT) is an evidence-based treatment to decrease depressive symptoms in seasonal and non-seasonal depression (Even et al., 2008; Golden et al., 2005; Kripke, 1998; Lieverse et al., 2011; Martiny, 2004; Nussbaumer et al., 2015; Pail et al., 2011; Schwartz & Olds, 2015; Tuunainen et al., 2004; Wirz-Justice et al., 1993, 2011). Previous research has shown that BLT influences cortisol concentrations in depressed adults of the general population (Leproult et al., 2001; Lieverse et al., 2011; Thalen et al., 1997). In elderly with depression, those exposed to BLT had decreased 24 h urinary free cortisol levels compared to those exposed to the placebo treatment with dim red light (Lieverse et al., 2011). In the population of adults with intellectual disabilities, cortisol concentrations have so far been examined with traditional methods in specific syndromes (Beauloye et al., 2015; de Lind van Wijngaarden et al., 2008; Peters et al., 2016; Sniecinska-Cooper et al., 2015). One study has investigated long-term cortisol levels in adults with intellectual disabilities and Prader–Willi syndrome (PWS) (Shukur et al., 2020). In this specific population, they found large variations of hair cortisol, and long-term hair cortisol levels were higher in adults with intellectual disabilities and PWS compared to controls (age- and sex-matched participants without intellectual disabilities and PWS). Further, in patients with intellectual disabilities and PWS, hair cortisol increased with higher BMI and stress levels (Shukur et al., 2020).

Hair cortisol and cortisone levels in adults with intellectual disabilities and depressive symptoms, or the effect of BLT on long-term cortisol or cortisone in this population has not yet been investigated. Therefore, the aim of the current study was to explore HairF (hair cortisol) and HairE (hair cortisone) in adults with intellectual disabilities and depressive symptoms and to investigate whether BLT could alter these long-term glucocorticoid levels. We hypothesize that BLT will decrease hair glucocorticoids levels in adults with intellectual disabilities. We additionally explored associations between hair glucocorticoids and depressive symptoms, co-morbid anxiety symptoms, and the number of (negative) life events in the previous year and examined mean HairE/HairF ratios. Based on studies of the general population, positive associations between hair glucocorticoids and depressive symptoms, anxiety symptoms and life events are expected. Further, we explored the feasibility of collecting hair samples for cortisol measurements in adults with intellectual disabilities.

2 | METHODS

2.1 | Participants

This study is carried out in the Academic Collaborative Center 'Healthy Ageing and Intellectual Disabilities' (HA-ID), which is a collaboration between three healthcare provider services for people
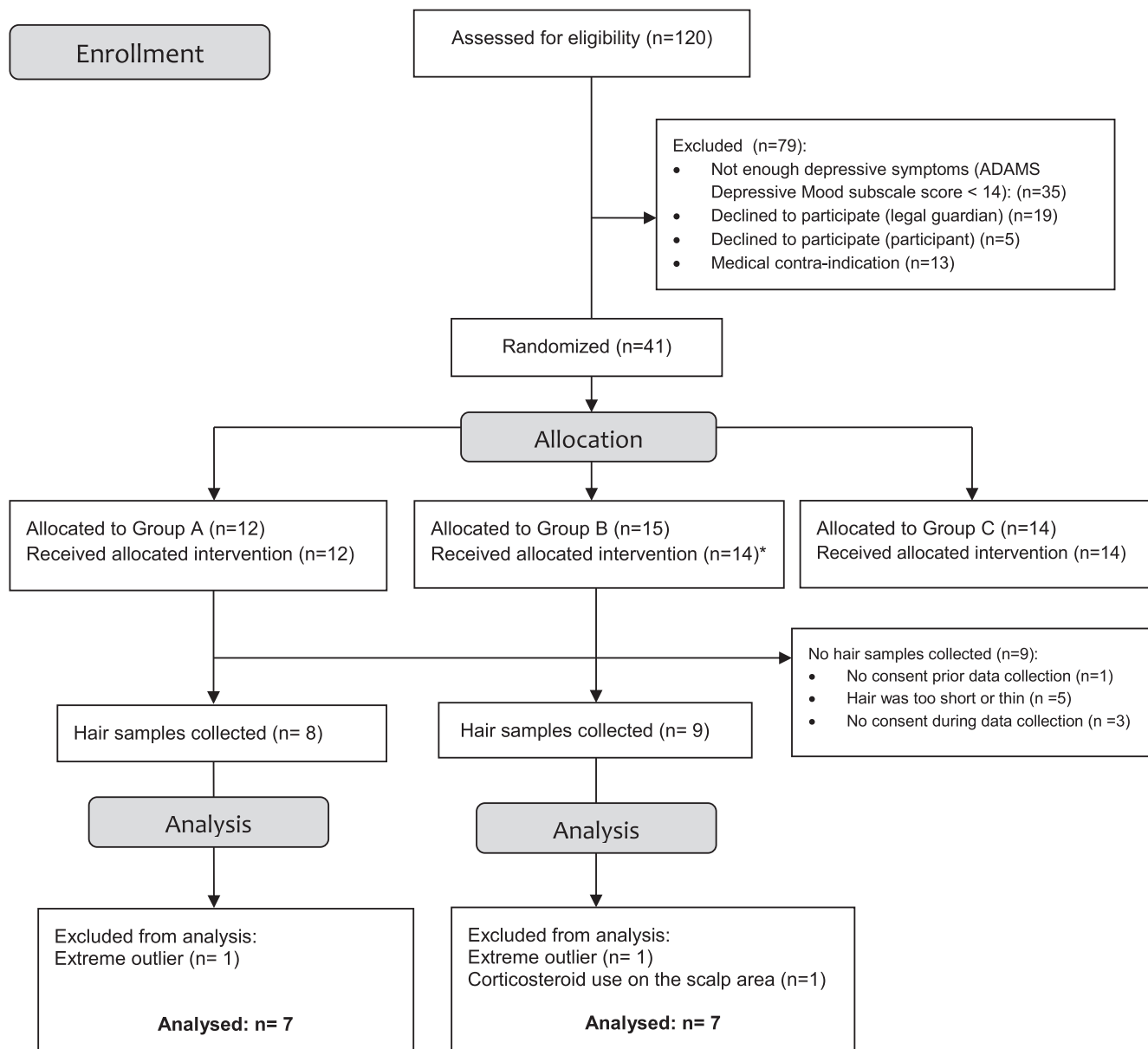
FIGURE 1 Flow diagram of data collection. *One participant was excluded from the analyses because of no compliance with the study protocol

with intellectual disabilities in the Netherlands and the research group of Intellectual Disability Medicine of the Erasmus University Medical Center Rotterdam in the Netherlands. All participants of the current study on long-term glucocorticoid levels were included in a multicentre randomized controlled trial, which investigated the effect of BLT on depressive symptoms in adults with intellectual disabilities (Hamers et al. 2020). In the published protocol of that study (Hamers et al. 2017), it was mentioned that we wanted to include a minimum of 135 and a maximum of 171 participants. After an inclusion period of 1 year, we extended the inclusion period by more than a year and screened a group of 500 patients on depressive symptoms. After an inclusion period of 2.5 years, 120 participants were assessed for eligibility and 41 participants could be included in our trial (Hamers et al. 2020). Of these 41 participants, 27 participants

got bright light therapy (BLT) (*n* = 12 group A 10.000 lux and *n* = 15 group B 300 lux), and 14 were randomized in the care as usual group without bright light therapy (group C). In group B, one participant did not comply to the study protocol; therefore, 26 participants who underwent bright light therapy were left. Only in the two BLT groups (group A and group B) hair samples were collected because of ethical and pragmatic reasons. Figure 1 describes the data collection of this study. Inclusion criteria were as follows: adults with intellectual disabilities (IQ ≤ 70) and depressive symptoms. A minimum score of 14 (clinical cut-off point) on the Depressive Mood subscale of the Dutch ADAMS was needed to be included in this study (Hamers et al., 2019; Hermans et al., 2018). In the current study, participants using corticosteroids on the scalp area, and those who used systemic corticosteroids, were excluded.

2.2 | Light intervention

We used two light interventions in this study in addition to care as usual: group A received BLT (10,000 lux) with the Philips energy light type HF3319 (UV-filtered lightbox). Participants in group B received a light intervention with the same lightbox with a LEE filter (no. 299) installed to reduce the amount of lux to 317 lux (mean). The colour of the light was not changed with the use of the filter. All participants received the light intervention in the morning before 12 AM, 30 min a day for a period of 14 consecutive days, usually during breakfast. The lightbox was placed at 20 centimetres distance in order to receive the right amount of lux, according to the product manual. We provided a detailed BLT manual with pictograms before the start of the intervention. A provided tape measure made sure that the light box was placed at the right distance. Daily adherence was recorded in a log.

2.3 | Hair glucocorticoids

We collected three centimetres of scalp hair (proximal) from participants to analyse HairF and HairE in segments before and after the light interventions. Details on the scalp hair sample collection process are published previously in 2015 by Noppe et al. (2015). As scalp hair grows approximately one centimetre a month (Wennig, 2000), the scalp hair samples in our study were cut 6 weeks after the end of the intervention at the posterior vertex, as close to the scalp as possible. Trained professionals cut the hair samples and attached the hair sample to a provided paper with tape. We marked the spot which was cut close to the scalp. The first centimetre closest to the scalp was assumed to reflect the period of approximately 4 weeks after the end of the intervention (T2), since we took also into account the days needed for hair to grow out of the scalp from the hair follicle. The second centimetre of the sample, which is not used in the analyses of this study, contained the intervention period. The third centimetre of the hair sample was our baseline measurement (T0). The hair samples were stored in an envelope and kept at room temperature.

2.4 | Hair processing and hair analyses

We weighed 10 mg of each hair sample (3 cm proximal) and cut the sample in three 1 cm segments. Hair samples were washed with isopropanol and dried for a period of 48 h. Then methanol was added for the 18-h extraction process (25°C). After the methanol was evaporated, solid phase extraction was used for purifying the samples. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to measure the levels of cortisone and cortisol (Russell et al., 2015). This method is described in detail elsewhere (Noppe et al., 2015). All hair samples were analysed in one batch. We used the first cm of the hair sample (post-light intervention) and the third cm (baseline, pre-light intervention) for the analyses.

2.5 | Questionnaires

In this study, the Dutch version of the Anxiety, Depression and Mood Scale (ADAMS) is used to screen for anxiety and depressive symptoms on baseline and post-intervention (1 week [T1] and 4 weeks after intervention [T2]) (Hamers et al., 2019; Hermans et al., 2018). This proxy instrument contains 28 items and is specially developed for adults with intellectual disabilities. The Anxiety subscale contains seven items (score range 0–21) and the Depressive Mood subscale contains 13 items (score range 0–39). The ADAMS is a valid and reliable instrument with good sensitivity and specificity rates (Hamers et al., 2019; Hermans et al., 2012, 2018). Besides the ADAMS, the Dutch Signalizing Depression List for people with Intellectual Disabilities (SDL-ID) is used to measure depressive symptoms as well. This instrument contains 18 items (score range 18–72), is complementary to the Dutch ADAMS Depressive Mood subscale, and has good internal consistency and inter-rater reliability (Roeden, 1989). With the PAS-ADD Clinical Interview (which is developed for adults with intellectual disabilities), we examined if the participants could be diagnosed with a MDD (Moss, 2011). Participant's life events are counted with the Checklist Life Events (CLE). This questionnaire, developed by our research group, measures the number of life events of the participant in the year prior to enrolment in the study (Hermans & Evenhuis, 2012). Information about the use of topical and/or systemic corticosteroids and hair-related factors, including hair washing frequency and the use of hair products and hair treatment, are obtained with a self-constructed questionnaire. The use of other medications was retrieved from medical files. All questionnaires were filled in by the professional caregiver of the participant. Other participant characteristics (sex, age, level of intellectual disability and genetic syndrome) were retrieved from the personal files.

2.6 | Ethical approvement

Ethical approval was obtained for all three care provider services by the Ethics Committee of the Erasmus University Medical Center Rotterdam in theNetherlands (MEC-2014-632). We followed the guidelines of the Declaration of Helsinki (64ste WMA General Assembly, October 2013). Participants gave informed consent to participate in this study. When the participant was not able to decide to participate due to the intellectual disability, the legal guardian gave informed consent for the participant. The current study is part of a trial which is registered prior to the start of the study (NTR number: NTR5162).

2.7 | Statistical analyses

We used Statistical Package for the Social Sciences version 24 (SPSS Inc.) for all statistical analyses. HairF values above 100 pg/mg were excluded from all analyses because those were extreme outliers. Participants using corticosteroids on the scalp area, and those who used systemic corticosteroids, were excluded. Other corticosteroid

use was included in our analyses as a confounder (Wester et al., 2017). Group comparisons on baseline characteristics were analysed with independent samples *t*-tests for continuous data and chi-square tests for categorical data. Paired samples *t*-tests were used to examine the differences between depression scores on T0 (baseline) and T1 (1 week after BLT), and between T0 and T2 (4 weeks after BLT). The same analyses were used to examine the differences in anxiety subscale scores. The Kolmogorov–Smirnov tests showed that our hair glucocorticoid data (baseline and T2) were not normally distributed, and therefore $\log_{10}$ transformations were used in our analyses. The geometric means and 95% confidence intervals (CI) of the antilog-transformed data are reported. To examine if there were baseline differences between group A and group B on HairF and HairE, we used one-way analysis of covariance (ANCOVA) and we corrected for corticosteroid use. To examine the HairE/HairF ratio, we divided the values of cortisone by cortisol. Repeated measures ANCOVA were used to examine differences in HairE/HairF ratio between baseline and post-intervention. In these analyses, we also corrected for corticosteroid use. Multivariate analysis of covariance (MANCOVA) repeated measures, which included both HairF and HairE pre (T0) and post-intervention (T2), were used to check for differences within and between our two groups. In these analyses, we also corrected for corticosteroid use. Baseline correlations were tested with partial correlations and we included corticosteroid use as a confounder. Overall, we used a significance level of $\alpha = .05$. A corrected significance level (Bonferroni correction) was used when there was an increased risk of a type 1 error due to multiple comparisons. This means that a significance level of $p = .025$ (0.05/2) was used to calculate the mean change in depression scores.

3 | RESULTS

3.1 | Hair samples

Scalp hair samples with sufficient length of three centimetres were available in 17 out of 26 participants (65.3%) who underwent a light intervention. Of the nine participants with no hair sample, one participant gave no consent prior to the intervention to cut a hair sample. Hair of five participants was too short because it was cut recently, or the participant's hair was too thin to collect a hair sample. Three participants refused a hair sample to be taken during the cutting procedure. All untransformed hair glucocorticoid data can be found in Table 1. Two participants (number 4 and 13) were excluded from the analyses because their HairF concentrations were extreme outliers (>100 pg/mg), and one participant (number 8) was excluded because of corticosteroid use on the scalp area. No participants used systemic corticosteroids.

3.2 | Participant characteristics

Finally, 14 participants (nine females and five males) were included in our analyses: seven participants were exposed to BLT with 10.000

TABLE 1 Untransformed hair glucocorticoids data of adult participants with intellectual disabilities and depressive symptoms before and after light intervention

Patient number	HairF pg/mg Baseline	HairF pg/mg Post-intervention	HairE pg/mg Baseline	HairE pg/mg Post-intervention	Intervention group
1	3.9	3.3	10.4	13.6	B
2	5.4	3.8	7.9	7.4	B
3	23.7	26.1	8.3	15.0	B
4[a]	151.7	128.8	7.3	8.3	B
5	4.0	3.1	14.1	13.2	A
6	8.5	6.4	3.5	10.3	A
7	36.8	48.4	8.9	9.5	A
8[b]	1.3	1.4	7.3	9.6	B
9	1.0	1.3	6.8	11.8	A
10	3.4	3.6	11.6	13.6	A
11	4.5	4.3	14.1	17.7	A
12	1.6	1.6	11.4	15.7	B
13[a]	>210.0	>210.0	12.2	14.6	A
14	11.0	11.0	34.1	36.1	A
15	1.0	3.1	4.4	12.2	B
16	10.2	4.4	19.9	22.0	B
17	2.1	3.4	8.7	12.8	B

Note: HairF: cortisol; HairE: cortisone; Intervention A: 10.000 lux bright light therapy; Intervention B: dim light intervention.

[a]Patient 4 and 13 were excluded from the analyses because their results were extreme outliers.

[b]Patient 8 was excluded because of corticosteroid use on the head hair area.

lux (group A) and seven participants underwent the dim light intervention (group B). 64.3% of our participants were females, and the mean age was 51.8 years (SD = 9.4, range 40–65 years). All levels of intellectual disabilities (IQ < 70) were included in this study. Participant characteristics are shown in Table 2. At inclusion, all participants had ADAMS Depressive Mood subscale scores of 14 points or more (clinical cut-off point [Hermans et al., 2018]), indicating clinically significant depressive symptoms. Depressive symptoms scores on baseline (T0), 1 week after BLT (T1), 4 weeks after BLT (T2), and the mean change of these symptoms between the time points can be found in Table 2. None of the participants met the diagnostic criteria of Major Depressive Disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Further, none of the participants in our study had acute illnesses or type 1 diabetes. In our sample, only one participant (group B) had type 2 diabetes. On baseline, we found no significant differences between group A and group B on age, sex, level of intellectual disabilities, use of medications, mean days of intervention, life events in the past year, ADAMS Depressive Mood subscale score, ADAMS Anxiety subscale score, SDL-ID Total score, and HairF and HairE. There were also no significant differences regarding hair-related factors. Regarding compliance with the light therapy, in group A (10.000 lux) one participant got light therapy in nine of the 14 consecutive days, and three participants missed only 1 day of light therapy. In this group, three participants got light therapy on all 14 consecutive days. In group B (dim light intervention), also one participant got light therapy in nine of the 14 consecutive days. One participant got 12 days of light therapy, and three participants missed 1 day of light therapy. In this group, two participants got light therapy on all 14 consecutive days. There were no significant differences between the two light therapy groups regarding compliance with the light therapy schedule (p = .420).

3.3 | Associations between HairF, depressive symptoms, co-morbid anxiety symptoms and life events

We found a moderate correlation between baseline HairF (hair cortisol) and baseline ADAMS Depressive Mood subscale scores (r = .605, p = .028), and baseline SDL-ID Total scores (r = .605, p = .028), which both were statistically significant. We did not find significant correlations between baseline HairF and baseline ADAMS Anxiety subscale scores (r = .355, p = .234), life events in the past year (r = −.275, p = .362), and negative life events in the past year (r = −.124, p = .687).

3.4 | Associations between HairE, depressive symptoms, co-morbid anxiety symptoms and life events

There were no significant associations between baseline HairE (hair cortisone) and baseline ADAMS Depressive Mood subscale scores

(r = −.120, p = .696), and baseline SDL-ID Total scores (r = −.143, p = .641). We found a trend towards an inverse correlation between baseline HairE and baseline ADAMS Anxiety subscale scores (r = −.512, p = .073). We did not find significant correlations between HairE and life events in the previous year (r = −.356, p = .233), and negative life events in the previous year (r = −.397, p = .179).

3.5 | Change in hair glucocorticoids after light intervention

In Table 3, the geometric means and 95% CI of the hair glucocorticoids pre and post-intervention (T2) are shown. In the total sample, we did not find significant differences between pre- and post-intervention in HairF (hair cortisol) (p = .802), but we found a significant increase in HairE (hair cortisone) (geometric baseline mean: 10.0 pg/mg [95% CI: 7.2–13.9] versus post-intervention: 14.0 pg/mg [95% CI: 11.2–17.4], p = .003). In group A (10.000 lux BLT), we found no significant differences between pre- and post-intervention in HairF (p = .619) and HairE (p = .108). In group B (dim light intervention), we found no significant change in HairF (p = .682). However, we found a significant increase in HairE in this group (geometric baseline mean: 9.3 pg/mg [95% CI: 6.1–14.1] versus post-intervention: 13.5 pg/mg [95% CI: 10.0–18.3], p = .020).

3.6 | HairE/HairF ratio

We found a significant increase in mean HairE/HairF (hair cortisone/hair cortisol) ratio after the light intervention in the total sample (baseline: 3.1 [95% CI: 1.8–4.3] versus post-intervention: 4.0 [95% CI: 2.4–5.5], p = .010). In group A (10.000 lux BLT), we also found a significant increase in mean HairE/HairF ratio after the light intervention (baseline: 2.9 [95% CI: 0.97–4.9] versus post-intervention: 3.8 [95% CI: 1.3–6.2], p = .036). In group B (dim light intervention), no significant difference was found between baseline and post-intervention mean HairE/HairF ratio (baseline: 3.2 [95% CI: 0.9–5.4] versus post-intervention: 4.2 [95% CI: 1.3–7.1], p = .143). HairE/HairF ratio on baseline and post-intervention are shown in Table 3.

4 | DISCUSSION

We performed a first explorative study on long-term glucocorticoid exposure in adults with intellectual disabilities and depressive symptoms. Collecting hair samples for investigating hair glucocorticoids in adults with intellectual disabilities was feasible in the majority of our participants (65%). In our study, we found significant positive correlations between baseline HairF and depressive symptoms measured with two different questionnaires. We also found a trend towards an inverse correlation between baseline HairE and anxiety symptoms. In our study, we found a significant increase in mean HairE, but not in HairF, in our total sample and after dim light intervention. This might

TABLE 2 Participant characteristics

	Total group n = 14	Group A (10.000 lux) n = 7	Group B (Dim light) n = 7
Mean age (SD)	51.8 (9.4)	51.4 (9.3)	52.1 (10.2)
Median age (range)	50.5 (40–65)	50.0 (40–65)	53.0 (40–64)
Sex (M/F)	5/9	3/4	2/5
Level of intellectual disability (%)			
Mild (IQ 50–70)	2 (14.3)	2 (28.6)	0 (0.0)
Moderate (IQ 35–50)	3 (21.4)	2 (28.6)	1 (14.3)
Severe or profound (IQ < 35)	9 (64.3)	3 (42.8)	6 (85.7)
Genetic syndrome (%)			
Down syndrome	1 (7.1)	0 (0.0)	1 (14.3)
DiGeorge syndrome[a]	1 (7.1)	0 (0.0)	1 (14.3)
No specific syndrome reported	12 (85.8)	7 (100.0)	5 (71.4)
Medication use (%)			
Corticosteroids[b]	2 (14.3)	1 (14.3)	1 (14.3)
Antidepressants	7 (50.0)	4 (57.1)	3 (42.6)
Antipsychotics	10 (71.4)	6 (85.7)	4 (57.1)
Benzodiazepines	5 (35.7)	3 (42.6)	2 (28.6)
Anti-epileptics	5 (35.7)	3 (42.6)	2 (28.6)
Contraception	4 (28.6)	2 (28.6)	2 (28.6)
Mean days of intervention (SD, min-max)	12.7 (1.7, 9–14)	12.9 (1.8, 9–14)	12.6 (1.7, 9–14)
Mean n of life events (SD)	5.4 (2.0)	4.9 (2.0)	5.9 (2.1)
Mean n of negative life events (SD)	2.6 (2.1)	1.7 (2.1)	3.4 (1.9)
ADAMS Depressive Mood subscale score, Mean (SD)			
T0	20.1 (5.5)	21.9 (7.3)	18.3 (2.0)
T1	15.0 (4.9)	15.0 (5.9)	15.0 (4.2)
Mean change T0-T1 (95% CI)[c]	5.1* (1.4–8.8)	6.9 (−0.8 to 14.5)	3.3 (−0.1 to 6.7)
T2	12.9 (6.9)	13.4 (8.3)	12.4 (5.8)
Mean change T0-T2 (95% CI)[c]	7.1* (2.9–11.4)	8.4 (−0.1 to 17.0)	5.9 (0.8–10.9)
ADAMS Anxiety subscale score, Mean (SD)			
T0	9.3 (3.8)	9.1 (5.0)	9.4 (2.5)
T1	6.4 (3.0)	5.9 (2.8)	6.9 (3.3)
Mean change T0-T1 (95% CI)[c]	2.9* (0.8–5.0)	3.3 (−0.6 to 7.1)	2.6 (−0.5 to 5.7)
T2	6.3 (3.4)	5.9 (4.0)	6.7 (2.9)
Mean change T0-T2 (95% CI)[c]	3.0* (0.8–5.2)	3.3 (−1.8 to 8.3)	2.7* (1.2–4.2)
SDL-ID Total scores, Mean (SD)			
T0	39.6 (5.2)	38.9 (6.7)	40.3 (3.5)
T1	32.9 (4.7)	31.6 (4.4)	34.1 (5.0)
Mean change T0-T1 (95% CI)[c]	6.7* (2.8–10.7)	7.3 (−0.6 to 15.2)	6.1* (1.3–11.0)
T2	31.6 (6.3)	30.6 (7.1)	32.7 (5.8)
Mean change T0-T2 (95% CI)[c]	7.9* (2.8–13.0)	8.3 (−1.8 to 18.4)	7.6 (1.1–14.1)

Note: T0 = baseline, T1 = 1 week after BLT, T2 = 4 weeks after BLT.

Abbreviations: IQ, intelligence quotient; SD, standard deviation.

[a]DiGeorge syndrome is also known as 22q11.2 deletion syndrome.

[b]Corticosteroid use not on the scalp area and no systemic use.

[c]A significant level of p = .025 (0.05/2) was used to correct for increased risk of a type 1 error due to multiple comparisons.

*Significant difference.

TABLE 3 Hair glucocorticoids pre and post-light intervention

	Total sample *n* = 14	Group A (10.000 lux) *n* = 7	Group B (Dim light) *n* = 7
Geometric mean (95% CI) HairF (pg/mg)			
Baseline	4.8 (2.6–9.0)	5.8 (2.0–16.3)	4.0 (1.4–11.2)
Post-intervention (T2)	4.9 (2.8–8.7)	5.8 (2.0–16.6)	4.2 (1.9–9.4)
Geometric mean (95% CI) HairE (pg/mg)			
Baseline	10.0 (7.2–13.9)	10.8 (5.6–20.7)	9.3 (6.1–14.1)
Post-intervention (T2)	14.0 (11.2–17.4)[*]	14.5 (9.5–22.0)	13.5 (10.0–18.3)[**]
Ratio HairE/HairF Geometric mean (95% CI)			
Baseline	3.1 (1.8–4.3)	2.9 (0.97–4.9)	3.2 (0.9–5.4)
Post-intervention (T2)	4.0 (2.4–5.5)[***]	3.8 (1.3–6.2)[****]	4.2 (1.3–7.1)

Note: CI: confidence interval; HairF: cortisol; HairE: cortisone; to achieve a normal distribution, raw data of the hair glucocorticoid values (Table 1) were logarithmically transformed (log10) to achieve a normal distribution. The geometric means and 95% confidence intervals (CI) of the antilog-transformed data are reported here. We corrected for corticosteroid use in the pre-post intervention analyses.
Significant change: [*]*p* = .003, [**]*p* = .020, [***]*p* = .010, [****]*p* = .036.

point towards an increased conversion of the cortisol to the bio-inactive cortisone by the enzyme 11βHSD type 2. With regard to the HairE/HairF ratio, this ratio was elevated after light intervention in our total sample and in the group with 10.000 lux BLT. Our findings suggest that after light therapy, and in particular after 10.000 lux BLT, the activity of the cortisol-lowering enzyme 11βHSD type 2 is slightly higher. This might be interpreted as a protective mechanism leading to enhanced inactivation of the stress hormone cortisol. This may be of particular interest when cortisol levels are high (e.g., due to stress, depression, pain, sleep deprivation or cardio metabolic co-morbidities). However, our study sample was small, with 14 participants, limiting a strong interpretation of our results.

Previous research in the general population has shown that BLT lowered 24 h urinary free cortisol levels (Lieverse et al., 2011) and reduced plasma cortisol levels (Jung et al., 2010). In contrast, another study found elevated plasma cortisol levels after BLT (Leproult et al., 2001). The influence of BLT on cortisone levels or hair glucocorticoids has not been investigated yet. The geometric means of HairF (4.8 pg/mg) and HairE (10.0 pg/mg) of our total sample are higher than those found in the general population without depressive symptoms (HairF 2.67 pg/mg and HairE 8.21 pg/mg) (Wester et al., 2017). The median age of our sample is 9 years higher than in the general population study (median age 51 [range 40–65] versus median age 42 [range 18–85], respectively). Previous research showed that HairF could increase with age, which can be caused by changes in HPA axis function related to ageing (Kudielka et al., 2004). Therefore, it is possible that the observed higher glucocorticoid levels in our study population were caused by increased stress, but it may also be related to a higher mean age with potential accompanying age-related physical co-morbidities of our study population. Besides, other factors, such as sleep deprivation or pain, may have influenced the glucocorticoid levels as well. In a group of patients with MDD, much higher mean HairF concentrations (measured with chemo luminescence assay) were found compared to our results (Dettenborn et al., 2012). The different way of measuring HairF in this study compared to the

method used in our study may have caused the differences, but this may also because we included participants with depressive symptoms, but without a diagnosis of MDD.

It is known, that depressive symptoms are positively associated with stress (Constance, 2005). In the population of adults with intellectual disabilities, a large proportion experiences (chronic) anxiety and/or depressive symptoms, as well as stressful (negative) life events (Bond et al., 2019; Deb et al., 2001; Hermans, 2012; Hermans & Evenhuis, 2012). In a recent study in adults with intellectual disabilities, more life events and levels of stress (measured on a 3-point Likert scale) were associated with more symptoms of depression and anxiety (Bond et al., 2019). Hermans and Evenhuis (2012) also reported that more (negative) life events were associated with a greater incidence of depressive and anxiety symptoms and MDD in elderly with intellectual disabilities. In our study, higher HairF concentrations were associated with more depressive symptoms.

4.1 | Limitations

The small sample size of our study is a limitation, and therefore, the results of this first exploration of HairF and HairE in adults with intellectual disabilities and depressive symptoms must be interpreted with caution. Besides, we did not measure hair glucocorticoids in a control group without light intervention. The participants of our study had intellectual disabilities, elevated depressive symptoms and received light therapy; consequently, the results of our study cannot be generalized to adults with intellectual disabilities without depressive symptoms. In our study, we did not measure the participant's overall light exposure, so it is not known whether natural or artificial light exposure affected hair glucocorticoids outcomes. Previous research has shown that natural light can decrease glucocorticoids in scalp hair (Wester et al., 2016). It is unknown whether the artificial light of the light interventions in our study influenced the hair glucocorticoids concentrations, although ultraviolet (UV) filters were installed in the light boxes used

in our trial, ruling out the possible influence of UV radiation. Since the light intervention with 10.000 lux concerned a significantly higher light intensity than the dim light intervention, we would then expect this effect of light on glucocorticoids to be even greater in the 10.000 lux BLT group, which was not the case.

4.2 | Implications for future research and clinical practice

Retrospectively examining stress in adults with intellectual disabilities by using hair glucocorticoids may be a promising method to obtain insight in the level of stress they experienced. Usually, proxy instruments are used to measure stress in adults with intellectual disabilities because self-report is not possible due to cognitive and/or verbal limitations, especially in the population of adults with moderate to profound intellectual disabilities. The proxy results can be biased because a proxy has to make a judgement of the stress of the adult with intellectual disabilities using observations. Further, high rates of transition in caregivers are often seen in clinical practice, which can make it difficult to compare the results on outcome measures. Another advantage of the use of a biomarker is the fact that no specific cognitive level or level of communication is needed, which makes this method even more interesting for the population of people with intellectual disabilities, especially for those with a severe intellectual disability.

In studies focusing on the effect of light (treatment) on hair glucocorticoids, patient's total exposure to light should be measured with a valid instrument and included in the data analyses. An example of a valid instrument to measure patient's light exposure is the HOBO data logger light sensor. In elderly with intellectual disabilities, this sensor has been used successfully in a previous study (Böhmer et al., 2021).

Besides the HPA axis, the autonomic nervous system plays an important role in the physiological response to stress (Won & Kim, 2016). The autonomous regulation of people with intellectual disabilities may be different from that of the general population (Hilgenkamp & Baynard, 2018), and therefore, more studies on hair glucocorticoids in adults with intellectual disabilities, with and without depressive symptoms, are needed. Furthermore, attention must be paid to the variety of syndromes causing intellectual disabilities (Shukur et al., 2020), which may influence the working mechanism of the HPA axis. Additionally, HairF concentrations are associated with cardiovascular disease and type 2 diabetes in the general population (Manenschijn et al., 2013). Both diseases occur frequently in elderly with intellectual disabilities, and an association is found between symptoms of anxiety and diabetes (de Winter et al., 2015). Therefore, more research is needed into associations between hair glucocorticoids and related diseases in this population to fill the gaps of knowledge. In this way, more will be known about hair glucocorticoids in adults with intellectual disabilities, and about how this can be a potential biomarker for (chronic) stress in this specific population, which is often affected by both mental and physical stress caused by the diseases which are co-morbid to many syndromes.

At present, no implications for clinical practice can be given due to the lack of knowledge regarding hair glucocorticoids in adults with intellectual disabilities.

5 | CONCLUSION

This first explorative study on hair glucocorticoids in adults with intellectual disabilities and depressive symptoms showed that at baseline higher HairF concentrations were significantly correlated with more depressive symptoms. We also found a trend towards an inverse correlation between baseline HairE and anxiety symptoms. Further, we found a significant increase in mean HairE, but not in HairF, in our total sample and after dim light intervention, which might point towards an increased conversion of the cortisol to the bio-inactive cortisone by the enzyme 11βHSD type 2. The use of hair glucocorticoids to retrospectively examining biological stress in adults with intellectual disabilities may be a promising method to gain more insight in the level of stress adults with intellectual disabilities may have experienced.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Requests for sharing the anonymous database of this study should be addressed to the corresponding author.

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